Cannabis as a Potential Therapeutic Agent

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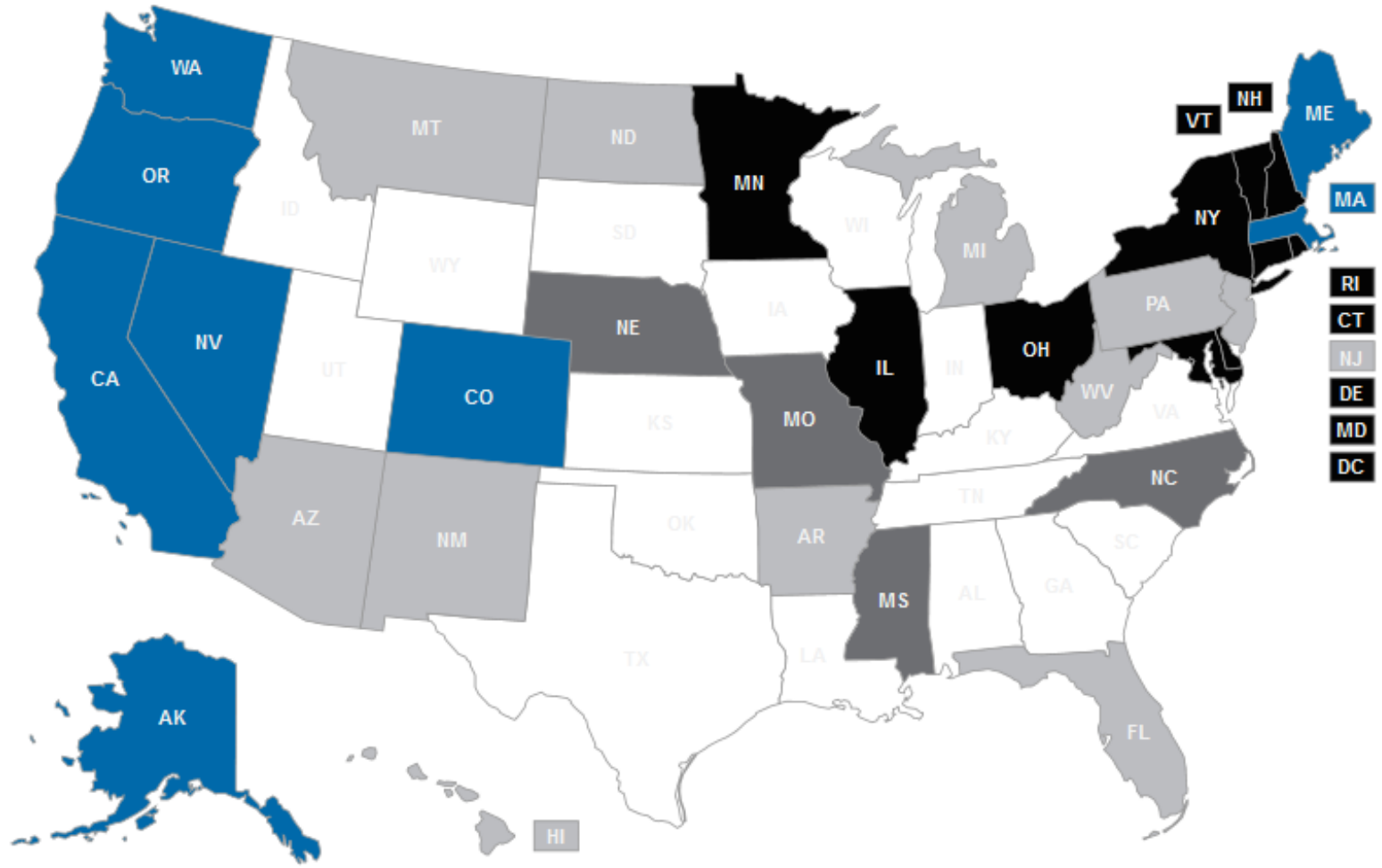
Funding and Conflicts of Interest

- I have no conflicts to report regarding this research
- I am Co-PI of a CDPHE funded study of cannabis use and sleep

Topics

- Background
  - History, Advocacy & Legislative Action
- Cannabinoids
  - Endocannabinoid system
  - Exogenous cannabinoids
- Cannabis Biology
  - Cannabis as a consumable product
- Cannabis as a potential Therapeutic Agent



States with medical marijuana laws

States that have removed jail time for possessing small amounts of marijuana

States that have both a medical marijuana law and have removed jail time for possessing small amounts of marijuana

