Clinical Relevance of Cannabis Tolerance and Dependence

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Abstract: Psychoactive drugs are often widely used before tolerance and dependence is fully appreciated. Tolerance to cannabis-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and behavioral changes is acquired and, to a great degree, lost rapidly with optimal conditions. Mechanisms appear more functional than metabolic. Acquisition rate depends on dose and dose schedule. Dependence, manifested by withdrawal symptoms after as little as 7 days of THC administration, is characterized by irritability, restlessness, insomnia, anorexia, nausea, sweating, salivation, increased body temperature, altered sleep and waking EEG, tremor, and weight loss. Mild and transient in the 120 subjects studied, the syndrome was similar to sedative drug withdrawal. Tolerance to drug side effects can be useful. Tolerance to therapeutic effects or target symptoms poses problems. Clinical significance of dependence is difficult to assess since drug-seeking behavior has many determinants. Cannabis-induced super sensitivity should be considered wherever chronic drug administration is anticipated in conditions like epilepsy, glaucoma or chronic pain. Cannabis pharmacology suggests ways of minimizing tolerance and dependence problems.

IT would be surprising if some degree of tolerance and dependence did not develop to some effects of cannabis. Virtually every psychoactive drug, if given at a dose and a dose schedule producing sustained tissue levels, after a period of time produces measurable tolerance on some indices of drug effects if tested with sensitive, reliable, and appropriate measures at the right time.[1-3] Tolerance generally does not develop to all effects at the same rate. Thus, the more interesting question with cannabis and cannabinoid-like drugs is whether tolerance develops to side effects or to proposed therapeutic effects. To put it another way, is the level of tolerance or dependence likely to be of practical significance? What

follows is a brief review of several published studies along with some unpublished data from our laboratories that may help to answer this question.

When considering tolerance or dependence, terminology is important. Imprecise use of the terms leads to misunderstanding.[1-3] We use the term tolerance to mean a diminished drug effect following repeated doses and a return of effect if dose is increased. Dependence refers to the appearance of fairly predictable signs and symptoms when drug administration is stopped. The symptoms are decreased or disappear when the drug is restarted or when a pharmacologically similar drug is readministered. Dependence, as used here, does not imply addiction, increased drug seeking or related behavior that may have some relationship to dependence. Such behavior is also determined by environment and personality and genetic, social, and mostly unknown factors.[1,3,8]

In theory, it would be unusual for a drug not to be associated with dependence when significant tolerance develops.[4,5] For many psychoactive drugs, the mechanisms of tolerance and dependence seem to be intimately related.[1,2] Thus, it would be unexpected to have one without the other, assuming the phenomenon is properly looked for. Of course, as with tolerance, dependence is determined by many factors including dose, dose schedule, past drug and behavioral history, genetics, species differences, and biologic systems studied. The time of onset and intensity of withdrawal symptoms depends on the elimination kinetics of the drug or its active metabolites, particularly rate of clearance from the body.[3,6] In general, drugs with half-lives longer than 35 to 40 hours do not produce an intense withdrawal syndrome. However, the metabolism of cannabis is particularly complex, with many metabolites and non-linear kinetics so that generalizations may not fit.[7]

When considering therapeutic use of cannabis or cannabinoids, it is appropriate to review issues of tolerance and dependence. Psychoactive drugs are often widely used therapeutically before implications of tolerance and dependence are fully appreciated. This should not be surprising. As experience is accumulated over time with higher doses, many time- and dose-related phenomena become clearer than is usually possible in early clinical studies where limited doses, limited dosage range, and limited time of administration are necessarily the case. With the amphetamines, opiates, barbiturates, alcohol, antipsychotics, benzodiazepine derivatives, and tricyclic antidepressants, as long as 20 to 50 years had passed before the clinical significance of early clinical or experimental reports of tolerance and dependence were appreciated.[9-12] For example, one of the earliest benzodiazepine clinical studies was a report of tolerance and dependence.[13] Yet it was not until approximately 15 years later and after about 10 to 20 per cent of the nonhospital-

ized adults in the United States and other western nations were ingesting benzodiazepine derivatives regularly that benzodiazepine dependence became a clinical issue.[3,14,15] Its relative importance still remains unresolved.[15] Tardive dyskinesia, possibly related to neuroleptic-induced dopamine receptor supersensitivity, might be considered to be related to dependence by some, except that it appears to take, in most cases, some years of chronic neuroleptic exposure. Withdrawal symptoms following sudden discontinuation of phenothiazine or tricyclic antidepressants, often occurring with enough intensity to be of therapeutic significance, have received relatively little attention.[16,17]

