Medical Marijuana Reflects an Indifference to Public Health

by Bertha K. Madras, PhD

In 1996 a ballot initiative in California was approved (Prop. 215, and its successor SB420), which allowed for a smoked (!) leaf of unknown chemical composition, unregulated doses of psychoactive ingredients and hundreds of other potentially hazardous chemicals, to treat serious medical conditions, including "AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms, seizures, epilepsy, severe nausea, any other chronic or persistent medical symptom that substantially limits the ability of the person to conduct major life activities". Prop 215 passage had nation-wide ramifications and set off a cascade of ballot initiatives in other states, including Montana.

A. MARIJUANA AS MEDICINE

1. ***The most obvious objection to Prop 215*** **is the use of smoking as a delivery system for drugs, after a 50 year national campaign to end smoking.**

2. ***The second objection*** **is the poor quality or no evidence for marijuana's safety and efficacy in treating a myriad of diseases listed in the ballot initiatives (Figure 1 below).** A few years after Prop 215 passed in California, Governor G. Davis funneled millions of dollars into medical marijuana research, to seek validation, after the fact, for these "ballot-approved" medical claims. After a decade of funding, this California Center for Medicinal Cannabis Research has issued 24 publications. Only 3/24 reports focus specifically on clinical studies to examine the effectiveness of marijuana in treating diseases listed in the ballot initiative. Only one medical condition is explored, neuropathic pain in AIDS patients. *Intriguingly, recruited subjects were required to be experienced marijuana smokers and all subjects were maintained on other painkillers, but the manuscripts do not report any details on other painkillers, nor do some report side effect profiles.* These include whether marijuana produced a feeling of "high" ("euphoria"), being impaired, feeling sedated and showing cognitive impairment in objective tests of learning, speed recall, attention. As for the other medical indications for marijuana, five major clinical trials were discontinued because the investigators were unable to recruit enough patients, despite extensive advertising and outreach, to study marijuana effectiveness for relief of cancer pain, muscle spasticity, multiple sclerosis, severe nausea and vomiting, neuropathic pain. The intent to investigate was present, but candidate patients refused to enroll. It raises significant questions as to why 16 of the remaining research projects did not address the core reason for the state funding, whether marijuana is effective in all the medical conditions and indications specified in 215 and SB420. In the majority of observational studies published on the "therapeutic" effects of smoked marijuana, there is no reporting of side effects (e.g. intoxication, cognitive impairment, etc), information that the FDA considers essential for FDA approval.

3. ***The third objection,*** **of national significance, is that ballot initiatives circumvent stringent Federal FDA standards, a direct threat and challenge to our elaborate, technical- and science-based, national drug approval system**. FDA standards have protected Americans from fraudulent, dangerous or ineffective drugs for decades, with an approval system, although imperfect, that is among the most rigorous in the world. Consider the astute FDA response to ballot initiatives for the sham cancer treatment laetrile, FDA denial of thalidomide approval and a myriad of other drugs deemed ineffective, unsafe and unacceptable by rigorous standards. To circumvent FDA approval by a ballot initiative is a dangerous precedent, a slippery slope that can create chaos in the science-based approval process for medicines. (Figure 1)

B. FDA REQUIREMENTS

The FDA requires (among other documentation) that:

- A drug is a pure compound, not a smoked mixture of hundreds or thousands of compounds
- A drug's chemistry, manufacturing, and composition of matter are tightly controlled so that each batch is identical
- A drug's production methods are validated
- A drug's shelf life is known and can be dated to protect patients from a degraded chemical
- A drug's microbiology is known (batches of chemicals contaminated with bacteria are rejected)
- A drug's pharmacology and toxicology in animals is documented
- A drug rate of entry, bioavailability, toxicology are documented
- A drug's dose response, efficacy, safety are documented in Phase I, II, III clinical trials, usually involving thousands of people in randomized, double blinded, clinical controlled trials
- A drug side effect profile is documented.
- After approval, requires case reports and safety updates to be submitted to the FDA for ongoing evaluation.
- This may lead to 100,000 pages of scientific evidence/documentation, for each medical indication

Ballot initiatives for alleged treatments erode this carefully constructed process and lead to compromised quality of our nation's medications. Drugs are administered in doses, dose ranges, based on results from clinical trials involving thousands of patients. **(Figure 2)**
The FDA ruling on marijuana as medicine is summarized below. It has not changed since this ruling. Marijuana is listed in schedule I of the Controlled Substances Act (CSA), the most restrictive schedule.