Marijuana is legal for adults and is taxed and regulated similarly to alcohol; state also has a medical marijuana law

www.mpp.org/states accessed 10/18/2017

Journal of Experimental Botany, Vol. 59, No. 15, pp. 4171–4182, 2008
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Journal of Experimental Botany
www.jxb.oxfordjournals.org

RESEARCH PAPER

Phytochemical and genetic analyses of ancient cannabis from Central Asia

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Abstract

The Yanghai Tombs near Turpan, Xinjiang-Uighur Autonomous Region, China have recently been excavated to reveal the 2700-year-old grave of a Caucasoid shaman whose accoutrements included a large cache of cannabis, superbly preserved by climatic and burial conditions. A multidisciplinary international team demonstrated through botanical examination, phytochemical investigation, and genetic deoxyribonucleic acid analysis by polymerase chain reaction that this material contained tetrahydrocannabinol, the psychoactive component of cannabis, its oxidative degradation product, cannabinol, other metabolites, and its synthetic enzyme, tetrahydrocannabinolic acid synthase, as well as a novel genetic variant with two single nucleotide polymorphisms. The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination. To our knowledge, these investigations provide the oldest documentation of cannabis as a pharmacologically active agent, and contribute to the medical and archaeological record of this pre-Silk Road culture.

Key words: Archaeology, botany, cannabis, cannabinoids, archaeobotany, ethnopharmacology, genetics, medical history, phytochemistry.

Introduction

Uighur farmers cultivating the land at the base of the Huoyan Shan ('Flaming Mountains') in the Gobi Desert near Turpan, Xinjiang-Uighur Autonomous Region, China some 20 years ago uncovered a vast ancient cemetery (54 000 m^2) that seemingly corresponds to the nearby Aidinghu, Alagou, and

Discussion

The results presented collectively point to the most probable conclusion which is that the *Gūshī* culture cultivated cannabis for pharmaceutical, psychoactive or divinatory purposes. In examining the botanical evidence from this 'old and cold' site with its unique degree of preservation, the cannabis consisted of a processed (pounded) sample whose seed size, colour, and morphology, at least according to principles of Vavilov (Vavilov, 1926), suggest that it was cultivated rather than merely gathered from wild plants. The considerable amount of cannabis present (789 g) without any large stalks or branches would logically imply a pooled collection rather than one from a single plant. Importantly, no obvious male cannabis plant parts (e.g. staminate flowers, not infrequently observed in Indian herbal cannabis, or *bhang* (Russo, 2007) were evident, implying their exclusion or possible removal by human intervention, as these are pharmacologically less psychoactive.

Schedule I

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Some examples of Schedule I drugs are:

heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote

Criteria for Scheduling and Schedules under the Controlled Substance Act (CSA)

CRITERIA

Abuse Potential				
High	**High**	**Low relative to CII**	**Low relative to CIII**	**Low relative to CIV**
No Medical Use	**Medical Use**			
Lack of accepted safety under medical supervision	**Psychological or Physiological Dependence**			
	Severe Psych or Physical	**High Psych or Moderate to low Physical**	**Ltd Psych or Physical relative to CIII**	**Ltd Psych or Physical relative to CIV**

SCHEDULES

SCHEDULE I	SCHEDULE II	SCHEDULE III	SCHEDULE IV	SCHEDULE V
Heroin Hallucinogens Marijuana Others	Opioids Barbiturates Cocaine Amphetamine Methylphenidate Methamphetamine PCP	Opioids (Codeine combinations, Buprenorphine) Barbiturates (combinations and products) Ketamine GHB Marinol Anabolic Steroids	Benzodiazepines and other depressants (Zaleplon, Zolpidem, Eszoplicone) Fenfluramine Modafinil Butorphanol Tramadol	Opioids in limited quantities and in combinations (Codeine, Dihydrocodeine, Difenoxin) Pregabalin Lacosamide

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM498077.pdf

Statutory Basis for Scheduling Recommendation

CSA requires HHS to considered 8 Factors :

1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effect
3. Current scientific knowledge regarding the substance
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. Risk to public health
7. Psychic or physiological dependence liability
8. Immediate precursor of a substance already controlled

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM498077.pdf

Case Law on Meaning of "Currently Accepted Medical Use"

1. The drug's chemistry is known and reproducible
2. There are adequate safety studies
3. **There are adequate and well-controlled studies proving efficacy**
4. The drug is accepted by qualified experts
5. The scientific evidence is widely available