Of course, tolerance to some drug effects, for example, side effects such as benzodiazepine-associated drowsiness or phenothiazine and tricyclic antidepressant-induced dry mouth, is useful. Tolerance to therapeutic effects (which may be considered side effects in other situations) poses problems. Both aspects of tolerance are important in the therapeutic use of cannabis. The occurrence of withdrawal symptoms and signs may be little more than a pharmacologic curiosity in some situations but may be of therapeutic importance in others.

Methods

Data from our laboratories collected over the past eight years indicate that both tolerance and physical dependence develop after surprisingly short periods of cannabis or THC administration when the conditions are optimal.[18] Optimal conditions include doses and a dose schedule and route that maximized the possibility of sustained blood and presumably brain levels of THC.[2,5,6] We tried to evaluate cannabis with the same laboratory conditions as were necessary to experimentally demonstrate tolerance and dependence with opiates and sedative hypnotic drugs.[5,10,11,19] The volunteers lived on a hospital research ward for two- to six-week periods. All 120 volunteer subjects were male and were well expe-

rienced marihuana users. Although varying slightly from substudy to substudy, there was generally a three- to seven-day placebo treatment period after admission. Then, under double-blind conditions, this was followed by a five- to 21-day period of 10- to 30-mg oral doses of cannabis extract or Δ^9-tetrahydrocannabinol (THC) given every 3 or 4 hours. Fifteen subjects who received only cannabidiol (CBD) during their hospitalization provided what amounted to a placebo-only comparison group since the cannabidiol was without apparent behavioral or psychologic effect.[20]

THC doses were selected to produce a maximal level of intoxication consistent with safe ambulatory care. The 3- to 4-hour dosage schedule was selected because the pharmacokinetics of THC and observed time course of effects suggested frequent doses if a reasonably constant THC blood level or at least a steady level of intoxication was to be maintained. Given the very short alpha phase of THC clearance from the blood and relatively short duration of measurable effects, we guessed that an oral dose every 3 to 4 hours would be required. Later, with the availability of blood level and better pharmacokinetic data, this turned out to be a good guess.[7] Peak plasma levels of THC after 30-mg oral THC doses in sesame oil were similar to or less than those after smoking medium-potency cannabis cigarettes. Because of the dosage schedule and oral route, blood THC levels seemed to remain at pharmacologically active levels between doses.

After the five- to 21-day period of sustained intoxication, under double-blind conditions, subjects were abruptly switched back to placebo medication for four to eight days. On some occasions, cannabinoids were then restarted to see if whatever physiologic and behavioral changes following THC cessation could be reversed. Depending on the goals of a particular study, occasionally challenge doses of smoked marihuana or intravenous doses of THC were given to study crosstolerance and pharma-

cokinetic and pharmacodynamic changes during the period of observation. The procedural details and results have been described in a number of publications.[18,20–25]

Results

Tolerance to many subjective drug effects was measurable after only a few days on the 10-mg dose. For example, a 50 per cent decrease in intoxication level produced by a 30-mg oral dose followed even four days exposure to 10-mg doses. On drug symptom ratings and as judged by nursing staff observations, the intensity of initial drug effects diminished 60 to 80 per cent after about 10 days at the sustained THC doses. Increasing a single dose by 30 to 50 per cent would usually produce a prompt and temporary return in symptoms. The rate of tolerance to subjective effects was almost identical to that following sustained administration of about 100 mg morphine daily to former opiate addict volunteers.[19]

With sustained THC administration, the initial heart rate increase, skin temperature decrease, and a host of other drug-induced autonomic changes gradually disappeared (Table I). Orthostatic hypotension decreased within 12 to 24 hours or sooner. Intraocular eye pressure, REM sleep EEG, and salivary flow all had a pattern of initial drug-induced decrease, partial or complete recovery with about 10 days of continued THC administration, and rebound above pre-THC levels after sudden cessation.

