

Marijuana: Lessons From Colorado

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Introduction

Marijuana has been used for thousands of years. There are many compounds that can be derived from the *Cannabis sativa* plant, all of which may have activity in the human body¹. It is felt that the most psychoactive ingredient in marijuana is delta-9-tetrahydrocannabinol (THC). Marijuana is becoming more socially acceptable and several states have moved to legalize it for medical and recreational purposes^{2,3}. The State of Colorado is beginning to experience negative sequelae as a result of more widespread marijuana use through accessibility and normalization.

History of Marijuana and Colorado

In 2000, the Colorado voters approved marijuana for medical purposes⁴ by approving Amendment 20. It permitted a qualifying patient and/or caregiver to possess up to two ounces of marijuana and grow six marijuana plants for medical purposes. It provided identification cards for a “qualifying, debilitating condition”. The system was managed by the Colorado Department of Public Health and Environment (CDPHE), which issued cards to patients based on a doctor’s recommendation. Applications from patients began in June 2001.

Between 2001 and 2008, there were only 5,993 patient applications received and only 55% designated a primary caregiver. During that time, the average was three patients per caregiver and there were no known retail stores selling marijuana (dispensaries). Dispensaries were not an issue due to the fact CDPHE regulations limited a caregiver to no more than five patients.

In 2007, a Denver District Judge, ruled that CDPHE violated the state’s open meeting requirement with the 5:1 patient:caregiver ratio and overturned that rule. This allowed caregivers to expand their patient base to an unlimited number of patients for whom they were providing and growing marijuana. This caused problems for local prosecutors seeking legal consequences for marijuana distribution by caregivers. Many ceased or significantly limited filing for those types of cases.

In February 2009, the U.S. Attorney General reported that raids in California on medical marijuana dispensaries would no longer continue, referencing the President’s campaign promise related to medical marijuana. In mid-March 2009, the U.S. Attorney General clarified the position, noting the Department of Justice enforcement policy would be restricted to traffickers who pretended to be a medical dispensary and used medical marijuana laws as a shield.

Beginning spring 2009, Colorado experienced a significant increase of to over 20,000 new medical marijuana applications and development of over 250 medical marijuana dispensaries, allowed to operate as “caregivers”. There was one dispensary owner claiming over 1,200 patients.

In October 2009, U.S. Deputy Attorney General David Ogden provided guidelines that advised “no focus federal resources in your state on individuals who are in clear compliance with existing state law providing for the use of the medical use of marijuana”.

By the end of 2009, patient applications in Colorado increased from 6,000 between 2001 and 2008, to 38,000 in that one year. The number of card holders increased from 4,800 by the end of 2008, to 41,000 in 2009. By mid-2010, there were over 900 marijuana dispensaries identified by the state of Colorado. Despite efforts to return to the 5:1 patient:caregiver ratio, the Colorado Legislature passed HB-1284, legalizing marijuana dispensaries, marijuana cultivation operations, and manufacturers for edible/infused products.

In November 2012, Colorado passed Amendment 64, which legalized marijuana for recreational use⁵. It allows individuals 21 years and older to grow up to six marijuana plants, possess/use one ounce or less and transport/furnish an ounce or less of marijuana if not for remuneration.

Amendment 64 permits marijuana retail stores, marijuana cultivation sites, marijuana edible factories, and marijuana testing sites. There are already cannabis clubs and formed co-ops for larger grow operations and/or supplied marijuana for no fee other than “donations”.

The Endocannabinoid System

The endocannabinoid system has identified how marijuana may work in the human body. The cannabinoid 1 (CB1) and cannabinoid 2 (CB2) have been the most widely studied receptors in the endocannabinoid system⁶. The CB1 receptors are more concentrated in the central nervous system and the CB2 receptors are more concentrated in the periphery, more so on immune cells. The parts of the brain dense in CB1 receptors are the hippocampus and amygdala. These areas of the brain are strongly associated with memory and emotion, respectively. Other areas of the brain noted to have increased density of these receptors include the cerebellum (balance and reaction time), hypothalamus (appetite), and frontal cortex (judgement and higher level cognitive function). The endocannabinoid system is proving to be more and more complex the more it is studied.

