

Marijuana Dosing Issues: Notes From the Literature

By Deborah Malka

A new medical sub-specialty has developed in the past decade, that of the medical marijuana clinician. In California and other states that have legalized physician-approved marijuana use, hundreds of thousands of patients have been advised that marijuana may be a beneficial medicine for their condition.

Clinicians who learned nothing about marijuana in medical school have been giving advice regarding use, dosage, effects, interactions, etc. We have had to learn as we go, relying on feedback from colleagues and patients, as well as the few papers which are excerpted here.

The beneficial compounds in marijuana can be delivered by various methods—smoking, vaporization, ingestion via the GI tract or mucous membranes, or topical application to the skin. Each delivery system involves its own dosage regimen.

Route of administration is an important determinant of the pharmacokinetics of the various cannabinoids in cannabis, particularly absorption and metabolism.

Most of the emerging body of literature regarding dosage has focused on smoked or vaporized cannabis, notably the 2004 paper by Carter *et al* (Source 1)

As the use of medical marijuana becomes more refined, we see that many of our patients are using it in edible, topical, and other non-smoked other forms.

This paper reviews dosage considerations for all modes of delivery of cannabis as reported in the emerging literature. It is intended to help clinicians discuss dosing issues with their patients.

Much more investigation is needed regarding dosage, and we expect serious studies to be carried out in the years ahead.

Dosing Variables

Carter *et al* wrote in 2004, “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. All of these points make it imperative that the dosing is highly individualized, so a patient-determined, self-titrated dosing model is recommended.

“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 gram of cannabis containing 10% of THC would be 16.3 milligrams.

“Applying the known pharmacokinetics of cannabis... to a conservative dronabinol dosing model of 2.5 to 60 mg/day, we calculated the doses for cannabis containing particular percentages of

THC. 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...

“In informal surveys from patients in Washington and California, the average reported consumption of cannabis by medicinal users typically ranges between 10 to 20 grams of raw cannabis per week, or 1.42 to 2.86 grams/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.

Source 1: Gregory T Carter, Patrick Weydt, Muraco Kyashna-Tocha & Donald I Abrams, Medicinal cannabis: Rational guidelines for dosing, Drugs 2004 Vol 7, p464-470

“The National Institute on Drug Abuse provides by prescription a standard dose of smoked cannabis to patients in the Compassionate Investigational New Drug (IND) program. This is about two ounces per week - a half-pound per month - mailed in canisters of 300 pre-rolled cigarettes consumed at a rate of 10 or more per day...

“Chronic pain patients tend to use larger amounts, while acute and terminal patients may use less. Health conditions may periodically or cyclically improve or get worse, causing usage to fall or rise. Some require daily and multiple-daily dosages.

Source 2: Chris Conrad, Cannabis Yields and Dosage (Part 2) 2004, www.safeaccessnow.net/fedmmj.htm

“Cannabis medicines are most often an adjunctive treatment. Concurrent use of pharmaceutical drugs may adversely affect the bioavailability of cannabis. Powerful drugs can also reduce physiological responses, creating the need for higher-than-average dose levels.

Some patients depend on medical marijuana to keep from vomiting their oral medications so their need for a specific dose of cannabis compounds may fluctuate with day-to-day reactions to those nauseating pharmaceutical drugs.”

Source 3: Martin Martinez, Marijuana patient dosage and cultivation limits, Oct 2007 www.cannabismd.org/foundation/MMJCUltext.php

Cannabinoid Concentration

“The concentration of THC and other cannabinoids in cannabis varies greatly depending on growing conditions, plant genetics and processing after harvest. The highest concentrations of bioactive compounds are found in the resin exuded by the flowering female plants. Leaf mixtures of cannabis have concentrations of THC ranging from 0.3 to 4% by weight. However, cannabis today is typically distributed as flowers and can contain 8 to 25% of THC. Thus, 1 gram of cannabis flowers would typically contain 80 to 250 mg of THC.”

Source 4: Workshop on the Medical Utility of Marijuana, www.nih.gov/news/medmarijuana/MedicalMarijuana.htm

“California NORML published [an] assay of medical marijuana in 1999. Those test results showed a wide disparity in potency.

The study, consisting of three rounds of testing by two different DEA-licensed laboratories, measured the concentrations of THC, the primary active ingre-

redient of marijuana, and its two commonest chemical relatives, known as cannabinoids, CBD and CBN.

In all, 49 samples of medicinal cannabis were analyzed for potency by standard gas chromatograph mass spectrometry. The sample showing the lowest THC (less than or equal to 3.9%) was the government’s own marijuana, grown for the National Institute on Drug Abuse (NIDA) to supply researchers and eight legal medical marijuana patients. Nearly all other samples tested over 8%, with averages in the range of 12.8% -15.4%, and many samples above 20%. One sample of hashish (concentrated resin) tested above 44%.” —Martinez

Smoking

“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. The minimum dose of THC required to get a person ‘high’ is 10 micrograms per kilogram of body weight. For a 165-pound person, this would be 750 micrograms of THC, about what is delivered by one bong hit.

