Listening to Marinol

Rational Guidelines for Dosing

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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 of plasma appear about the time smoking is finished.

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.

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. An experienced cannabis smoker can titrate and regulate dose to obtain the desired acute effects and to minimize undesired effects.

Each puff delivers a discrete dose of cannabinoids 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.

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Some studies found frequent users to have higher puff volumes than did 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.

During smoking, as the cigarette length shortens, the concentration of THC in the remaining cannabis increases. Thus, each successive puff contains an increasing concentration of THC. However, up to 40% of the available THC may be completely combusted in the process of smoking and not be biologically available.

1. Maximum absorption of THC per gram of cannabis

For 1 gram of cannabis with:	Maximum delivery to patient is
10% THC	16.2 mg THC
15% THC	24.3 mg THC
20% THC	32.4 mg THC
25% THC	40.5 mg THC

Post smoking assay of cannabinoids in blood or urine can partially quantify dose actually absorbed after smoking, but the analytic procedures are methodologically demanding.

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 dosages. Thus we will use the dronabinol prescription guidelines as published by the manufacturer and accepted by United States Food and Drug Administration (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 noted, there are significant differences in pharmacokinetics between oral consumption and smoking. There are varying physiological effects when other cannabiods are present, as is the case with 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.

By directly applying these figures to the recommended dronabinol dosing model of 30-90 mg per day, we arrive at the dosages shown in table 2 (assuming negligible amounts of cannabidiol present in the cannabis)

Our derived figures lie very 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 - 20 g per week, or approximately 1.42 to 2.86g per day.

If the mean strength of the medical cannabis is 19% THC (negligible CBD),

2. Amount of Cannabis Equivalent to 30-90 mg dronabinol

%THC in cannabis	amount in grams needed to obtain:		
	30mg	60mg	90mg
10% THC	1.85g	3.70g	5.55g
15% THC	1.23g	2.46g	3.69g
20% THC	0.93g	1.86g	2.79g
25% THC	0.75g	1.50g	2.25g
30% THC	0.62g	1.24g	1.86g

and the average strength is 15% THC as reported by Geiringer, then the amount of cannabis needed to absorb a 30mg THC dose is .88-1.23g, and the amount needed for 90mg of THC is 2.65-3.69g. of cannabis. These figures all share a strikingly similar range.

Our recommended dosages are reinforced by two of the only studies that utilized smoked cannabis in a dosing regime (Chang, 1975, and Vinciguerra, 1988). These dosages are also within the medical cannabis guidelines allowed in the Canadian medical system. (The Canadian medical allowance is for 1-12 g a day with less than 5 g being the mean.)

Thus, despite all of the noted variables, there is remarkable consistency among the derived and reported doses noted here. The biggest limitations of our dosing model is that it is based on THC concentrations, despite growing evidence that THC may not even be the most clinically useful cannabinoid. However, given the current state of the known, published pharmacology of cannabis, this is the best dosing model that can be derived.

Table 3 shows our final derived dosing recommendations.

Tolerance

An issue that warrants discussion is physiological tolerance, which plays a role in dosing cannabis. 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 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 use cannabis by ingestion 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. It is therefore critical that legal authorities consult with medical experts before arriving at any conclusions at to the appropriateness of the amount of usage.

3. Dosing Recommendations

%THC in cannabis	Daily dosage to = 2.5 - 90 mg of THC
10% THC	.15 g - 5.55g
15% THC	.12 g - 3.69g
20% THC	.08 g - 2.79g
25% THC	.04 g - 2.25g
30% THC	.01 g - 1.86g

We have outlined reasonable guidelines for dosing of medical cannabis, based on the known pharmacology. However, because of the complexities of the cannabis plant, the chemistry of the various forms of cannabinoids, patient tolerance, differing routes of intake and delivery systems, there are inherent limitations to these guidelines.

Recognizing this, we recommend that an individual, patient-controlled, self-titration dosing model be used. The guidelines we have described provide a dosing construct for patients and physicians to do this. These guidelines also provide legal authorities some reference points as to what would be considered a reasonable amount of cannabis to use for medicinal purposes.

DRONABINOL is synthetic THC in sesame-oil capsules. It was marketed as Marinol by Roxane Laboratories in 1987. By comparing rates at which THC from dronabinol and smoked natural cannabis are absorbed into the bloodstream, the authors calculated equivalent doses. The FDA originally approved Marinol as a treatment for nausea and subsequently approved it as an appetite stimulant. After years on Schedule II it was moved to Schedule III by the DEA in 1999.

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http://cannabismd.org/foundation/mmjdosingguidelines.php

Case Note:

Extreme Sensitivity to Marinol

A married 51-year-old male computer scientist with severe migraines for some 16 years experienced serious adverse effects from conventional treatments of Immitrex, Maxalt, amitriptyline, antivert; lives in a state with no legal access to medical marijuana; discovered that small amounts of Marinol would control his headaches. (And concurrently his irritable bowel syndrome as well.) Sensitive to most medications, he discovered cannabis to be efficacious without adverse effects. Because of its illegal status, Marinol (dronabinol) was begun. The 2.5 mg dose would put him to sleep and he would wake up feeling stoned. So he took to extracting a quarter of the 2.5 milligram dose with a needle. That worked for a couple of years but now he's developed sensitivity even to the lower dose. He's tried discontinuing on several occasions times but the migraines return. Suggested that the patient explore the legality of obtaining Sativex through Canada.

I contacted the regional representative from Solvay, who will forward this case report to their medical department. The preparation of dronabinol of lesser concentration might solve the problem. The other possibility is an inhaled preparation for finer titration. Solvay is working on this, I was told by the representative.

—Tod Mikuriya, MD