Medicinal cannabis: Rational guidelines for dosing

Gregory T Carter[1]*, Patrick Weydt[2], Muraco Kyashna-Tocha[3] & Donald I Abrams[4]

Addresses
[1]Department of Rehabilitation Medicine
[2]Departments of Neurology and Laboratory Medicine
University of Washington School of Medicine
Seattle
WA 98531
USA
Email: gtcarter@u.washington.edu

[3]The Cyber Anthropology Institute
Seattle
WA 98145
USA

[4]San Francisco General Hospital
Division of Hematology/Oncology
Department of Medicine
University of California
San Francisco
CA 94110
USA

*To whom correspondence should be addressed.

IDrugs 2004 **7**(5):
 ISSN 1369-7056

The medicinal value of cannabis (marijuana) is well documented in the medical literature. Cannabinoids, the active ingredients in cannabis, have many distinct pharmacological properties. These include analgesic, antiemetic, antioxidative, neuroprotective and anti-inflammatory actions, as well as modulation of glial cells and tumor growth regulation. Concurrent with all these advances in the understanding of physiological and pharmacological mechanisms of cannabis, there is a strong need for developing rational guidelines for dosing. This paper will review the known chemistry and pharmacology of cannabis and, on that basis, discuss rational guidelines for dosing.

Keywords Cannabinoids, cannabis, dosing, marijuana, pharmacology

Introduction and brief historical background

Possibly the first references to the medicinal use of cannabis are found in the Chinese pharmacopoeia of Emperor Shen-Nung, written in 2737 BC. This document recommended cannabis for analgesia, rheumatism, beriberi, malaria, gout and poor memory [1]. Eastern Indian documents in the Atharvaveda, dating to about 2000 BC, also refer to the medicinal use of cannabis [2]. Archeological evidence has been found in Israel indicating that cannabis was used therapeutically during childbirth as an analgesic [3]. This use of cannabis continued in the West until the mid-1880s and continues today in parts of Asia. In ancient Greece and Rome, both the Herbal of Dioscorides and the writings of Galen refer to the use of medicinal cannabis [4].

The medicinal use of cannabis in western medicine occurred much later. There is mention of it in a treatise by Culpepper written in medieval times. British East India Company surgeon William O'Shaughnessy introduced cannabis for medicinal purposes into the United Kingdom following his observations while working in India in the 1840s. He used it in a tincture for a wide range of uses, including analgesia [5], and Queen Victoria used cannabis for relief of dysmenorrhoea in the same era [6]. In 1937, against the advice of most of the medical community and much of the

American Medical Society, the federal government criminalized non-medical cannabis. Cannabis was removed from the United States Pharmacopoeia in 1942 but up until that time physicians were still able to write a prescription for it [7].

The physiological mechanisms and therapeutic value of cannabinoids continue to be well documented in the medical literature [6-36]. However, there has been little written on appropriate dosing regimens for the medicinal use of cannabis. With current and emerging laws allowing physicians in many areas of the world to recommend the use of cannabis to treat symptoms of certain diseases and medical conditions, there is a need for medical literature describing rational dosing guidelines. This paper will review the known chemistry and pharmacology of cannabis and then, on that basis, discuss rational guidelines for dosing.

Chemistry and pharmacology of cannabis

Cannabis is a complex plant, with several existing phenotypes, each containing over 400 chemicals [14,15]; approximately 60 are chemically unique and classified as plant cannabinoids [11,15]. Naturally occurring cannabinoids are also produced in the human body [8]. The cannabinoids are 21 carbon terpenes, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway [16], and are lipophilic. Δ^9-tetrahydrocannabinol (THC) and Δ^8-THC appear to produce the majority of the psychoactive effects of cannabis. Δ^9-THC, the active ingredient in dronabinol (Marinol) is the most abundant cannabinoid in the plant and this has led researchers to hypothesize that it is the main source of the drug's impact [15]. Dronabinol is available by prescription as a schedule III drug.