Another way to follow the magnitude and rate of tolerance acquisition and loss was to give periodic doses of smoked or intravenous THC during the course of the oral THC administration. In Table II, peak changes after the smoking of a 20 mg THC-containing marihuana cigarette or after a 2 mg/70 kg intravenous dose of THC are contrasted at the various stages of THC administration. Diminished effect of the smoked or intravenous THC was evident after only a few days of repeated 20 or 30 mg of oral administration. Rapid loss of tolerance appeared when repeated once-daily smoked

TABLE I

Mean Physiologic Measures Before, During, and After THC Administration

Measure	N	Before	THC administration stage		After (24 hr)	After (25–48 hr)	After (49–240 hr)
			Early	Late			
Intoxication (high) ratings (0 = sober to 100 = maximum)	20	0	55	8*	0.8	0	0
Heart rate, supine (bpm)	12	68.4	70.0	62.3*	64.4	—	—
Postural hypotension, systolic BP drop, 1 min standing (mm Hg)	12	9.6	15.5*	11.2	6.5	—	—
Finger skin temperature (°C)	13	34.2	29.3*	33.6	35.1	34.4	33.8
Body temperature oral (°C)	29	36.2	36.4	36.2	36.5*	36.2	36.2
Intraocular pressure (mm Hg)	13	15.9	13.6*	15.2	16.9*	18.3*	15.6
Salivary flow, 5-min total (ml)	14	2.4	1.2*	1.9	3.5*	3.0	2.6
Finger tremor, relative (volts/sec/sec)	6	181	196	208	416*	210	190
Body weight (kg)	20	69.5	72.3*	72.6*	71.5	70.0	69.6
REM sleep (% time)	7	31.4	26.1*	28.7*	41.4*	—	—

* $P < 0.05$ compared to predrug by analysis of variance.

TABLE II
Maximum Changes After Cannabis Smoking and Intravenous THC During Sustained Oral THC Administration

Measure	N		Before	THC Administration stage					
				Early	Late	After (24 hr)	After (25–48 hr)	After (49–240 hr)	
Intoxication rating (0 = sober to 100 = maximum)	6	smoked**	52	42	10*	38	52	40	
		I.V.**	70	—	27	—	—	—	
Heart Rate, increase (bpm)	6	smoked	48	15*	8*	32	41	40	
		I.V.	49	—	9*	—	—	—	
Finger Temperature, (°C) decrease	6	smoked	7.1	4.1*	.2*	.9*	4.0	3.8	
		I.V.	5.2	—	.1*	—	—	—	
Intraocular pressure, decrease (mm Hg)	8	smoked	1.5	1.1	.2*	1.8	2.2*	1.8	

* $P < 0.05$ compared to predrug by ANOVA.

** Cigarette weight 1 Gram, contained 20 mg THC; intravenous THC dose was 2 mg.

TABLE III

Symptoms During Phases of Drug Administration*

	Predrug (%)		Early drug (%)		Late drug (%)		Postdrug (%)	
	THC	CBD	THC	CBD	THC	CBD	THC	CBD
Disturbed sleep	28	20	6	6	4	0	89	6
Decreased appetite	6	6	9	13	9	6	81	0
Restlessness	4	6	11	13	6	0	89	13
Irritability	15	13	23	13	9	6	62	6
Sweating	2	6	4	6	6	0	55	6
Chills	4	0	4	0	6	0	40	6
Feverish feeling	2	6	6	0	2	6	38	13
Nausea	9	0	23	13	4	0	34	0
Muscle spasm	0	0	17	0	0	0	17	0
Tremulousness	2	0	15	0	2	6	21	0
Loose stools	2	0	0	6	2	0	23	6
Abdominal distress	0	6	9	13	2	6	36	0
Stuffy nose	2	0	2	6	2	0	11	0
Hiccups	0	0	0	0	2	0	17	0
Wild dreams	0	6	0	0	0	0	19	0

* THC = 47 subjects; CBD (cannabidiol) = 15 subjects.