Anandamide was the first endocannabinoid to be isolated in 1992. It was thought to be a neurotransmitter involved in the regulation of stress and pain⁷. In 1995, 2-arachidonoyl-sn-glycerol (2-AG) was identified and may work at excitatory synapses in

the brain⁷. There are several ongoing studies on the effects of the endocannabinoids in the human body⁸. The majority of these studies are in the mental health and behavioral arena.

There are known physiologic effects of marijuana once it becomes available in the bloodstream, regardless of the delivery system. There are effects on the cardiovascular, pulmonary, and central nervous systems primarily as well as the immune system and others. There is evidence of both tachycardia as well as bradycardia and hypotension⁹. There are reports of angina and myocardial infarction⁵⁹. There is evidence of lung tissue injury although no clear link to pulmonary cancers has been established^{10,11}. The effects on the central nervous system have been well studied and demonstrate impaired memory, coordination, processing, reaction time, problem solving and learning¹². This has implications for those who may be trying to perform tasks that involve complex thinking (operating a vehicle or heavy equipment for example).

There are several reports of cerebellar infarction and other brain tissue injuries^{13,14}. Structural changes in the hippocampus have been demonstrated in long term chronic marijuana users which may have obvious impacts in memory and learning¹⁵. There have been studies on the effect of IQ in marijuana users as well¹⁶. It has been noted that cessation of marijuana use may actually improve the recall of newly learned material¹⁷.

Pain

The chronic pain patient can be very difficult to manage. Chronic pain can be quite complex and may involve several biopsychosocial issues which will not be covered in this article. The negative effect on the body, a person's mental health, their families and other people in their lives, as well as their vocational and avocational activities are well documented in the medical literature.

The current literature regarding marijuana and pain can be contradictory and confusing for those practitioners treating patients with pain. There are few studies available with a small number of patients and with very specific diagnoses^{18,19}. The results of these studies in very specific diagnoses cannot translate well to other pain disorders, just as treatment of other well studied medical conditions may have varying treatment (breast cancer, as an example may have varying treatment, particularly if the cancer is estrogen receptor positive or not). There are several ongoing studies regarding marijuana or its derivatives and their effects on pain⁸. There is emerging data which suggests that cannabis-derived compounds, particularly those which are much less intoxicating, may have analgesic properties similar to opioids^{20,21}. There is evidence that there may be an overlap on how opioids and endocannabinoids work in pain^{22,23}.

There are known products available for certain medical conditions¹. Marinol (dronabinol) has been commercially available since 1986 and can be used for appetite stimulation or chemotherapy-associated nausea and vomiting. Cesamet (nabilone) can be used for chemotherapy-associated nausea and vomiting. Sativex (THC plus cannabidiol) may show promise in cancer pain, neuropathic pain, and spasticity associated with multiple sclerosis. We know how these substances work and they are prescribed at a recommended dose and frequency. We know potential side effects and drug interactions as well as what may happen in an overdose situation.

As a result of Amendment 20, Colorado developed the Colorado Medical Marijuana Registry²⁴. As of July 2013, there were over 109,000 card holders in the State of Colorado. The average “medical marijuana” patient was a 42 year old male. The number one diagnosis was “severe pain” with 94% of the cardholders carrying this diagnosis. The number two diagnosis was “muscle spasms” at 15% of the cardholders and far down the list, almost last, was cancer at 3% of the cardholders. Card holders may have more than one “debilitating condition” on their marijuana recommendation, therefore the numbers do not add up to 100%. The Colorado Medical Marijuana Registry cannot and does not differentiate between malignant and benign pain syndromes or any other very specific diagnoses which may be painful. It is unknown whether these patients have pain from metastatic breast cancer or a back ache. It also does not differentiate between terminal and nonterminal illnesses.