Other major plant cannabinoids include cannabidiol and cannabinol, both of which may modify the pharmacology of THC and have distinct effects of their own. Cannabidiol is the second most prevalent active ingredient in cannabis and may produce most of its effects at moderate, mid-range doses. Cannabidiol becomes THC as the plant matures and this THC over time breaks down into cannabinol. Up to 40% of the cannabis resin in some strains is cannabidiol [15]. The amount varies according to plant; some varieties of *Cannabis sativa* have been found to contain no cannabidiol [6]. As cannabidiol may help reduce anxiety symptoms, cannabis strains without cannabidiol may produce more panic or anxiogenic side effects. Cannabidiol may exaggerate some of the effects of THC, including increasing THC-induced euphoria, while attenuating others. Cannabidiol competitively slows THC metabolism in the liver. Consequently, a dose of THC combined with cannabidiol will create more psychoactive metabolites than the same dose of THC alone [14,15]. In mice, pretreatment with cannabidiol increased brain levels of THC by ~ 3-fold and there is strong evidence that cannabinoids can increase the brain concentration and pharmacological actions of other drugs [16,17]. Some researchers have proposed that many of the negative side effects of dronabinol, including sedation and altered mental activity, could be reduced by combining it with cannabidiol or possibly other non-psychoactive cannabinoids [8].

Cannabidiol breaks down to cannabinol as the plant matures [15]. Much less is known about cannabinol, although it appears to have pharmacological properties that are quite different from cannabidiol. Cannabinol has significant anticonvulsant, sedative and other pharmacological activities likely to interact with the effects of THC [14]. Cannabinol may induce sleep and may provide some protection against seizures for epileptics [15-17].

Two physiologically occurring lipids, anandamide (AEA) and 2-arachidonylglycerol (2-AG), have been identified as endogenous cannabinoids (endocannabinoids), although there are likely to be more [18]. The physiological roles of these endocannabinoids have been only partially clarified but available evidence suggests that they function as diffusible and short-lived intercellular messengers that modulate synaptic transmission. Recent studies have provided strong experimental evidence that endogenous cannabinoids mediate signals retrogradely from depolarized postsynaptic neurons to presynaptic terminals to suppress subsequent neurotransmitter release, driving the synapse into an altered state [18-20]. Signaling by the endocannabinoid system appears to represent a mechanism by which neurons can communicate backwards across synapses to modulate their inputs.

There are two known cannabinoid receptor subtypes. Subtype 1 (CB_1) is expressed primarily in the brain whereas subtype 2 (CB_2) is expressed primarily in the immune system [10,20]. Cannabinoid receptors constitute a major family of G protein-coupled, seven-helix transmembrane nucleotides, similar to the receptors of other neurotransmitters such as dopamine, serotonin and norepinephrine. In fact, they are the most abundant G protein-coupled receptor in the brain [8,10,11]. Activation of protein kinases may be responsible for some of the cellular responses elicited by the CB_1 receptor

[21].

Because of this biochemical complexity, characterizing the clinical pharmacology of cannabis is challenging. Further complicating the evaluation of cannabis is the variable potency of the plant material used in research studies. The concentration of THC and other cannabinoids in cannabis varies greatly depending on growing conditions, plant genetics and processing after harvest [19]. The highest concentrations of bioactive compounds are found in the resin exuded by the flowering female plants [18,19]. Leaf mixtures of cannabis have concentrations of THC ranging from 0.3 to 4% by weight [18-20]. However, cannabis today is typically distributed as flowers and can contain anything from 8 to ≥ 25% of THC. Thus, one gram of cannabis flowers would typically contain 80 to 250 mg of THC [19].

The clinical pharmacology of cannabis containing high concentrations of THC may differ from plant material containing small amounts of THC and higher amounts of the other cannabinoids. Moreover, the bioavailability and pharmacokinetics of inhaled cannabis are substantially different than when cannabis is ingested [17,18].

Clinical pharmacology

Although it is a potent drug that may produce psychoactive effects, THC (and the other cannabinoids) have relatively low toxicity, and lethal doses in humans have not been described [23,24]. The theoretical LD_{50} is estimated to be 1 to 20,000 or 1 to 40,000, using a single cannabis cigarette as a unit of dose. Conversely stated, a human would have to consume 20,000 to 40,000 times the amount of cannabis contained in one cigarette, in a short period of time, to achieve lethality. Using this as a basis, it has been estimated that it would require 1500 pounds of cannabis smoked in 15 min to induce a lethal effect [25].