57 FR 10499, 10504-06 (March 26, 1992).

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM498077.pdf

The current state of affairs at the federal level

1. FDA has supported cannabis based drug development (dronabinol and nabilone) for specific treatment
2. FDA/DEA/HHS supports cannabis research by providing legally produced cannabis product to researchers what have that HHS has found to be scientifically meritorious.
3. NIDA will work to provide a variety of potencies of cannabis for research purposes
4. DEA considers cannabis to be less dangerous than other schedule 1 drugs but schedule 1 is not based on “relative danger”, rather that the drug meets “specific statutory criteria”.
5. “If the scientific understanding about cannabis changes” then the scheduling decision can change

The current state of affairs at the federal level

Drugs in development focus on two molecules specifically, Tetrahydrocannabinol and Cannabidiol, not the full botanical product based on “assured quality manufacturing”.

This is in opposition to the common philosophy of supporters of cannabis as medicine who say that there is evidence of an “entourage effect” that is not duplicated by single molecule therapy

Colorado Civics Lesson

1998; Amendment 19 trying to legalize Medical Marijuana in Colorado fails to make it onto the ballot*

2000; Amendment 20 makes it on the ballot and passes 54% to 46% legalizing Medical Marijuana

2005; Denver initiative I-100 passes allowing recreational use of one ounce for >21

2006; Amendment 44 to legalize recreational use fails 60% to 40%

2009; US Attorney General says that there will be no further action taken against dispensaries following state and local laws

2010: HB10-1284 creates a state regulatory agency and business licensing for full-scale dispensaries

2012; Amendment 64 passes 55% to 45% legalizing recreational cannabis

2013; regulation of A64 is enacted, SB13-317(licensing and regulation), SB13-318 (taxation), SB13-238 (education and enforcement)

2014; SB14-215 allocates $9,000,000 to fund research administered through CDPHE to investigate potential therapeutic benefits of cannabis use (among other things)

Medical Marijuana Acceptable Medical Conditions

19. The above-named patient has been diagnosed with and is currently undergoing treatment for the following chronic, debilitating medical condition **or** has a chronic, debilitating disease or medical condition that produces one or more of the following:

☐ a. Cancer	☐ b. Glaucoma	☐ c. HIV or AIDS positive
☐ d. Cachexia*	☐ e. Severe nausea*	☐ f. Seizures*
☐ g. Persistent muscle spasms*		☐ h. Severe pain*

20. Etiology is required for medical conditions with an asterisk (*), if known.
Etiology: _____ **or** ☐ Etiology unknown.

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  - Endocannabinoid system
  - Exogenous cannabinoids
- Cannabis Biology
  - Cannabis as a consumable product
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Endocannabinoid System

- 1964 THC is isolated, its believed to have non-specific activity
- In the mid 1980's Allyn Howlett suggested that specific receptors existed
- 1990 Matsuda et al published a paper detailing the structure and function of a receptor that bound THC and was present in the central and peripheral nervous system eventually named CB-1
- A second receptor (CB-2) was identified in immune cells, various peripheral nerves and organ systems but also in CNS tissue
- 1992 Devane identifies the first endogenous molecule that binds to these receptors, eventually named Anandamide
- 1995 Mechoulam et al identified 1-arachidonoylglycerol (2-AG)

Therapeutic applications of ECS related drugs in the periphery

Endocannabinoid signaling at the periphery: 50 years after THC

Mauro Maccarrone, Itai Bab, Tamás Bíró, Guy A. Cabral, Sudhansu K.Dey, Vincenzo Di Marzo, Justin C. Konje, George Kunos, Raphael Mechoulam, Pal Pacher, Keith A. Sharkey, Andreas Zimmer, Trends in Pharmacological Sciences Volume 36, Issue 5, May 2015