Adult use (18-25 years of age) have been steadily on the rise in Colorado since 2009²⁵, Table 1. The national “past month use” rate is 18.8%, whereas in Colorado it is 27.3%. Within the state of Colorado the “past month use” rate has increased from 21.4% in 2006 to 27.3% in 2011 (an increase of 27%), Table 2. The national “past month use” in adults greater than 26 years of age is 4.8%, where in Colorado it is 8.2%, nearly double the national average. “Past month use” in Colorado has increased from 5.3% in 2008 to 8.2% in 2011 reflecting an increase of 54%²⁵. According to the Drug Abuse Warning Network (DAWN), Colorado’s Emergency Department admissions for marijuana only, are 25%, compared to the national average of 18%²⁶.

Table 1

Last 30 Day Use Average, Age 18 - 25, Comparison

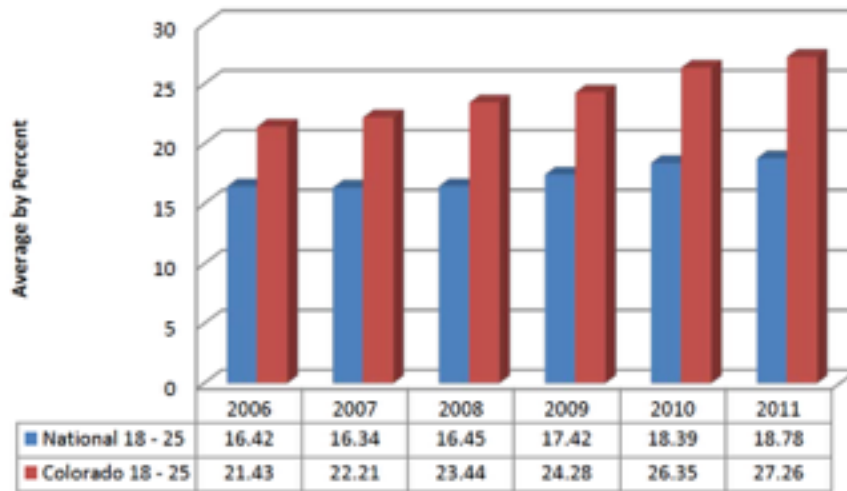
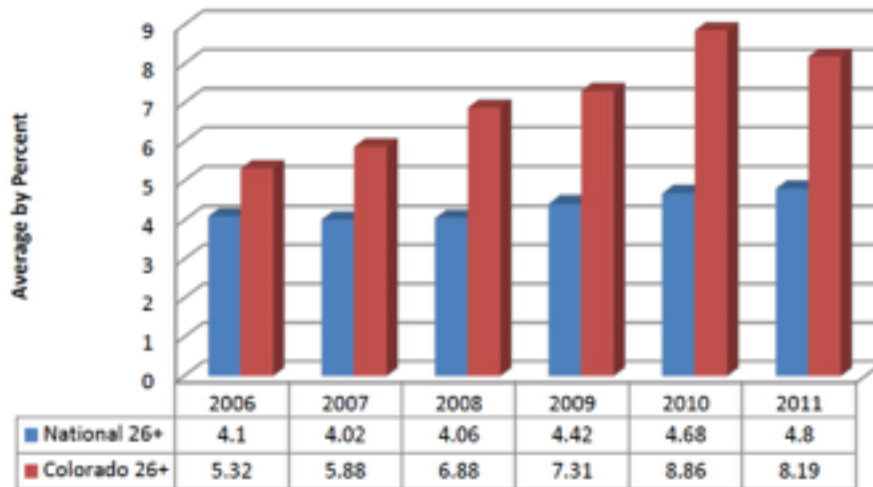


Table 2

Last 30 Day Use Average, Age 26+, Comparison



Effects on Learning

Marijuana has acute (up to 6 hours), subacute (6 hours to 20 days) and long term effects (more than 20 days)²⁷. This may impact a student's ability to learn new material, even if they have not used for up to 3 weeks. There is emerging evidence that the earlier one begins to use marijuana, the less likely they may be to complete a high school or college education and there may be negative effects on IQ²⁸. A New Zealand study of 6,300 children demonstrated those children who began using marijuana between the ages of 15-17, are nearly 4 times less likely to obtain a high school or

college degree, compared to those whose use began after 18 years of age²⁹. The ability to learn material in the classroom may be impaired, even by occasional use³⁰. Memory, speed of thinking, and other cognitive abilities worsen over time with marijuana use, noted during functional MRI, during spatial working memory tasks³¹.