Central effects of cannabinoids include disruption of psychomotor behavior, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis will develop some tolerance [37]. A study by Hart and colleagues demonstrated that acute cannabis smoking produced minimal effects on complex cognitive task performance in experienced cannabis users, while still subjectively providing a euphoric 'high' [38]. The potential medical applications of both natural and synthetic cannabinoids are currently being tested in a number of clinical trials.

Delivery system and pharmacokinetics

Route of administration is an important determinant of the pharmacokinetics of the cannabinoids in cannabis, particularly absorption and metabolism [39-42]. Typically, cannabis is smoked as a cigarette weighing between 0.5 and 1.0 g. After combustion and inhalation, peak venous blood levels of 75 to 150 nanograms per milliliter (ng/ml) of plasma appear when smoking is finished [39,43,44]. The main advantage of smoking is rapid onset of effect and easy dose titration. When cannabis is smoked, cannabinoids in the form of an aerosol in the inhaled smoke are absorbed and delivered to the brain rapidly, as would be expected of a highly lipid-soluble drug [41,45].

A person's smoking behavior during an experiment is difficult for a researcher to control, and smoking behavior is not easily standardized, although some research protocols for standardization of smoking have been developed [44]. An experienced cannabis smoker can titrate and regulate dose to obtain the desired acute effects and to minimize undesired effects [46,47]. Each inhalation delivers a discrete dose of cannabinoids to the body. Inhalation volume changes with phase of smoking, tending to be highest at the beginning and lowest at the end of smoking a cigarette. Some studies found frequent users to have higher inhalation volumes than less frequent cannabis users. Heavy users could absorb as much as 27% of available THC, which may be twice as much as an infrequent user may absorb [47]. During smoking, as the cigarette length shortens, the concentration of THC in the remaining cannabis increases. Thus, each successive inhalation contains an increasing concentration of THC [47]. However, up to 40% of the available THC may be completely combusted in the process of smoking and may not be biologically available. Assays of cannabinoids in blood or urine after smoking can partially quantify dose actually absorbed, but the analytic procedures are methodologically demanding [47,48].

After smoking, venous blood levels of THC fall precipitously within minutes, and an hour later they are ~ 5 to 10% of the peak level [40,41,43,44]. Plasma clearance of THC is quite high at ≥ 950 ml/min which is essentially the rate of hepatic blood flow. However, the rapid disappearance of THC from blood is largely due to redistribution to other tissues in the body rather than cannabinoid metabolism [40,41]. Metabolism in most tissues is relatively slow. Slow release of cannabinoids from tissues and subsequent metabolism results in a long elimination half-time. The terminal half-life of THC is estimated to be from ~ 20 h to as long as 10 to 13 days, although reported estimates vary considerably and are likely to reflect the sensitivity of the measurement assay.

Smoking anything, including cannabis, is not healthful for the lungs and airway system [49,50]. A healthier option may be vaporization; because cannabinoids are volatile, they will vaporize at a temperature much lower than actual combustion [51]. Heated air can be drawn through cannabis and the active compounds will vaporize, and these can then be inhaled. Vaporization delivers the substance in a rapid manner that, like smoking, can be easily titrated to the desired effect [9]. Theoretically this removes most of the health hazards of smoking, although this has not yet been studied. Furthermore, there may be differing vaporization points for the individual cannabinoids. Vaporized cannabis may have differing concentrations and ratios of cannabinoids compared to smoked cannabis, although this also needs further study.