Table 2. Therapeutic applications of ECS-related drugs at the periphery

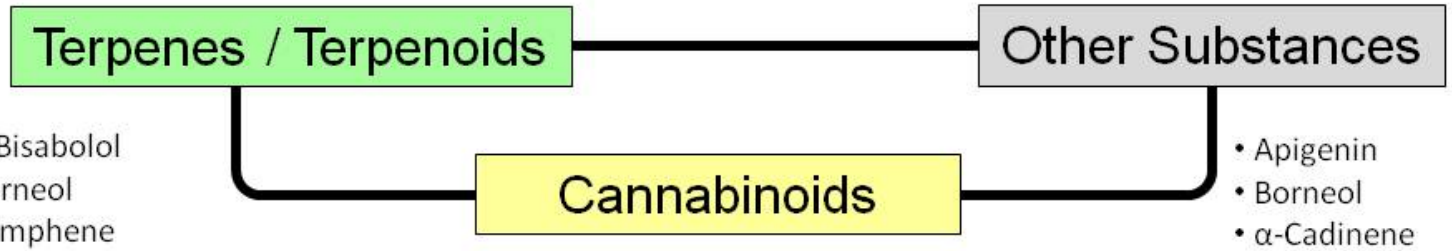
Compound/category	ECS target	Model	Therapeutic indication	Clinical condition	Refs
(Peripherally restricted) CB_1 antagonists	CB_1	Rodent/human	Cardiomyopathies, heart failure, diabetic cardiovascular complications, atherosclerosis, circulatory shock	Doxorubicin-induced and cirrhotic cardiomyopathies, diabetic cardiomyopathy and vasculopathy, circulatory shock, atherosclerosis, heart failure	[27–29,31–33,35, 63,159,160]
CB_2 agonists	CB_2	Rodent	Myocardial infarction, stroke, myocarditis? cardiomyopathies?	Myocardial infarction, stroke, myocarditis? cardiomyopathies?	[28,160]
(Peripherally restricted) CB_1 agonists	CB_1	Dog/human	Transient lower esophageal relaxation	Gastroesophageal reflux disease	[161,162]
(Peripherally restricted) CB_1 agonists	CB_1	Mouse/rat	Diarrhea Inflammation Visceral pain	Irritable bowel syndrome Inflammatory bowel disease Gastric ulcer	[163] [164–166] [167]
(Peripherally restricted) CB_1 antagonists	CB_1	Mouse	Metabolic endotoxemia Food intake Dysmotility	Obesity Paralytic ileus	[43] [40] [168,169]
CB_2 agonists	CB_2	Mouse/rat	Diarrhea Inflammation, visceral pain	Irritable bowel syndrome Inflammatory bowel disease	[44,170] [44,170]
FAAH inhibitors	CB_1, CB_2, PPARs	Mouse	Diarrhea Inflammation	Irritable bowel syndrome Inflammatory bowel disease Gastric ulcer	[45,171] [166,172] [173]
MAGL inhibitors	CB_1, CB_2, PPARs	Mouse/rat	Diarrhea Inflammation	Irritable bowel syndrome Inflammatory bowel disease Gastric ulcer	[174] [175] [47,176]
Peripherally restricted CB_1 antagonists	CB_1	DIO mice, *ob*/*ob* mice, *db*/*db* mice,[a] ZDF rats[b]	Lipogenesis, inflammation	Obesity/metabolic syndrome, fatty liver disease, type 2 diabetes	[61,177,178]
Rimonabant	CB_1	Mouse C2C12 myoblasts	Defective myotube differentiation and muscle regeneration	Muscular dystrophy	[100]
Synthetic CB_2 agonists	CB_2	Mouse	Bone mineralization	Osteoporosis	[113]
PEA	CB_1? CB_2? TRPV1? PPARs? GPR55?	Human	Vestibulodynia, vulvodynia, proctodynia	Infertility	[179,180]
THC	CB_1	Mouse	Parturition	Infertility	[125,128]
PEA	CB_1? CB_2? TRPV1? PPARs? GPR55?	Human	Inflammation, pruritus	Atopic dermatitis, prurigo, uremic itch	[140,141]
(Peripherally restricted) CB_1 antagonists	CB_1	Rodent	Diabetic and other nephropathies and tubulopathies	Diabetic and other nephropathies and tubulopathies	[151,152,154]
CB_2 agonists	CB_2	Rodent	Diabetic and other nephropathies and tubulopathies	Diabetic and other nephropathies and tubulopathies	[153,154]

What is Cannabis

TaxonomicHierarchy

Kingdom	Plantae – plantes, Planta, Vegetal, plants
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta – land plants
Superdivision	Embryophyta
Division	Tracheophyta – vascular plants, tracheophytes
Subdivision	Spermatophytina – spermatophytes, seed plants, phanérogames
Class	Magnoliopsida
Superorder	Rosanae
Order	Rosales
Family	Cannabaceae – hemp
Genus	Cannabis L. – hemp
Species	Cannabis sativa L. – hemp, grass, hashish, Mary Jane, pot, marijuana
	Direct Children:
Subspecies	Cannabis sativa ssp. indica (Lam.) E. Small & Cronquist – hemp, grass, hashish, Mary Jane, pot, marijuana
Subspecies	Cannabis sativa ssp. sativa L. – hemp, grass, hashish, Mary Jane, pot, marijuana