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.

—Carter *et al*

“After smoking, venous blood levels of THC fall within minutes, and an hour later they are 5 to 10% of the peak level. THC bioavailability, i.e., the actual absorbed dose as measured in blood, from smoked marijuana, varies greatly among individuals. Bioavailability can range from 1 percent to 24 percent with the fraction absorbed rarely exceeding 10 percent to 20 percent of the THC in a marijuana cigarette or pipe.

This relatively low and quite variable bioavailability results from significant loss of THC in sidestream smoke, from variation in individual smoking behaviors, from incomplete absorption from inhaled smoke, and from metabolism in lung and cannabinoid pyrolysis. A smoker’s experience is probably an important determinant of dose actually absorbed.” —Martinez (3)

“A person’s smoking behavior during an experiment is difficult for a researcher to control. People differ. Smoking behavior is not easily quantified. An experienced marijuana smoker can titrate and regulate dose to obtain the desired acute psychological effects and to avoid overdose and/or minimize undesired effects.

Each puff delivers a discrete dose of THC to the body. Puff and 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 puff volumes than did less frequent marijuana users. During smoking, as the cigarette length shortens, the concentration of THC in the remaining marijuana increases; thus, each successive puff contains an increasing concentration of THC.”

—Workshop (4)

“While most users are familiar with varying potencies of marijuana, many are only vaguely aware of differences in the efficiency of various ways to smoke it. Clinical studies indicate that only 10 to 20% of the available THC is transferred from a joint cigarette to the body. A pipe is better, allowing for 45% of the available THC to be consumed. A bong is a very efficient delivery system for marijuana; in ideal conditions the only THC lost is in the exhaled smoke.”

Source 5: Jon Gettman, Marijuana and the Brain, Part II: The Tolerance Factor. High Times, July 1995 www.marijuanalibrary.org/brain2.html

Smoking behavior is not easily standardized. “An experienced cannabis smoker can titrate and regulate dose to obtain the desired acute effects and to minimize undesired effects. 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. 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. However, up to 40% of the available THC may be completely combusted in the process of smoking and may not be biologically available.” —Carter *et al*

Vaporization

“Smoking anything, including cannabis, is not beneficial for the lungs and airway system. A healthier option may be vaporization. Due to their volatility, cannabinoids will vaporize at a much lower temperature than combustion, allowing them to be inhaled as a warm air mist. Heated air can be drawn through cannabis, the active compounds will vaporize, and these can then be inhaled.

However, there may be differing vaporization points for the individual cannabinoids. Thus, vaporized cannabis may have differing concentrations and ratios of cannabinoids compared with smoked cannabis. Cannabinoids in the form of an aerosol in inhaled smoke or vapors are absorbed and delivered to the brain and circulation rapidly, as expected of a highly lipid-soluble drug.

Vaporization delivers the substance in a rapid manner that, like smoking, can be easily titrated to the desired effect. Theoretically, this removes most of the health hazards of smoking.”

—Carter *et al*

Ingestion

“Cannabinoids are fat-soluble, meaning that they bind to fat cells and can be broken down with solvents; this also means that they don’t break down well in water. As a result, high fat products like butter, oil or alcohol are ideal to extract and deliver cannabinoids to the human body...”

“When oil-based cannabis products (like cookies or olive oil) are ingested, they are broken-down through the stomach and then the duodenum before being processed by the liver. The strong

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alkaline produced by this process is called 11-hydroxy THC, a cannabinoid with stronger psychotropic effects than simple THC. This [onset] can take from 30 to 120 minutes and limits control of dosage. The advantage is that a small dose is often very effective.”

–6. *The Vancouver Island Compassion Society*, www.thevics.com/publications/vics/VICSByProductsGuide2007.pdf

“When cannabis is taken orally, the effects take much longer to develop and peak, (1-2 hours, as opposed to a few seconds), and subside more slowly. THC, not being water-soluble, must be taken with some fat, oil or alcoholic carrier to permit absorption into the blood.

“It is generally considered that up to three times as much cannabis is required when taken orally compared to smoking the drug, as evidenced by the equivalent analgesic efficacy of THC doses of 20mg taken orally and 7.5mg smoked.”

7. *House of Lords, Section 4. Methods of cannabis ingestion*, www.idmu.co.uk/hol4.htm

“Due to its delayed onset and varied metabolic activity, eaten cannabis is hard to titrate. Orally ingested in cannabis THC has quite different pharmacokinetics than when it is inhaled. The onset of action is delayed and titration of dosing is more difficult. Maximum THC and other cannabinoid blood levels are only reached one to six hours after an oral dose, with a half-life of 20 to 30 hours.