Cannabis can also be ingested orally or through a feeding tube. Orally ingested THC or cannabis has quite different pharmacokinetics than when it is inhaled. The onset of action is delayed and titration of dosing is more difficult [52-55]. Maximum THC and other cannabinoid blood levels are only reached 1 to 6 h after an oral dose, with a half-life of 20 to 30 h [52-55]. The same is true of dronabinol capsules, which contain only synthetic THC and none of the other cannabinoids [54]. When orally ingested, THC is broken down in the liver to the byproduct 11-hydroxy-THC, which also has potent psychoactive effects. This metabolite occurs at a much lower concentration when cannabis is inhaled. Thus, when THC (dronabinol or cannabis) is ingested orally, more sedation occurs because of the 11-hydroxy-THC psychoactive metabolite [54].

Metabolism, bioavailability and drug interactions

Some inactive carboxy metabolites have terminal half-lives of 50 h to 6 days or more and thus serve as markers of prior cannabis use in urine tests [55,56]. Most of the absorbed THC dose is eliminated in feces, and ~ 33% is eliminated in urine. THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-Δ^9-THC (9-COOH-9-THC). The glucuronide is excreted as the major urine metabolite along with ~ 18 nonconjugated metabolites. Frequent and infrequent cannabis users are similar in the way that they metabolize THC [53].

THC bioavailability from smoked cannabis varies greatly among individuals and also depends on the composition of the specific cannabis preparation. Bioavailability can range from 1 to 27% with variable bioavailability resulting from significant loss of THC in side stream smoke, as well as variation in individual smoking behaviors. This includes incomplete absorption from inhaled smoke, metabolism in lung, and cannabinoid pyrolysis (ie, destruction by combustion).

Cannabinoids appear to partially inhibit the metabolism of drugs metabolized by the hepatic cytochrome P450 enzyme system [57-60]. Thus, the absorption or clearance of other drugs taken with cannabis may be slowed or hastened depending on timing and sequence of drug ingestion and past exposure. THC is highly bound to plasma proteins (97 to 99%) and is likely to interact with other highly bound drugs because of competition for binding sites on plasma proteins [61,62].

Dronabinol

The Food and Drug Administration (FDA) first licensed and approved dronabinol in 1986 for the treatment of nausea and vomiting associated with chemotherapy. The indication was expanded in 1992 for the treatment of anorexia associated with weight loss in patients with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled, 6-week study involving 139 patients, dronabinol provided statistically significant improvement in appetite and non-statistically significant trends toward improved body weight and mood, and decreases in nausea [63]. In 1999, the United States Drug Enforcement Administration, in cooperation with the FDA, reclassified the scheduling status of dronabinol from a Schedule II (CII) to a Schedule III (CIII) controlled substance (for definitions of schedules refer to

http://www.dea.gov/pubs/csa/812.htm).

In 454 patients with cancer who received a total of 750 courses of treatment for various malignancies, dronabinol capsules provided complete or partial success in easing nausea and vomiting in 68% of patients given dronabinol (< 7 mg/m^2/day) and 64% of patients given dronabinol (> 7 mg/m^2/day) [64].

According to the manufacturer the prescribed dose of dronabinol for appetite stimulation is 2.5 mg twice-daily, to be taken before lunch and dinner. For nausea, vomiting, and pain the dosing is 5 mg/m^2. If the 5 mg dose is ineffective, incremental increases of 2.5 mg, up to a maximum of 15 mg, is recommended. The same dose can be taken every 2 to 4 h for a maximum of four to six doses a day. Regardless of the clinical setting in which it is prescribed, the maximum total recommended dose of dronabinol is 15mg/m^2 four- to six-times daily or ~ 100 to 120 mg a day [65].

Clinical trials

There are a limited number of well-performed clinical trials from which to draw succinct dosing regimens. Clinical trials have typically used cannabis cigarettes supplied by the NIDA (National Institute on Drug Abuse) containing 3.5 to 4.0% of THC by weight [59,66,67]. Recently, Abrams *et al* conducted an open-label study in patients with confirmed HIV neuropathy with persistent neuropathic pain [68]. All patients had prior experience of smoking marijuana but had ceased for 30 days prior to admission. After a 2-day lead-in period, patients smoked one cigarette containing 3.56% of THC three times/day for 7 days. A heat-capsaicin-induced experimental pain model was used to clarify the effects of the THC. Marijuana smoking caused a drop in pain score to 20/100 with ten of 16 patients experiencing a 30% reduction in average daily pain. An excellent correlation was noted in the response to the heat-capsaicin model, as 14 of 16 patients experienced a 30% reduction in the area of secondary hyperalgesia after smoking [68].