doses were given after oral THC was stopped. Tolerance was acquired more rapidly with 20 mg THC given every 3 hours than when 30 mg THC was given every 4 hours. This suggests that it is the THC levels or rapidly formed and cleared metabolites which are most important rather than the more slowly produced and slowly cleared metabolites. That is, changes in the effects we measured seemed to be more a function of the rapid alpha phase of the THC clearance, lasting minutes, rather than the beta phase with the slower clearance ($t_{1/2} = 18.7 \pm 4.2$ hours).[7]

The mechanisms of tolerance in humans are probably more related to adaptation at sites of drug action than to changes in drug metabolism. The pattern of diminished peak effects from smoked or intravenous doses of THC in people tolerant to oral THC is more in keeping with functional rather than metabolic tolerance. Intravenous ^{14}C-labeled THC was given to six subjects before and at the end of the oral THC administration period. The small increases in clearance of THC and its metabolites could not account for the degree of tolerance.[7]

Tolerance and dependence are best reflected in subjective reports and observed symptoms. Table III lists percentage of subjects reporting various symptoms before, during, and after drug administration. Early and late drug periods are the first and last half of the THC or cannabidiol administration phase. The postdrug period is the placebo administration period beginning at 8 A.M. on the day after THC was stopped. The last THC dose was usually at the 4 to 8 P.M. dose. The percentages are of subjects who complained of at least one occurrence of the symptom at some time during the period covered. Intensity of complaints varied, and the listing in the table only attempts to show frequency measured by interviews each morning and from daily self-ratings of symptoms and mood. Nurses' and research staff observations were consistent with the subjects' own reports. Subjects living on the research ward for 30 days but given only cannabidiol reported fewer and much less intense symptoms after five to 12 days of cannabidiol administration at a 100-mg-every-4-hour dosage schedule. The THC-related with-

drawal symptoms were similar in intensity to those produced by 400 to 600 mg pentobarbital given four times daily or a quart of whiskey daily administered in divided doses for a week or so.[10,11]

Coincident with the subjective reports, there were sudden and often dramatic changes in behavior beginning 5 to 6 hours after the last THC dose and consisting of increased irritability, restlessness, insomnia, anorexia, nausea, and sweating. Body weight decreased as much as 5 kg in four days (mean = 3.2 kg) and stabilized at pre-THC levels. Quantitative measures of increased tremor, increased intraocular pressure, altered sleep EEG characteristics, salivary flow, and oral temperature are shown in Table I. Objective and subjective withdrawal phenomena were diminished for 2 to 3 hours by smoking a marihuana cigarette containing 20 mg THC. They were partially relieved by modest doses of alcohol or hexobarbital. The intensity of most of the signs and symptoms was greatest at about 8 to 12 hours after stopping THC. Most symptoms were diminished 24 hours after and were not measurable after three to four days. Some subjects reported disturbed sleep for up to a few weeks.

As with many other drugs, the more frequent and the greater the dose, the more intense the withdrawal. THC given every 3 hours rather than every 4 hours or at 30 mg per dose as compared to 20 mg per dose produced more intense withdrawal symptoms. Withdrawal symptoms did not appear in two subjects given 10-mg doses of THC every 3 hours for 10 days. At least five days of steady intoxication seemed necessary to produce a minimal withdrawal syndrome. The longer the period of intoxication, the greater the withdrawal intensity. None of the subjects given cannabidiol over similar periods of time had similar subjective or physiologic changes when switched from cannabidiol to placebo, indicating that what we observed was not a result of hospitalization, impending discharge, or similar nonpharmacologic explanation.

Thus, cannabis, THC, and presumably other cannabinoids can produce tolerance and physical dependence after certain doses and dose schedules. In other studies where only smoked cannabis was given, some similar but fewer and less intense withdrawal symptoms followed cessation of smoking.[26-29] The absence of placebo controls, intermittent and subject controlled smoking patterns, and the use of different measures make the oral administration and smoking data not completely comparable.