Hemp Plant Chemistry Is Complex



- α-Bisabolol
- Borneol
- Camphene
- Campher
- Δ^3-Carene
- β-Caryophyllene
- α-Cedrene
- β-Eudesmol
- Geraniol
- Guaiol
- α-Humulene
- Limonene
- Linalool
- Menthol
- Myrcene
- Nerol
- α-Pinene
- α-Terpinene
- Over 150 more

- Cannabidiol
- Cannabichromene
- Cannabichromevarin
- Cannabicyclol
- Cannabitriol
- Cannabidivarin
- Cannabidodiol
- Cannabigerol
- Cannabigerovarin
- Cannabinol
- Cannabivarin
- Tetrahydrocannabinol
- Tetrahydrocannabivarin

- Apigenin
- Borneol
- α-Cadinene
- Cannabisin-A
- Cannflavin-A
- *N-trans*-Caffeoyltyramine
- Docosnoic Acid
- Epifriedelanol
- *N-trans*-Feruloytyramide
- β-Eudesmol
- Grossamide
- Kaempferol
- Orientin
- Quebrachol
- β-Selinene
- α-Spinasterol
- Stigmasterol
- Vitexin
- Vomifoliol
- Hundreds more

http://www.isascientific.com/wp-content/uploads/2013/12/Chemistry-Complexity.jpg

TABLE 4. Arithmetic means[a], standard deviations, and ranges of the dry-weight percentages of cannabichromene (CBC), cannabidiol (CBD), cannabigerol (CBG), Δ^9-tetrahydrocannabinol (THC), and (CBD + THC) for 253 *Cannabis* plants assigned to seven putative taxa. Statistics are also given for the peak areas (determined by gas chromatography) relative to the internal standard (i.s.) of cannabidivarin plus Δ^9-tetrahydrocannabivarin (CBDV + THCV), and of cannabigerol monomethylether (CBGM). *N* = number of plants analyzed.

Compound	*C. indica* Hemp Biotype *N* = 45	*C. indica* Feral Biotype *N* = 14	*C. indica* NLD Biotype *N* = 68	*C. indica* WLD Biotype *N* = 40	*C. sativa* Hemp Biotype *N* = 62	*C. sativa* Feral Biotype *N* = 16	*C. ruderalis* *N* = 7
CBC%	0.34 A	0.18 AB	0.19 B	0.17 B	0.18 B	0.13 B	0.07 B
(SD)	(0.47)	(0.27)	(0.21)	(0.25)	(0.24)	(0.20)	(0.10)
Range%	0.0–1.9	0.0–0.9	0.0–0.9	0.0–1.4	0.0–1.2	0.0–0.8	0.0–0.2
CBD%	1.43 BC	1.95 BC	0.02 D	1.21 C	4.01 A	3.62 A	3.02 AB
(SD)	(2.45)	(2.82)	(0.02)	(2.78)	(2.66)	(1.80)	(1.29)
Range%	0.0–8.5	0.0–7.9	0.0–0.1	0.0–11.0	0.0–13.6	1.7–8.3	1.0–4.6
CBG%	0.18 AB	0.22 AB	0.24 A	0.19 AB	0.14 B	0.08 B	0.11 AB
(SD)	(0.20)	(0.23)	(0.27)	(0.32)	(0.16)	(0.11)	(0.16)
Range%	0.0–1.0	0.0–0.7	0.0–1.1	0.0–1.8	0.0–0.7	0.0–0.3	0.0–0.5
THC%	3.54 B	3.04 B	5.48 A	6.49 A	1.16 C	0.39 C	0.17 C
(SD)	(2.58)	(2.12)	(2.41)	(4.09)	(2.05)	(0.61)	(0.08)
Range%	0.1–9.3	0.3–6.0	1.4–12.4	0.1–14.7	0.1–11.5	0.1–2.5	0.1–0.3
(CBD + THC)%	4.97 BC	4.99 BC	5.50 B	7.70 A	5.17 BC	4.01 C	3.19 C
(SD)	(2.61)	(1.91)	(2.42)	(3.45)	(2.59)	(1.83)	(1.37)
Range%	0.6–11.4	1.7–8.2	1.4–12.4	1.7–14.8	1.2–14.3	1.7–8.8	1.0–4.8
(CBDV + THCV)/i.s.	0.19 B	0.90 A	0.25 B	0.14 BC	0.05 C	0.09 BC	0.05 BC
(SD)	(0.35)	(0.80)	(0.40)	(0.30)	(0.06)	(0.10)	(0.05)
Range	0.0–1.6	0.0–2.7	0.0–2.1	0.0–1.4	0.0–0.3	0.0–0.3	0.0–0.1
CBGM/i.s.	0.05 A	0.00 C	0.01 C	0.02 B	0.01 BC	0.00 BC	0.01 BC
(SD)	(0.05)	(0.01)	(0.01)	(0.03)	(0.03)	(0.01)	(0.01)
Range	0.0–0.18	0.0–0.02	0.0–0.05	0.0–0.14	0.0–0.15	0.0–0.03	0.0–0.03

[a] Means (in rows) not connected by the same letter are significantly different using Student's *t* test ($P \leq 0.05$).