The Drug Enforcement Administration (DEA), which administers the CSA, continues to support that placement and FDA concurred because marijuana met the three criteria for placement in Schedule I under 21 U.S.C. 812(b)(1).

- *Marijuana has a high potential for abuse has no currently accepted medical use in treatment in the United States.*
- *It lacks accepted safety for use under medical supervision.*
- *There is sound evidence that smoked marijuana is harmful. A past evaluation by HHS agencies, FDA, SAMHSA and NIDA, concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States.*
- *No animal or human data supported the safety or efficacy of marijuana for general medical use.*
- *There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana.*
- *A growing number of states have passed voter referenda (or legislative actions) making smoked marijuana available for a variety of medical conditions upon a doctor's recommendation.*
- *These measures are inconsistent with efforts to ensure that medications undergo the rigorous scientific scrutiny of the FDA approval process and are proven safe and effective under the standards of the FD&C Act.*
- ***Accordingly, FDA, as the federal agency responsible for reviewing the safety and efficacy of drugs, DEA as the federal agency charged with enforcing the CSA, and the Office of National Drug Control Policy, as the federal coordinator of drug control policy, do not support the use of smoked marijuana for medical purposes.***

C. THE PRACTICE OF MEDICINE, PHARMACY IS IMPACTED BY MARIJUANA AS MEDICINE BALLOT INITIATIVES.

Medicine increasingly is evidence-based but marijuana has no academic presence in medical training or scholarship. **Contrary to good medical practice, there is no requirement:**

- to issue a prescription (only a recommendation)
- extract medical history
- give a detailed medical exam
- discuss long term treatment, effects or follow-up
- provide informed consent
- consult with other physicians
- keep proper records that support recommending marijuana instead of safe approved alternatives
- have a good faith relationship with a patient rather than a "marijuana mill"
- be able to identify substance abusers or the addicted.
- Forewarn patients on maintaining control of their product

Contrary to regulations governing pharmaceutical production, dispensaries have:

- no product liability

- no product regulation
- no chain of custody
- no accountability
- no pharmacists trained in drug-drug interactions of appropriate dose measures and requirements

Summary. Over the past 150 years the US moved rapidly away from plants as medicines to purified products, for obvious reasons: the composition of a plant is unknown, the composition of its thousands of constituents are uncontrolled and the long term effects of each of these chemicals, alone or together on body, brain, behavior are unknown. At the time these ballots passed and presently, marijuana's scientific record was not sufficient to fulfill FDA's rigorous standards of safety, efficacy, consistent dosing and side effect profile. The evidence for smoked marijuana as a safe and effective treatment for over 12 diseases (e.g. glaucoma, Alzheimer's disease), including the myriad forms of chronic pain that respond to different class of drugs does not begin to meet professional and FDA standards.

D. **RESTRICTIVE MARIJUANA LAWS ARE DRIVEN PRIMARILY BY PERSONAL AND PUBLIC HEALTH CONSIDERATIONS**.

Maintaining restrictions on marijuana are more compelling than ever, as marijuana potency and availability soar, in parallel with increasing scientific evidence of marijuana's adverse consequences.