Discussion

Our experiments did not study changes in drug-seeking behavior that might follow tolerance or dependence. However, keeping in mind that historically researchers have not been very successful in predicting addiction liability of many drugs, some prudence is indicated when predicting addiction potential of a drug such as cannabis (in terms of drug seeking and drug using) should large doses become readily available for widespread and uncontrolled use. Some might consider this position unduly alarmist and mainly derived from irrelevant studies that gave unrealistically large doses at a frequency unlikely to be used illicitly or therapeutically. Drug blood levels and magnitude of drug effects indicate that our doses were not large by those criteria. In a brief review like this, considerations of the frequency of dose are harder to deal with. With many drugs, for example, opiates, alcohol, barbiturates, and others, frequent dose schedules are necessary to study experimentally, in relatively short periods of time, levels of tolerance or dependence that take much longer to develop under more natural or clinically realistic conditions.[1,2,5,10,11] As evidence accumulates that an organism can, over time, in a sense "learn" to become tolerant or dependent by repeated but less frequent and smaller doses, the validity and utility of the quicker laboratory models such as we used becomes less questionable.[4,12] Repeated exposure to

low or more intermittent doses may produce ultimately a level of tolerance and dependence that would require enormous doses to arrive at over a short time. Unfortunately, the time–dose functions for most drugs are not well worked out.

The pattern of cannabis tolerance suggests that what might be unpleasant or unacceptable side effects for some patients, for example, hypotension, mental confusion, and cardiovascular and autonomic phenomena, can be minimized by gradual increases from a beginning 5- or 10-mg dose over four or five days. As with phenothiazines, tricyclic antidepressants, and other psychoactive drugs, by starting off with a low dose and gradually increasing it over a period of a few days, many of the unpleasant cannabis effects can be avoided. On the other hand, our data suggest that the initial drug-induced drops in intraocular pressure and initial brain wave alterations may disappear surprisingly rapidly with continued drug administration and that therapeutic efficacy may be compromised. When considering drug effects on abnormal epileptic brain electrical activity or on abnormal eye pressures in glaucoma, of course, the data from normal individuals may be of only limited predictive value. As with most drugs, the less frequent the dose, the lower the dose, and the shorter the duration of treatment, the smaller both the rapidity and magnitude of tolerance and the intensity of any withdrawal symptoms appear to be.

In summary, in matters of tolerance and dependence, it appears that cannabis follows similar principles and rules as most other psychoactive drugs. Thus, it would be advantageous to consider potential problems posed by tolerance or dependence prior to the introduction of cannabis-like therapeutic drugs rather than dealing with them 20 to 30 years later, as has sometimes been the case with other psychoactive drugs.

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Discussion of the Paper

Dr. Gilbert: I think for you to say that you usually do not see tolerance without physical dependence is an overgeneralization, because even after just one dose of morphine one can see tolerance to the various signs and there are no signs of physical dependence.

Dr. Jones: With naloxone-precipitated withdrawal, we and others have demonstrated physical dependence after a 10 mg dose of morphine given only once to opiate-naive human volunteers or with similar modest opiate doses given to rodents.

Dr. Gilbert: I do not think you can use body temperature as measured by you as a sign of abstinence; THC produced an increase in body temperature, and upon withdrawal from THC you see another increase in body temperature. Generally an abstinence sign on the Himmelsbach scale is in the opposite direction, so I don't see how a second increase in body temperature could be an absence sign in that system.

Dr. Jones: The body temperature increase after THC was not statistically significant. If it represents a true THC effect perhaps the well known biphasic effects of THC on body temperature makes the simple model

you are applying inappropriate to some indices of abstinence.

Dr. Ungerleider: Sometimes tolerance to all of the effects of cannabis can be functional rather than dysfunctional. Recently, I had the chance to study a group in Jamaica that were smoking 2 to 3 ounces of 4 to 8% THC every day as Ganja for religious reasons and despite the presence of urinary cannabinoids, they had no increase in pulse rate, no conjunctival injection and more importantly, no neuropsychological impairment on a Reitan test battery.

Dr. Merritt: How did you measure intraocular pressures and did you measure them at the same time of the day?

Dr. Jones: We measured pressures at about the same time 4 times a day with an American Optical Company non-contact tonometer. When compared to applanation tonometry in a small group of normal volunteers the non-contact and applanation techniques gave similar patterns of change after THC (correlations coefficient 0.88). The non-contact technique has obvious advantages for frequent and repeated measures particularly when following changes within a given individual.