Negative behavior in the classroom may be related to the use of marijuana. The Colorado Department of Education has been following trends related to Public School Drug Suspensions and Expulsions over time³², Table 3. Between the 2001-2002 and 2007-2008 school years, there was a steady decline in the total number of these offenses statewide. Beginning in the 2008-2009, there was a dramatic rise in the number of disciplinary actions compared to the one academic year prior by 32%, from 3,736 offenses to 4,956. This coincided with the proliferation of marijuana dispensaries across Colorado as well as with cuts in federal and state drug prevention and education programs.

Despite medical marijuana being primarily utilized by those over the age of 21 in Colorado, marijuana has infiltrated the school systems as noted above. The Rocky Mountain High Intensity Drug Trafficking Area and the National Survey on Drug Use and Health has been able to demonstrate that adolescent marijuana use is on the rise in Colorado and the state of Colorado now has much higher adolescent marijuana use rates compared to the rest of the country^{33,34}. On average, adolescent (12-17 years of age) use of marijuana nationally is 7.64%, whereas in Colorado it is 10.72%, Table 4. 12th grade use nationally is 22.6% and in Colorado is 31.2%. Daily marijuana use in 12th graders is 6.6% nationally and in Colorado is 7.8%.

Table 3

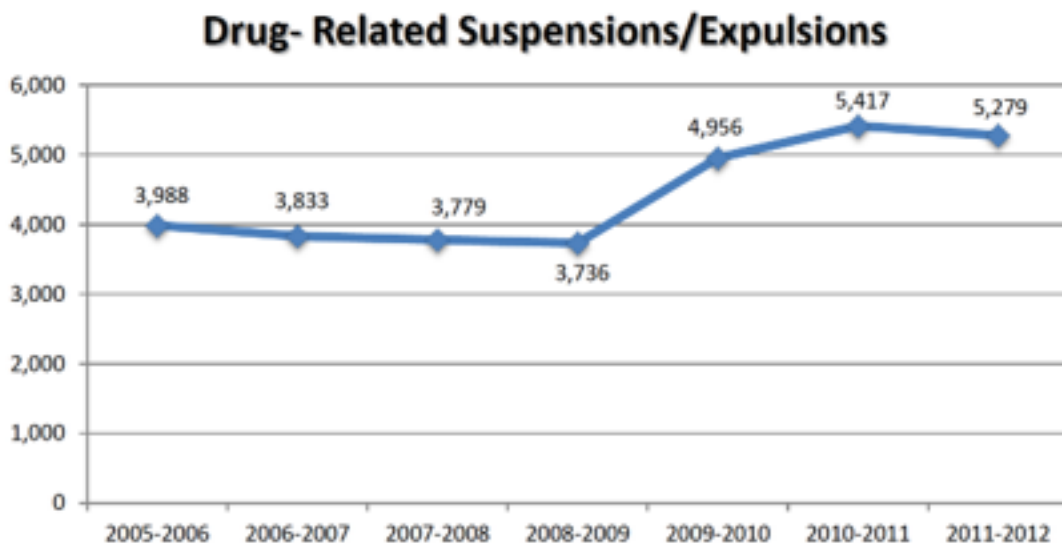
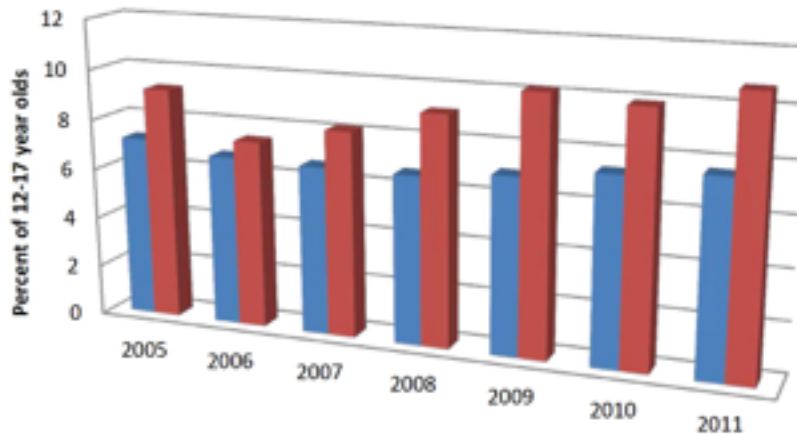