Acute effects of marijuana on brain function. Unlike opioids, marijuana is not likely to cause death by overdose but it resides in Schedule I because of its high abuse liability, and no medical indications – essentially because it adversely disturbs brain function and biology. A Saturday night marijuana binge is intoxicating in the short term, but it can also produce residual cognitive deficits (on learning and memory) for several days. (Marijuana research protocols generally wait at least 5-30 days for marijuana to clear, before measuring long term residual cognitive effects). These deficits are readily quantified, are exaggerated in schizophrenics, and refute advocacy for marijuana treatment of Alzheimer's disease. Who is compromised by marijuana? The student in class who can't focus, the construction worker at risk for injury, the unemployed who is less likely to find work, the poor, the high school drop-out, the criminal. It is unacceptable for soldiers, airline pilots, nuclear power plant operators, federal workers to test positive for marijuana. Should it be acceptable for teachers, day care providers, construction workers, students, machine operators, miners, parents, or drivers?

A 2009 National Highway Traffic Safety Administration (NHTSA) report showed that more people are driving on weekend nights under the influence of marijuana (8.3%) than alcohol (2.2%). Emergency department mentions of marijuana in the US have increased from 281,619 to 374,435 during 2004-2008, in parallel with linear increases in marijuana potency and marijuana addiction.

Enduring effects: marijuana addiction. Marijuana is addictive in about 9-10% of users and progression to addiction reportedly is more rapid than progression to nicotine addiction. Abstinence in the heavily addicted unmasks physical and psychological neuroadaptation, manifest by an unnerving withdrawal syndrome. Nation-wide, more

people harbor a medical (DSM-IV) diagnosis of marijuana abuse/addiction than any other illicit drug and more youth are DSM-IV positive for marijuana than for alcohol, as a percentage of users. Extrapolating from national statistics, an average cost for addiction treatment is $4,000 for ambulatory care and at least four times that amount for residential care. This can add billions of dollars for marijuana treatment needs nationally.

Marijuana and youth. There is no reasonable evidence that marijuana sold for "medical purposes" will prevent diversion to young adolescents. Our abysmal failure at preventing youth cigarette smoking or alcohol consumption should be our intuitive guide. Youthful users of marijuana are at particular risk. The prevalence of addiction to marijuana is 6-fold higher,, if they initiate marijuana use at age 14 or younger. Early onset of marijuana use is also associated with addiction to other drugs in adulthood, including alcohol and heroin. Some have speculated that genetics, cigarettes smoking, social environment, poverty, child abuse, psychiatric conditions confer this higher risk in the young. But how to explain that adolescent rats exposed to the most active constituent of marijuana, delta-9-tetrahydrocannabinol or THC, *only during adolescence*, seek heroin at higher rates after they mature into adults compared with matched controls, and display a fundamental change in brain opioid systems long after their last dose? Social, environmental, poverty, child abuse, psychiatric conditions do not apply to inbred rats – the drug alone alters the trajectory of brain and behavioral development.

Marijuana use and neuropsychiatric disorders. In nine population studies of more than 75,000 people from seven different countries, early marijuana use was found to be associated with an average two-fold higher risk for later-onset psychosis and schizophrenia. The influential medical journal Lancet, which declared in 1995 that "The smoking of cannabis, even long term, is not harmful to health." changed this conclusion in 2007, by stating that "Research published since 1995, including [the] systematic review in this issue, leads us now to conclude that cannabis use could increase the risk of psychotic illness… governments would do well to invest in sustained and effective education campaigns on the risks to health of taking cannabis." A current debate is being waged on whether to revise comparative risk assessment in the Global Burden of Disease (GBD) to include the attribution of psychosis to marijuana use. Degenhardt et al argue that the risk assessment should be included because the evidence is as good as that for many other risk factors in the GBD. Some scientists have estimated that marijuana contributes about 8% to new cases of schizophrenia. If this estimate is accurate, unfettered marijuana access in, for example, California conceivably would add 25,000+ cases of schizophrenia, with an estimated cost of caring for this cohort for 30 years in excess of $6 billion (based on a low estimate of $8,000/per patient/year).