Hillig and Mahlberg, American Journal of Botany, 2004

Table 4 Quantification results of cannabinoids in HPLC-MS/MS of different *Cannabis sativa L.* varieties

Sample	Indoor/Outdoor	THCA (mg/g)	THC (mg/g)	CBG (mg/g)	THCV (μg/g)	CBN (μg/g)	CBD (μg/g)
Parmir	I 1	81±4	2.6±0.2	0.37±0.03	35±2	11.2±0.8	1.6±0.2
Great White Sarck	I 2	99±5	3.7±0.2	0.37±0.03	56±3	7.5±0.5	2.9±0.3
Power Plant	I 3	107±5	2.0±0.1	0.39±0.03	70±4	11.6±0.8	1.8±0.2
AK 47	I 4	74±4	1.2±0.1	0.30±0.02	33±2	7.4±0.5	0.67±0.07
N.Y.C. Diesel	I 5	114±6	2.2±0.1	1.14±0.08	35±2	7.0±0.5	2.4±0.2
Jaggen	I 6	91±5	2.9±0.2	0.67±0.05	62±4	10.2±0.7	2.1±0.2
Medicine Woman	I 7	119±6	3.6±0.2	1.23±0.08	60±4	11.1±0.8	2.5±0.2
Amnesia	I 8	117±6	2.7±0.2	1.04±0.07	97±6	18±1	3.9±0.4
Cheese	I 9	70±4	1.1±0.1	0.54±0.04	13.7±0.8	4.6±0.3	1.5±0.2
Chocolope	I 10	94±5	2.9±0.2	0.55±0.04	12.4±0.8	10.9±0.8	3.4±0.3
Deep Chunk	I 11	71±4	1.3±0.1	0.16±0.01	31±2	6.1±0.4	1.9±0.2
OG Kush	I 12	67±3	1.8±0.1	0.34±0.02	27±2	2.4±0.2	1.9±0.2
Soul Diesel	I 13	70±4	1.4±0.1	0.19±0.01	26±2	4.5±0.3	2.5±0.2
Skunk Green	I 14	80±4	2.0±0.1	0.076±0.005	38±2	15±1	2.8±0.3
Super Lemon Haze	I 15	69±3	3.5±0.2	0.30±0.02	310±20	13.0±0.9	3.6±0.4
Super Silver Haze	I 16	105±5	3.2±0.2	0.53±0.04	134±8	9.1±0.06	3.5±0.4
Tijuana	I 17	92±5	3.6±0.2	0.73±0.05	135±8	13.0±0.9	4.5±0.4
Neviles Haze	I 18	63±3	1.9±0.1	0.067±0.005	63±4	5.9±0.4	2.2±0.2
Somango	I 19	86±4	4.6±0.3	0.68±0.05	240±10	10.0±0.07	3.7±0.4
Amnesia	O 1	91±5	16±1	0.74±0.05	94±6	91±6	9.1±0.9
Critical	O 2	112±6	7.6±0.5	0.38±0.03	153±9	61±4	5.0±0.5
Blueberry	O 3	30±2	6.5±0.4	0.100±0.007	28±2	60±4	3.3±0.3
Chocolope	O 4	80±4	25±2	0.75±0.05	5.8±0.3	84±6	14±1
Cream Caramel	O 5	113±6	10.8±0.7	1.17±0.08	103±6	63±4	6.9±0.7
Bubba Kush	O 6	69±3	9.1±0.5	0.018±0.001	52±3	61±4	6.0±0.6
Super Lemon Skunk	O 7	51±3	17±1	0.54±0.04	4.5±0.3	91±6	10±1
Super Skunk	O 8	76±4	5.0±0.3	0.39±0.03	69±4	59±4	6.0±0.6
Trainwreck	O 9	65±3	22±1	0.48±0.03	3.6±0.2	73±5	12±1
Trainwreck X HP	O 10	71±4	6.0±0.4	0.33±0.02	98±6	58±4	3.4±0.3
Grapefruit	O 11	73±4	9.6±0.6	0.39±0.03	107±6	470±30	10±1