Table 6: Data from Colorado Department of Education⁷

The Colorado Department of Education included all drugs in this data set. However, department officials reported that **most** drug related expulsions reported since the 2008-2009 academic year have been related to marijuana.⁷

Table 4

**Past Month Usage of Marijuana:
National to Colorado Rate**



	2005	2006	2007	2008	2009	2010	2011
■ National Average	7.2	6.74	6.67	6.67	6.98	7.38	7.64
■ Colorado Average	9.24	7.44	8.15	9.1	10.17	9.91	10.72

The exposure to children (less than 12 years of age) has also been on the increase in Colorado^{35,36}. This also coincides with the proliferation of marijuana dispensaries across the state. At Children’s Hospital in Denver, in the years 2005-2008, there were 790 unintentional drug exposures (all drugs) with zero related to marijuana. Between the years 2009-2011, the overall unintentional drug exposures (all drugs) were on the decline, however, there were 14 for marijuana, 7 of which were related to infused products. There were also on average of 12 incidents of marijuana-related exposures per year for the very young child (0-5 years of age) in that time frame, according to the Rocky Mountain Poison Control Center³⁷. Several of these young children required hospitalization.

Psychiatric Effects

The literature continues to demonstrate negative psychiatric effects related to marijuana use. The human brain continues to mature until a person is approximately 26 years of age. The brain of children and adolescents are in important stages of brain development that may make them prone to negative psychological effects of marijuana use. The “pleasure center” of the brain matures earlier than the prefrontal cortex, which is the last to mature. The drive for pleasure is strong, but the ability to determine the consequences of actions are not fully mature in the child and adolescent brain³⁸.

It has been shown that teens who smoke marijuana at least once a month are up to three times more likely to have suicidal thoughts and depressed teens are twice as likely to be dependent on marijuana³⁹. Studies show that teens who use marijuana increase their chances of developing psychosis in young adulthood by up to four times^{40,41,42}. There is also a strong relationship between marijuana use and

development of schizophrenia^{43,44}. This has significant impacts on patients and their families.

Marijuana dependency and addiction are becoming a huge problem in Colorado. It is now the number one admission diagnosis for adolescent illicit substance use treatment in Colorado^{45,46}. This trend began when the marijuana dispensaries began to proliferate in the Colorado in 2009. The relationship between marijuana use and dependency and addiction are well outlined in the literature^{47,48}. There is great debate whether or not marijuana is a gateway drug, similar to alcohol, but the literature is beginning to lean towards that marijuana use may lead to the use of other, more dangerous, illicit substances^{49,50}.

Regulatory Concerns

Drugged Driving

Marijuana use has been noted to effect reaction time, problem solving, and coordination¹². There may be distortion of spacial working memory⁵¹ which can have deadly results when operating a motor vehicle. In Colorado, there has been a steady decline in the number of traffic fatalities between 2006 and 2011 which is consistent with national trends⁵². Despite this gradual decline in overall traffic fatalities, those involving drivers testing positive for marijuana has increased from 5% to 13% between 2006 and 2011, Table 5. The total number of drivers involved in fatal crashes decreased from 721 to 587 in the same time frame. The drivers of fatal crashes involving all drugs steadily increased from 21 to 52, but the percentage of those drivers testing positive compared to other drugs increased from 28% to 56%, Table 6.