Wade *et al* compared plant-derived cannabis extracts to standard treatments for neurogenic symptoms unresponsive to standard treatment in a double-blind, randomized, placebo-controlled, cross-over trial with 2-week treatment periods [69]. There were 24 patients total, with diagnoses including multiple sclerosis (n = 18), spinal cord injury (n = 4), brachial plexus injury (n = 1), and limb amputation due to neurofibromatosis (n = 1). Whole-plant extracts of either THC only, cannabidiol only, a mixed cannabinoid extract of both THC and cannabidiol in a 1:1 ratio, or a matched placebo were self-administered by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5 to 120 mg/24 h. The results demonstrated that pain relief associated with both THC and cannabidiol was significantly superior to placebo. The mixed cannabinoid extract, compared to placebo, was significantly superior in providing pain relief and improving bladder control, muscle spasms and spasticity. Side effects were rare. Three patients had transient hypotension and intoxication with rapid initial dosing of the THC extract.

Deriving dosing recommendations and guidelines

Cannabis has many variables that do not fit well with the typical medical model for drug prescribing. If the plant is used, the variations are extreme. Plants vary immensely by phenotypes, and even the time of harvest affects which cannabinoids are present and in what percentages. One person may be much more sensitive than another, heavy smokers may get a different chemical 'smorgasbord' than light smokers and ingestion may alter bioavailability. The bulk of the research into cannabis has primarily examined THC, the other cannabinoids to a lesser degree, and the combinations hardly at all, although this is beginning to change. These combinations are very important to medicinal users of cannabis as a number of positive synergistic effects could be involved [70-72]. All of these points make it imperative that the dosing is highly individualized, so a patient-determined, self-titrated dosing model is recommended. This self-titration model is acceptable given the variables discussed above, as well as the low toxicity of cannabis. This construct is not unique to cannabis. There are other drugs that have relatively low toxicity and high dosing ceilings (gabapentin being one notable example), and are titrated to effect.

To facilitate an understanding of the determination of these guidelines, an estimate as to the actual amount of THC obtained by a patient when smoking different strengths of cannabis must be derived. As noted earlier, with smoking as the delivery, 40% of the active ingredients are lost in side stream or combustion, and a maximum of 27% of the remaining active ingredients can actually be absorbed by the patient. Given this, the maximum THC absorbed by a patient using 1 g of cannabis containing 10% of THC would be 16.3 mg.

The only form of cannabinoid that is available by a formal, dose-specific prescription is dronabinol. There are too many variables in the published clinical trials and case series with raw cannabis to use those studies as a basis for deriving doses. Therefore, we will use the dronabinol prescription guidelines as published by the manufacturer and accepted by the FDA as the basis for formulating our dosing recommendations for natural cannabis. It is critical to note that dronabinol is an oral preparation and contains only THC. Most medicinal cannabis patients use smoking as the route of delivery. As we have previously noted there are significant differences in pharmacokinetics between oral consumption and smoking. Furthermore, there are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material. It is also not clear how the original dosing construct for dronabinol was arrived at, although we assume it was done through clinical testing for therapeutic benefit versus side effects. Despite these inherent limitations, these calculations do provide approximate dose equivalents by weight and are useful as long as one recognizes these limitations.

Applying the known pharmacokinetics of cannabis, as described above, to a conservative dronabinol dosing model of 2.5 to 60 mg/day, we calculated the following doses for cannabis containing these percentages of THC (Table 1).

Table 1. Amount of cannabis equivalent to dronabinol (2.5 to 60 mg).