I: Indoor; O: Outdoor

Aizpurua-Olaizola and Usobiaga, Anal Bioanal Chem, 2014

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  - Cannabis as a consumable product
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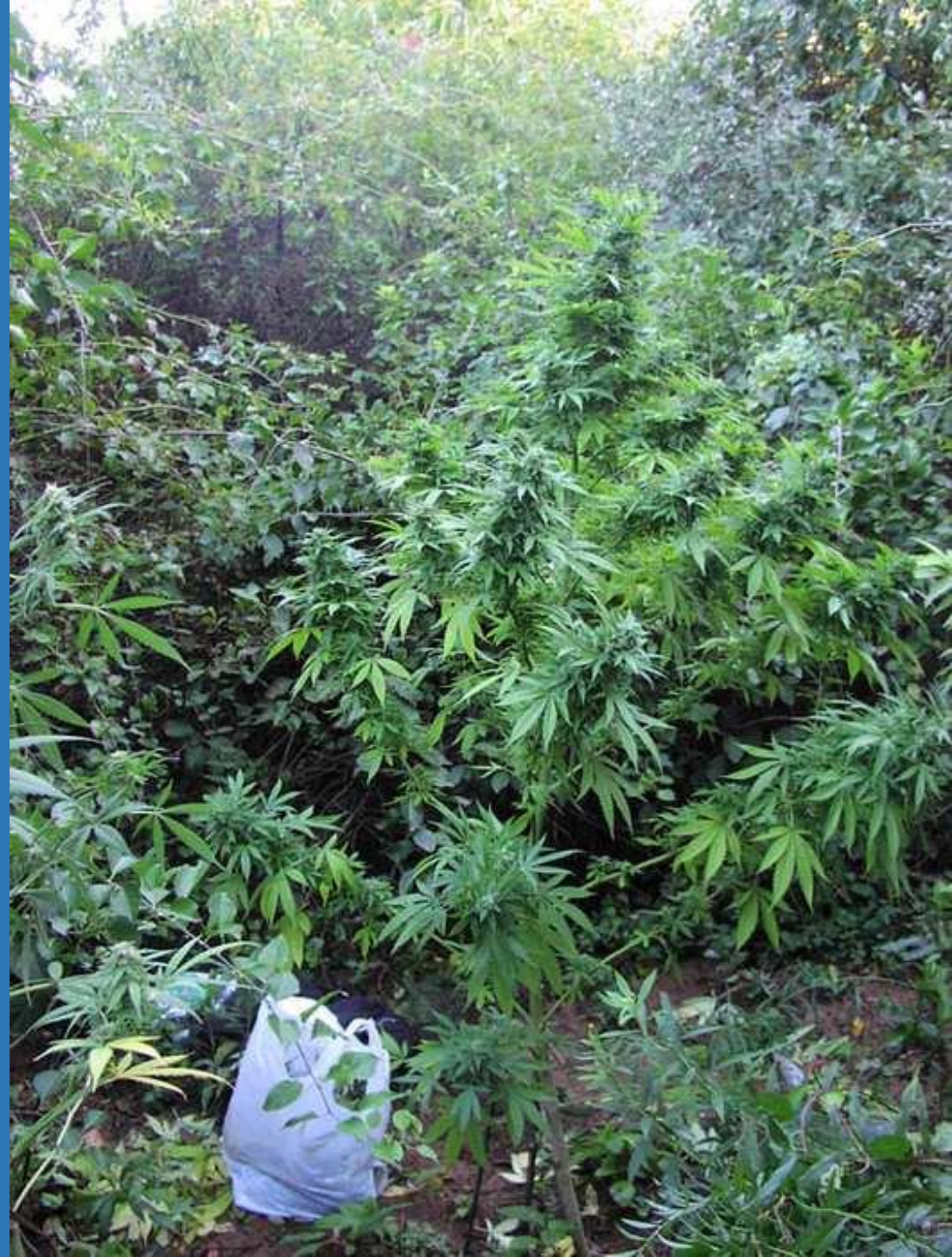
This is not what a modern cannabis grow typically looks like



http://www.cannabis-pictures.com/34notminey8OzOutdoorBogglegumBush.jpg

This is a modern industrial grow

MedicineMan Denver, 2014

*WeedMenu updated*2015-06-16 18:00:56 UTC

Indica

Triangle Kush X
Ghost OG
Rugburn
Emerald OG
Purple Urkle
Kurple Fantasy
OG Chem #3
Shaw #4

Sativa

Sharks Breath
Glass Slipper

Hybrid

White Master Kush
Blue Dream
Chem 91
KING CHEM
Lemonhead
Purple Dream
SFV OG Kush
Mixed Buds