Long term heavy marijuana use. Heavy daily marijuana use across protracted periods can exert harmful effects on brain tissue and mental health. Brain imaging of long-term heavy marijuana users has shown exposure-related structural abnormalities in brain regions critical for learning, memory and emotional responses, with changes associated with impaired verbal memory and other symptoms. Abnormal brain size and brain circuitry of adolescent marijuana users have also been recently documented. Compromised academic performance, school drop-out, and a host of other adverse consequences are

elevated in high school or college students who use marijuana. Accurate price tags for these lost educational and employment opportunities don't exist, but at the very least, they should weigh heavily on the citizens' conscience. Peripheral health is also affected, as marijuana use is associated with increased risks for bronchitis, compromised pulmonary function, precancerous lung changes, cardiovascular events, problematic pregnancies, teratogenic and hormonal effects.

Despite this evidence, 2009 was a banner year for marijuana use in our nation. Compared with 2008, 1.5 million more marijuana users were added to the ranks in 2009. The steady decline in marijuana use among youth over the past 6 years was reversed in 2009. Marijuana use among 12-17 year olds increased by over 7%, with a 14% increase among boys, and a 13% increase among college students. Expanding acceptance of medical marijuana and proliferating availability conceivably are driving reduced perception of harm and a pivotal rise in use.

Authors' Biography: Bertha K. Madras is a Professor of Psychobiology in the Department of Psychiatry at Harvard Medical School and former Deputy Director for Demand Reduction in the White House Office of National Drug Control Policy. She is author of over 130 scientific manuscripts, senior editor of a book: "The Cell Biology of Addiction", and holds 19 patents with collaborators. She directed the creation of a Museum of Science, Boston exhibit on how drugs affect the brain, and also developed a CD titled "Changing Your Mind: Drugs in the Brain", which was licensed by the Disney Corp. in 2006.

	CACHEXIA ANOREXIA	CANCER	CHRONIC PAIN	EPILEPSY	SEIZURES	GLAUCOMA	HIV-AIDS/Hep C	MULTIPLE SCLEROSIS	SPASTICITY OR CROHN'S	NAUSEA	MIGRAINE OR ALZHEIMER'
AK 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
CA 1996	Yes	Yes	Yes	✘	✘	Yes	Yes	✘	Yes		Yes
CO 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
HI 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
ME 1999	✘	Yes	✘	Yes	Yes	Yes	✘	Yes	Yes	Yes	✘
MT 2004	Yes	✘	Yes	Yes	Yes	✘	✘	Yes	Yes	Yes	✘
NV 2004	Yes	Yes	Yes	✘	Yes	Yes	Yes	✘	Yes	Yes	✘
NM 2007	✘	Yes	✘	Yes	✘	Yes	Yes	Yes	Yes	✘	✘
OR 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RI 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes/HepC	Yes	Yes	Yes	Yes
VT 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘	Yes	✘
WA 1998	Yes	Yes	Yes	Yes	✘	Yes	Yes/HepC	Yes	Yes	Yes	✘
MI 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes/HepC	Yes	Yes/ALS	Yes	Yes
NJ 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/ALS	Yes	

Figure 1. Chaos in state ballot initiatives for medical indications because approval is not based on scientific evidence.

STATE	POSSESSION	PLANT POSSESSION LIMITS	
Alaska	1 oz	6 immature	3 mature
California	8 oz	12 immature	6 mature or more
Colorado	2 oz	6 plants	
Hawaii	1 oz	7 plants	3 mature
Maine	1.25 oz	6 plants	3 mature
Montana	1 oz	6 plants	
New Mexico	Adequate supply	3 months uninterrupted supply	
Nevada	1 oz	7 plants	3 mature
Oregon	24 oz	18 seedlings	6 mature
Rhode Island	2.5 oz or		12 plants
Vermont	3 oz	7 plants	
Washington	60 day supply		
Michigan	2.5 oz	12 plants	
New Jersey	2 oz		

Figure 2. Chaos in possession limits because possession and use is not guided by scientific evidence.