% of THC in cannabis	Amount of cannabis required to obtain:			
	2.5 mg of THC	10 mg of THC	30 mg of THC	60 mg of THC
5% THC	0.60 g	1.24 g	3.70 g	7.40 g
10% THC	0.30 g	0.62 g	1.85 g	3.70 g
15% THC	0.16 g	0.41 g	1.23 g	2.46 g
20% THC	0.10 g	0.31 g	0.93 g	1.86 g
25% THC	0.08 g	0.25 g	0.75 g	1.50 g
30% THC	0.05 g	0.20 g	0.62 g	1.24 g

These derived figures lie closely within the range of reported amounts. In informal surveys from patients in Washington and California, the average reported consumption of cannabis by medicinal users typically ranges between 10 to 20 g of raw cannabis per week, or ~ 1.42 to 2.86 g/day of cannabis. The average strength of medical cannabis used by the patients who reported these doses was 15% THC. Thus these patients were actually absorbing between 34 and 68 mg/day of THC from the raw cannabis. The mean strength of medical cannabis in this study was ~ 19% THC, which corresponds to 44 to 88 mg/day of THC actually being consumed by the patient [72]. These figures are all within a similar range.

Our recommended doses are further reinforced by two of the studies that utilized smoked cannabis in a well-documented dosing regime. Chang *et al* studied the effects of smoked cannabis dosed at 10 mg/m^2 five-times-daily, equivalent to 87.5 mg of THC a day for an average-sized person. This would be the equivalent of 3.6g of cannabis containing 15% of THC [73]. Vinciguerra *et al* studied smoked cannabis dosed at 5 mg/m^2 four-times-daily, or 35 mg of THC a day for an average person. This is the equivalent of ~ 1.4g of cannabis containing 15% of THC [74]. For the purposes of these calculations, we assumed a 5'7" person weighing 140 lbs, with a body surface area of 1.75 meters squared.

These doses all fall within the medical cannabis guidelines allowed in the Canadian medical system. The Canadian medical allowance is for 1 to 12 g/day with an average of > 5 g. These doses are also very similar to the dosing range reported in a recent survey of patients who use cannabis to control symptoms of amyotrophic lateral sclerosis [75]. Thus, despite all of the noted variables, there is remarkable consistency among our derived doses and the reported doses from a number of different sources noted here.

A final comment should be made regarding physiological tolerance to cannabinoids. Tolerance does play a significant role in cannabis use and tolerance may develop to any of the various cannabinoids [76]. With regard to treating chronic, intractable pain, physicians will often prescribe increasingly larger doses of long-acting opioids as

patients develop tolerance. These patients are also generally given prescriptions of fast onset, short-acting opioids for 'breakthrough pain'. This is accepted practice, despite the fact that opioids, even in an opioid-dependent patient, still have the capacity to suppress breathing to the extent of inducing respiratory arrest. Long-term cannabis users can develop tolerance but, as previously discussed, there is essentially no risk for overdose. Thus, it is conceivable that a long-term cannabis user may require significantly larger amounts of cannabis to achieve a therapeutic effect. In addition, those who ingest cannabis may also require significantly higher amounts. Until more refined and purified cannabinoid preparations are available it will not be possible to derive a more specific or exact dosing schedule.

Conclusions

We have outlined reasonable guidelines for dosing of medical cannabis, based on the known pharmacology. Our dosing model is primarily derived from dronabinol (THC), since that is the only clearly defined, FDA approved dosing paradigm currently available. However, our derived dosing schedule did match reasonably well with the amounts of natural cannabis reported by medical users. In using our dosing guidelines clinicians must be aware that THC is not the only clinically useful and pharmacologically active cannabinoid. The effects of THC are clearly modulated by other cannabinoids, which may have unique effects of their own. The clinician must also be aware of patient tolerance, and differing routes of intake and delivery systems, which can affect pharmacokinetics and bioavailability. Recognizing this, we recommend that our guidelines are used as a construct to allow the physician and patient to develop an individual, self-titration dosing paradigm. Given the current state of the known, published pharmacology of cannabis, this is the best dosing model that can be derived.

Acknowledgments

Supported by Research and Training Center Grant HB133B980008 from the National Institute on Disability and Rehabilitation Research, Washington, DC, USA. The authors would like to acknowledge Dale Gieringer, Martin Martinez and Ethan Russo for their help in preparing this manuscript.

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