Medicinal cannabis: Rational guidelines for dosing

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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, anti-emetic, anti-oxidative, neuroprotective and anti-inflammatory activity, as well as modulation of glial cells and tumor growth regulation. Concurrent with all these advances in the understanding of the 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 Culpepperwritten in medieval times. British East India Company surgeon William O'Shaughnessy introduced cannabis for medicinal purposes into the United Kingdom following observations he made 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

dysmenorrhea in the same era [6•]. In 1937, against the advice of the majority 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, had still been prescribed by physicians [7].

The physiological mechanisms and therapeutic value of cannabinoids continue to be well documented in the medical literature[6•, 7, 11,12••,13,14,15••,16• ,17••,18••,19-21,22••, 23,24••,25-27,28•,29,30,31••,32-36]. 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. Δ9-tetrahydro-cannabinol (THC) and Δ8-THC appear to produce the majority of the psychoactive effects of cannabis. Δ9-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 effects of the drug [14]. 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 converts to THC as the plant matures and over time this THC degrades to cannabinol. Up to 40% of the cannabis resin in some strains is cannabidiol [6•,26]. 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 morepanic or anxiogenic side effects. Cannabidiol may exaggerate some of the effects of THC (including increasing THC-induced euphoria), while attenuating others, and 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 [27,31••]. In mice, pre-treatment 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 [10,11]. 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].

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 that are likely to interact with the effects of THC [14]. Cannabinol may induce sleep and may provide some protection against seizures for epileptics [14,28•,32].

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 [29]. The physiological roles of these endocannabinoids have been only partially clarified but availableevidence suggests that they function as diffusible and short-lived intercellular messengers that modulate synaptic transmission. Recent studies have provided strong experimental evidence that endocannabinoids mediate signals retrogradely fromdepolarized post-synaptic neurons to presynaptic terminals to suppress subsequent neurotransmitter release, driving the synapse into an altered state [29,31••]. 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 (CB1) is expressed primarily in the brain whereas subtype 2 (CB2) is expressed primarily in the immune system[29,31••]. Cannabinoid receptors constitute a major family of G protein-coupled, seven-helix transmembrane nucleotides, are similar to the receptors of other neurotransmitters such as dopamine, serotonin and norepinephrine, and 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 CB1receptor [9].

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 [6•,7,8]. The highest concentrations of bioactive compounds are found in the resin exuded by the flowering female plants [6•,7,8]. Leaf mixtures of cannabis have concentrations of THC ranging from 0.3 to 4% by weight [6•,7,8]. However, cannabis today is typically distributed as flowers and can contain 8 to ≥ 25% of THC. Thus, 1 g of cannabis flowers would typically contain 80 to 250 mg of THC [6•].

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 [6•].

Clinical pharmacology

Although it is a potent drug that may produce psychoactive effects, THC (and the other cannabinoids) has relatively low toxicity, and lethal doses in humans have not been described [25,26]. The theoretical LD50 value 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-fold 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 628 kg of cannabis would have to be 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 evidencethat 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 co-workers 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

The 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 with a mass of between 0.5 and 1.0 g. After combustion and inhalation, peak venous blood levels of 75 to 150 ng of THC per ml of plasma have been measured when smoking is finished [39,43,44]. The main advantage of smoking is rapid onset of effect and ease of 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].

Individual 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 maybe 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 ≥ 950 ml/min,

which is relatively high and 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-life. The terminal half-life of THC is estimated to range 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 beneficial 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, 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 [52-54,55•]. 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 [52-54,55•]. This is also reflected in the pharmacokinetics of dronabinol capsules, which contain only synthetic THC and none of the other cannabinoids [54].When orally ingested, THC is degraded 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 presence of the 11-hydroxy-THCpsychoactive metabolite [54].

Metabolism, bioavailability and drug interactions

Some inactive carboxy metabolites have terminal half-lives of 50 h to ≥ 6 days and thus serve as markers of priorcannabis 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 non-conjugated 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 [57,58,59••,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].

The Food and Drug Administration (FDA) first licensed and approved dronabinol in 1986 for the treatment of nauseaand vomiting associated with chemotherapy. The indication was expanded in 1992 to 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 a 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 < 7 mg/m 2/day of dronabinol and 64% of patients given > 7 mg/m2/day of dronabinol [64••]. According to the manufacturer, Unimed Pharmaceuticals Inc, 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/m2. 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 15 mg/m2 four- to six-times-daily or 100 to 120 mg/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 and co-workers 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-daily for 7 days. A heat-capsaicin-induced experimental pain model was used to clarify the effects of THC. Marijuana smoking led to a reduction 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 and co-workers 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]. The enrolled patients (n = 24) had 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. An individual may be much more sensitive than another, heavy smokers may experience different chemical effects than light smokers and ingestion may alter bioavailability. The bulk of the research into cannabis has primarily examined THC, the other cannabinoids have been studied to a lesser degree, while little research has been performed on combinations of cannabinoids, although this is beginning to change. These combinations are 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 limits (gabapentin being one notable example), and are titrated to effect.

To facilitate an understanding of the determination of these guidelines, an estimate of 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 derived from 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.

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 doses for cannabis containing particular percentages of THC (Table 1). These derived figures lie closely within the range of reported amounts. In informal surveys from patients in Washington and California (USA), 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.

Table 1. Amount of cannabis calculated to contain equivalent amounts of THC to dronabinol (2.5 to 60 mg).

Amount of cannabis (g) required to obtain:	% of THC in cannabis
2.5 mg of THC	5
10 mg of THC	0.60
30 mg of THC	1.24
60 mg of THC	3.70
	7.40
	10
	0.30
	0.62
	1.85
	3.70
	15
	0.16
	0.41
	1.23
	2.46
	20

0.10
0.31
0.93
1.86
25
0.08
0.25
0.75
1.50
30
0.05
0.20
0.62
1.24

Our recommended doses are further reinforced by two studies that utilized smoked cannabis in a well-documented dosing regime. Chang and co-workers studied the effects of smoked cannabis dosed at 10 mg/m2five-times-daily, which is equivalent to 87.5 mg/day of THC for an average-sized person. This would be the equivalent of 3.6 g of cannabis containing 15% of THC [73]. Vinciguerra and co-workers studied smoked cannabis dosed at 5 mg/m2 four-times-daily, or 35 mg/day of THC for an average person. This is the equivalent of 1.4 g of cannabis containing 15% of THC [74]. For the purposes of these calculations, we assumed an average-sized person to be 1.70 m in height with a mass of 63.6 kg and a body surface area of 1.75 m2.

These doses all fall within the medical cannabis guidelines allowed in the Canadian medical system. The Canadian medical allowance for cannabis is 1 to 12 g/day, with an average of > 5 g/day. These doses are also highly 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 notedhere.

A final comment should be made regarding physiological tolerance to cannabinoids. Tolerance plays a significant role in cannabis use since 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 prescribed fast onset, short-acting opioids for 'breakthrough pain'. This is accepted practice, despite the fact that opioids, even in an opioid-dependent patient, 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 activecannabinoid. 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 aconstruct 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.

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