Table 5

Fatalities Involving Driver with Positive Drug Test 2006–2011					
Crash Year	Fatalities by Driver with Positive Drugs (Includes Cannabis)	Fatalities by Driver with Positive Cannabis	Total Statewide Fatalities	Percentage of Total Fatalities (All Drugs)	Percentage Total Fatalities (Cannabis)
2006	85	27	535	15.9%	5%
2007	92	29	555	16.6%	5.2%
2008	84	39	548	15.3%	7.1%
2009	88	41	465	18.9%	8.8%
2010	88	46	449	19.6%	10.2%
2011	106	58	447	23.7%	13%

SOURCE: Colorado Department of Transportation Fatality Analysis Reporting System (FARS) 2006 – 2011

Table 6

Drivers with Positive Drug Tests in Fatal Crashes 2006-2011					
Crash Year	Drivers of Fatal Crashes of Positive Drug Tests (includes Cannabis)	Drivers of Fatal Crashes of Positive for Cannabis	Total Drivers Involved in Total Crashes	Percentage of Total Drivers with Positive Drugs	Percentage Total Drivers with Positive Cannabis
2006	75	21	721	10.4%	2.9%
2007	81	23	789	10.3%	2.9%
2008	72	31	712	10.1%	4.4%
2009	82	37	653	12.6%	5.7%
2010	79	42	600	13.2%	7%
2011	93	52	587	15.8%	8.9%

SOURCE: Colorado Department of Transportation Fatality Analysis Reporting System (FARS) 2006 - 2011

NOTE: Data only includes drivers who were tested for drugs and/or alcohol with the results that were reported to CDOT. (Revised December 24, 2012.) For instance, from 2006 through 2011, only about half of the drivers were tested for drugs (average 47.6 percent in years 2006 - 2008 and average 48.2 percent in years 2009 - 2011).²

Diversion

There is currently no mandatory process for law enforcement to report between states either the seizure or the source of marijuana. Voluntary reporting from some law enforcement entities was requested by Rocky Mountain High Intensity Drug Trafficking Area on those incidents where Colorado marijuana was seized in their jurisdiction (www.rmhidta.org/reports). Early marijuana era (2006-2008) was compared to the marijuana era (2009-2011) in Colorado. Recreational marijuana era begins in 2013.

2006-2008: 1,000-4,800 MJ cardholders
No known dispensaries

2009-2011: 108,000 MJ cardholders
532 licensed dispensaries

El Paso Intelligence Center (EPIC)⁵³ established the National Seizure System for voluntary reporting interdiction seizures country-wide in 2012. RMHIDTA has been able to identify marijuana destined for other states based on voluntary reporting. The data may not reflect those incidences not reported, Table 7, Table 8.

2005: 54 MJ interdiction seizures
2012: 274 MJ interdiction seizures
407% increase
Of the 274 seizures in 2012, MJ was destined for 37 different states.

2005-2008: 52.2 average number of interdiction seizures
2,220 average number of pounds of MJ seized

2009-2011: 242 average number of interdiction seizures (300% increase)
3,937 average number of pounds of MJ seized (77% increase)

In 2012 alone, there were 7,008 pounds of MJ seized destined to other states. Examples of interdiction seizures can be found at the Rocky Mountain High Intensity Drug Trafficking Area's website: www.rmhidta.org/reports⁵⁴.