This is also reflected in the pharmacokinetics of dronabinol capsules, which contain only synthetic THC and none of the other cannabinoids. 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 is ingested orally, more sedation occurs because of the presence of the 11-hydroxy-THC psychoactive metabolite.” –Carter et al

“Oral bioavailability of THC, whether given in the pure form or as THC in marijuana, also is low and extremely variable, ranging between five and 20 percent. Great variation can occur even when the same individual is repeatedly dosed under controlled and ideal conditions. THC’s low and variable oral bioavailability is largely a consequence of large first-pass hepatic elimination of THC from blood and due to erratic absorption from stomach and bowel.

“Because peak effects are slow in onset and variable in intensity, typically at least an hour or two after an oral dose, it is more difficult for a user to titrate dose than with marijuana smoking. When smoked, THC’s active metabolite 11-hydroxy-THC probably contributes little



to the effects since relatively little is formed, but after oral doses the amounts of 11-hydroxy-THC metabolite may exceed that of THC and thus contribute to the pharmacologic effects of oral THC or marijuana.” –Workshop (4)

“Effects of ingested cannabis tend to be much more pronounced than smoked cannabis, both physically and psychoactively, and vary depending on strain used in the preparation. An elevated dosage, though not lethal, can be very uncomfortable (i.e. vomiting, panic). Therefore it is important to take care in finding the right dosage. Small amounts should be ingested, and it is recommended to wait two hours before increasing the dosage gradually, if necessary.”

8. *BCCC, Safe and Effective Use of Cannabis Pamphlet pdf* at www.thecompassionclub.org/medical/safe

Tincture

“Cannabinoids can also be extracted into alcohol or glycerine, and made into tinctures. Tinctures may be dropped or sprayed into the mouth to be absorbed into the mucous membranes. Effects of tinctures are usually felt within 5 minutes up to 1 hour, and last about 4 hours.”

–BCCC

“Alcohol based tinctures may also be dropped into hot water in order to let the alcohol evaporate, and then ingested. Effects will be the same as they are for ingested cannabis. When alcohol-based products (like tincture) are ingested, the alcohol acts as a delivery method as it circumvents the digestive tract by being absorbed directly into the bloodstream through the pharynx and stomach lining. As a result, alcohol-based products are fast-acting (15-45 minutes) but not necessarily long-lasting.” –VICS

Topical

“The cannabinoids may also be made into a liniment and absorbed through the skin. This was a common treatment for arthritis around the turn of 20th century. However, this is the least efficient mode of delivery.

When extracts of cannabis were applied topically to treat TPA-induced erythema in mouse skin, a petroleum spirit extract was found to be four times more potent than the ethanolic extract. Because alcohol extracts may not provide the most efficient delivery system, others should be investigated.”

9. *Deriving Dosing Guidelines for Medical Marijuana: Clearing the Smoke*, *Medscape General Medicine*. 2007;9(3):52, www.medscape.com/viewarticle/562451_3

“Cannabinoids are ‘lipophilic in general,’ which means they are absorbed into the cell membrane. Whether or not the Cannabinoids make the transit through the various layers of the derma remain problematic. Anecdotal evidence indicates that topical tincture application is, in fact, efficacious...”

“Both osteoarthritis and muscle spasm from diabetes and MS are major indications for tincture relief. We know that there is a rich cannabinoid receptor field in the soma which tincture could interact with, even without psychotropic effect.”

10. <http://www.onlinepot.org/medi->

cal/topical.htm

“In a preferred method of topically applying the liniment, the liniment is sprayed onto the skin in the area of discomfort or the inflamed area. In another method of topically applying the liniment, a small amount of the liniment is applied directly to skin in the area of discomfort or the inflamed area and rubbed in by hand. The liniment may also be applied by either method over the entire body, with the exception of the face. The recommended dosage is to apply approximately 2 oz. of the liniment a day for a period of at least 1 week. The liniment may also be mixed with other liquids for various other applications.”(13)

Recipes are similar in preparation to the tinctures above, 0.01 to 0.5 g/ml x 2 ounces = 0.5g to 30 g per dose.

11. *Walter Wallace, Method of relieving analgesia and reducing inflammation using a cannabinoid delivery topical liniment*, 2005, <http://www.freepatentsonline.com/6949582.html>

Cannabis oil may also used for massage and topical delivery. Topical application of cannabis oil, while practiced by patients and used historically, is an area which has yet to be studied.

Metabolism and Clearance

“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.

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...

“Most of the absorbed THC dose is eliminated in feces and about 33 percent in urine. THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta-9-THC (9-COOH-9-THC). The glucuronide is excreted as the major urine metabolite along with about 18 nonconjugated metabolites. Frequent and infrequent marijuana users are similar in the way they metabolize THC.”