Table 7

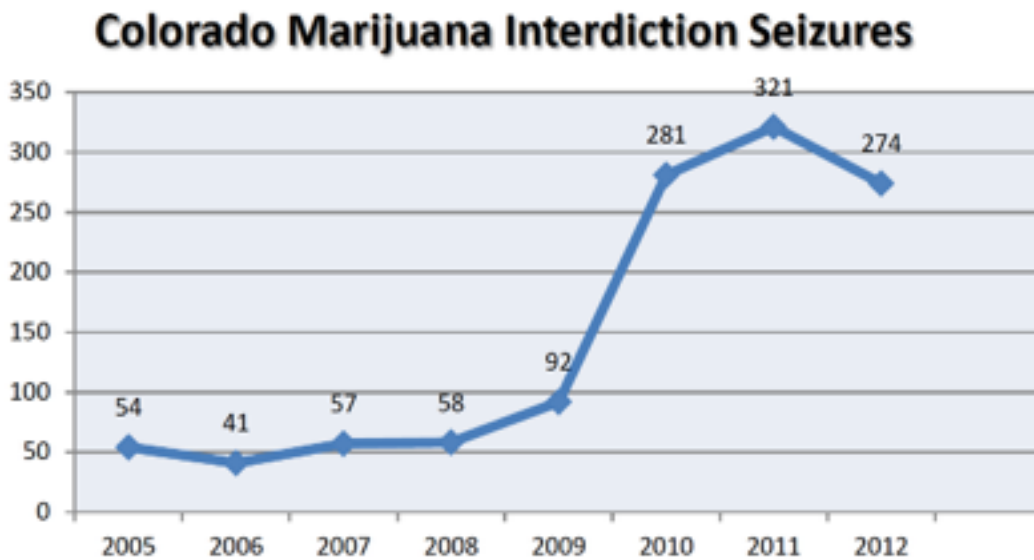
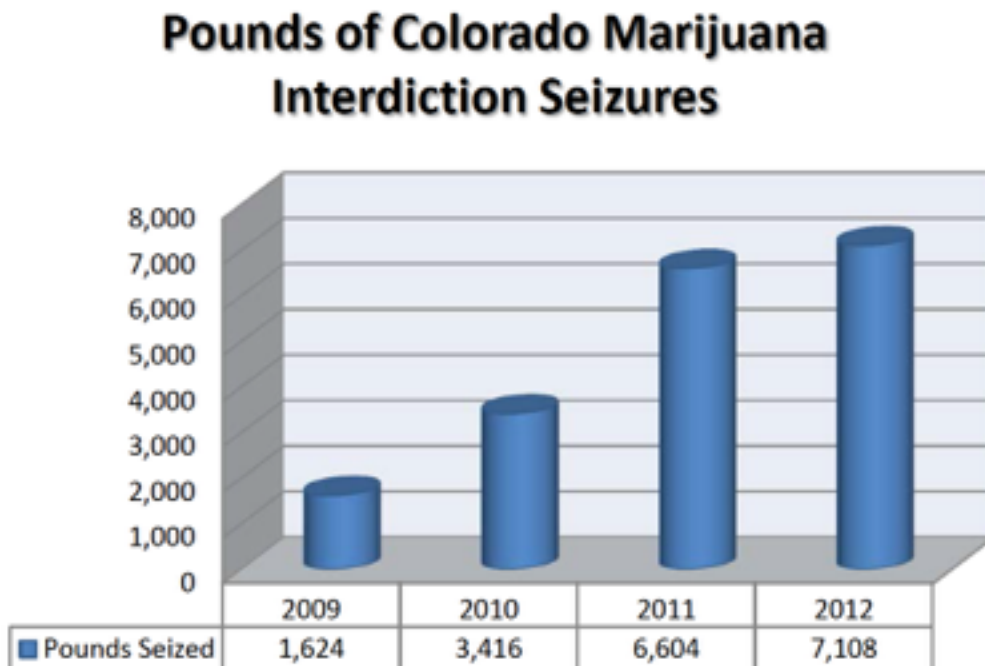


Table 8



The use of parcel packages is becoming more prevalent among drug traffickers who are using Colorado as a source of marijuana. Seizure data through the United States Postal Inspection Service began late 2009⁵⁵, Table 9.

INTERCEPTED PARCELS

2010: 15 intercepted parcels
 2011: 36 intercepted parcels
 2012: 158 intercepted parcels
 2013: 209 intercepted parcels (through May only)

The data reflects those parcels seized, not those that made it to their intended destination.

TOTAL POUNDS OF MJ SEIZED

2010: 57 pounds
 2011: 68 pounds
 2012: 206 pounds
 2013: 205 pounds (through May only)