Tolerance and Effects

“Perhaps the most important consideration in assessing amounts of marijuana required as medicine is the tolerance factor. Long-term marijuana patients may ingest relatively huge amounts of the herb because they develop a tolerance to the psychotropic effects.”

11. <http://cannabismd.org/foundation/mmjdosingguidelines.php> Posted on Sunday, August 3, 2008 at 10:56PM by *CannabisMD.net*

“As noted by the National Institute on Health: ‘After repeated smoked or oral marijuana doses, marked tolerance is rapidly acquired (after a day or two) to many marijuana effects, e.g., cardiovascular, autonomic, and many subjective effects. After exposure is stopped, tolerance is lost with similar rapidity. Measurable tolerance or tachyphalaxis is evident for some hours after smoking even a single marijuana cigarette.’ “

–Martinez

“Tolerance develops faster with high-potency cannabinoids. People who have irregular access to marijuana, and to low-

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quality marijuana at that, do not have the opportunity to develop sufficient tolerance to overcome the acute effects of the drug.

"Tolerance plays a significant role in cannabis use since tolerance may develop to any of the various cannabinoids. Long-term cannabis users can develop tolerance but 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...

"Small doses of THC provide stimulation, followed by sedation. Large doses of THC produce a mild hallucinogenic effect, followed by sedation and/or sleep. The effects of mild 'hypnagogic' states produced by THC are often undetected, contributing to mood variations from gregariousness to introspection...

"The effects of marijuana can be sorted into four categories.

1) First, there are modest physical effects, such as a slight change in heart rate or blood pressure and changes in body temperature.

2) Tolerance develops to these effects with familiarity and/or regular use.

3) Tolerance next develops to the depressant effects of marijuana, particularly to its effects on motor coordination. However, tolerance to these effects depends on the quality of the marijuana consumed as well as the frequency of use.

4) After a while, tolerance develops to even the stimulative effects of marijuana. Experienced users learn that there is an outer limit to how high they can get. Paradoxically, this limit can only be exceeded by lower consumption. Patients who require marijuana for medical purposes generally discover what dose provides steady maintenance of therapeutic benefits and tolerance to the side effects, both depressant and stimulative." —*Gettman*

Tolerance and Equilibrium

"There are three forms of tolerance to a (drug) substance:

1) Dispositional tolerance is produced by changes in the way the body absorbs a drug.

2) Dynamic tolerance is produced by changes in the brain caused by an adaptive response to the drug's continued presence, specifically in the receptor sites affected by the drug.

3) Behavioral tolerance is produced by familiarity with the environment in which the drug is administered. 'Familiarity' and 'environment' are two alternative terms for what Timothy Leary called 'set' and 'setting' — the subjective emotional/mental factors that the user brings to the drug experience and the objective external factors imposed by their surroundings." —*Gettman*

Summary

1) Marijuana can be delivered by smoking, vaporization, ingestion via the GI tract, ingestion as a tincture via mucous membranes, or topically. These all require different dosing regimens.

Smoking: small dose required, rapid onset in 5-10 minutes. LESS?

Effects last 2-4 hours CHECK THIS
Average amount in a joint = 0.5 to 1

gram.

Average amount in a bong hit = 0.5 to 1 gram.

Amount used daily: may range from 1 to 12 grams.

Vaporization: dose and onset as in smoking. May require up to twice as much marijuana to deliver the same amount, i.e. 1-2 grams/dose

Tincture: Higher dose required. Moderate onset in 15-30 minutes. Lasts two hours as mouth spray, three to five hours if swallowed.

Use depends on the potency of the tincture. Patients should begin with a few drops, up to 1 ml dropper per dose. May contain up to 0.5 grams/ml dropper. DON'T UNDERSTAND

Ingestion in oil, butter or food: higher dose required. Effects onset in one to two hours and last six to eight hours. Lasts 6-8 hours. May require three to five times the dose as smoking.

Use depends on the potency of the substance, i.e. 1/4 cookie, 1 teaspoon of oil or butter, 1-2 capsules. May contain 0.3-0.5 g per capsule.

(The use estimates for edibles can vary by a factor of 10, as do smoking estimates, due to potency of plant and the dilution factor.)

Topical: Dose is a function of area to be covered. Reported concentrations range from 0.01 to 0.5 g/ml. An alcohol-based topical applied to a sore shoulder or knee may require up to 30 grams per application.

Duration of action has not been studied. Once absorbed through the skin, effects may last four hours or more.

2) Tolerance develops with regular use. Chronic use and use of higher potency product causes faster development of tolerance. Irregular users may not develop tolerance. An herbal holiday of one day per week, three days per month or a week every season are reasonable detox protocols. DO YOU MEAN THIS TO APPLY JUST TO TOPICALS?

3) More research is needed to optimize dosing guidelines.

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