Table 9

Events of parcels containing marijuana mailed from Colorado to another state

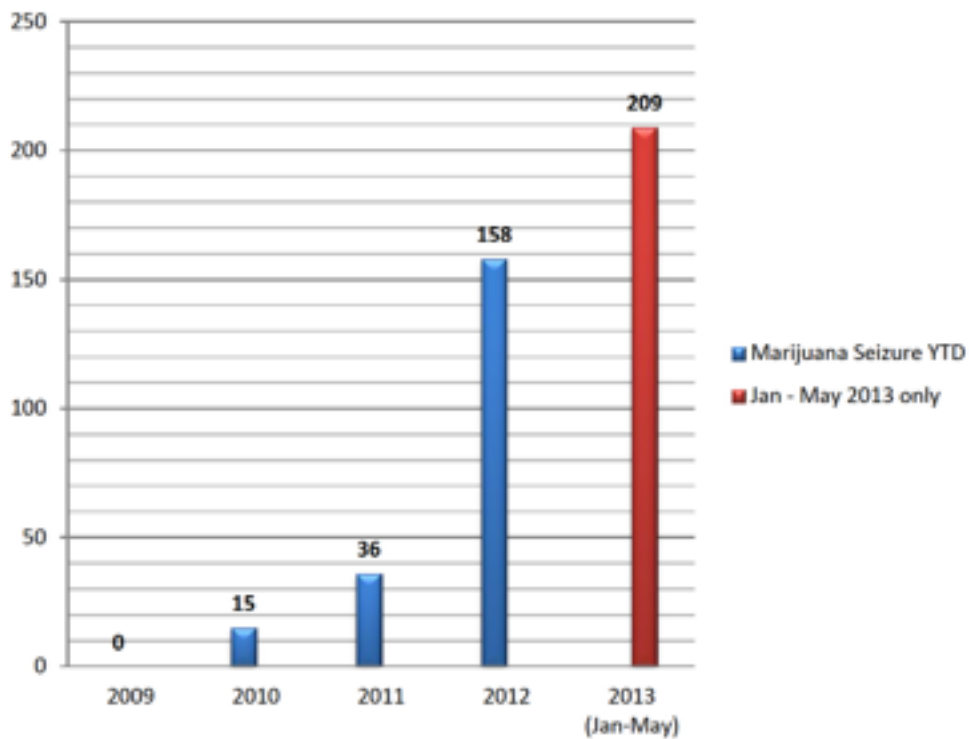


Table 1: USPS data (2009 – May 2013)

Summary

Marijuana use is becoming much more widely accepted and used, particularly in those states which have legalized it for medical purposes. Despite regulations which try and prevent access to minors, young adults are beginning to use the substance at a much more prolific rate. Colorado, as an example, is beginning to experience significant negative outcomes across several areas directly and indirectly related to marijuana use in young children, adolescents, and adults.

Although scientific data is beginning to emerge which may demonstrate benefits of less intoxicating components of the *Cannabis sativa* plant, the vast majority of these substances have yet to meet the rigors of the FDA in order to qualify as “medicine”. Marijuana is not a crop regulated by the FDA.

Marijuana is difficult to study because there are so many different strains available to the public that vary in THC content and potency and it is still a Schedule I drug. There is no education or training in medical school or residency regarding the pharmacokinetics or pharmacodynamics of marijuana. All of the potential drug-drug interactions are unknown. There is no standardization on dose or frequency as well as delivery systems. There are far too many products available on the market to obtain or maintain consistent blood levels.

There is smoked and vaporized marijuana as well as infused products available, which include cakes, cookies, brownies, gummy bears, lollipops, and pizzas, to name a few. There are infused liquids with varying concentrations of marijuana in them and include flavored waters, energy drinks, and soda pops. There are oils and other extracts which are very highly concentrated forms of THC (up to 80%) and are dangerous to produce (hash and honey oil).

The way Colorado law is written, there is virtually no protection of physicians who may be recommending marijuana in the event something serious happens to their patient, directly or indirectly, even if the physician had done nothing wrong. The legal term for this is vicarious liability. There are now physicians who are losing their licenses⁵⁶ because of the pitfalls of marijuana not qualifying as a “medicine” or because of misbehavior^{57,58}.

Given the effects of marijuana on several organ systems, should recommending physicians have an informed consent process for such patients who may have angina, asthma, a history of suicide, or other? How is a medical practitioner able to adequately manage a medical problem when there are too many variables effecting treatment? There are far too many unanswered questions about the use of marijuana as medicine. More research is clearly necessary despite current studies which are beginning to demonstrate promise in some areas. Science, not public opinion, should determine what is medicine.

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