Edible

CBD Capsules 10 pack
80mg CBD/40mg THC/40mg Dr. J's capsules
Highly Edible 100mg
Dixie Meda Mints 80mg
70mg Dixie Rolls
Incredible's Boulder Bar 100mg
Incredibles Affogato 100mg
Edi-Pure 100mg
84mg Dixie Toasted Rooster Bar
Incredible's Monkey Bar 50mg
80 mg Dr. J's PM Health Capsules
80 mg Dr. J's AM capsules
Gaia's Garden 80mg Garden Drops
Incredibles Peanut Budda 50mg
Blue Kudu 80mg
40mg Blue Kudu Chocolate
Gaia's Garden Single Serving Lollipop
Sweetgrass 10mg Snickerdoodle Cookie
Sweet Grass 10mg Peanut Butter Cookie
10mg Ganjala Taffy

Concentrate

O-Pen Vape Cartridge 500mg
Co2 Oil
Hummingbird Brand Co2 Cannabis Oil
Mahatma Shatter
TC Labs Shatter (Strain Specific)
O-Pen Vape Cartridge 250mg
O-Pen Vape Pen

Drink

Canna Punch 100mg
Dixie Elixir 90 mg
10mg Keef Kola Orange Krush, Root Beer

Tincture

200mg Charlotte's Web CBD Hemp Extract
Dixie Dew Drops 90mg

Topicals

Dixie Syngergy Relief Balm
Dixie 100mg Muscle Relief Lotion

The bioavailability of those molecules is based on how the plant is ingested

https://namelessintaipei.files.wordpress.com/2014/06/den28.jpg

http://www.slate.com/content/dam/slate/articles/news_and_politics/altered_state/2014/02/140205_ALT_Dabs_04.jpg.CROP.promovar-medium2.jpg

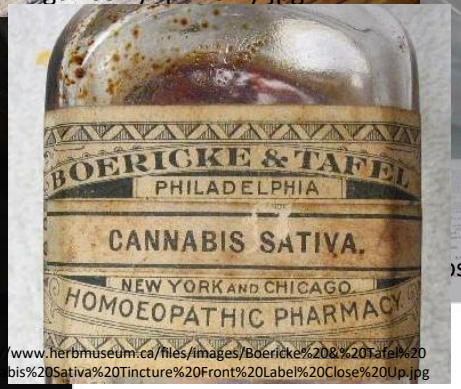
http://i.imgur.com/FpEnUNy.jpg

http://news.kgnu.org/wp-content/uploads/2014/10/1164871745_73ea1c4961_b-e1412710965978-700x350.jpg

https://lelandkim.files.wordpress.com/2012/01/img_51762.jpg

https://40.media.tumblr.com/e88d7e1fabce2dc5a1bb95276cf3cca9/tumblr_n8ogx0nk5j1tuqoiwo1_500.jpg

http://24.media.tumblr.com/801f1001aac87036f4f5dbe73868df42/tumblr_n2niyiNc7C1qdtzgpo1_500.jpg



http://www.herbmuseum.ca/files/images/Boericke%20&%20Tafel%20Cannabis%20Sativa%20Tincture%20Front%20Label%20Close%20Up.jpg

http://www.vividsmoke.com/image/data/categories/vape-devices-c.jpg

Measuring cannabis use; we need to update Donald Tashkin's 1993 survey used by UCLA

A AGE	B YEAR	C AMOUNT	D TIME FOR AMOUNT	E WAY USED
1.			Day .....1 Week.....2 Month.....3 Year.....4 Weekend...5 Every 2 months...6 Unable to determine.....7 Every 6 months...8 Missing.....9	Joints.....1 Pipes.....2 Bongs.....3 Other.....4
2.			Day .....1 Week.....2 Month.....3 Year.....4 Weekend...5 Every 2 months...6 Unable to determine.....7 Every 6 months...8 Missing.....9	Joints.....1 Pipes.....2 Bongs.....3 Other.....4

29. Now we would like to find out something about the type of marijuana that is generally available in Southern California. Thinking about the last time you bought marijuana, what kind of marijuana did you buy?

(PROBE FOR NAME AND/OR LOCATION IN WHICH GROWN.)

SINSEMILLA 1

JAMAICAN 2

COLOMBIAN. 3

HAWAIIAN 4

PANAMANIAN 5

DOMESTIC/COMMERCIAL/MEXICAN. . 6

HOME GROWN 7

AFGHANISTAN. 8

THAI 9

OTHER. 10

SPECIFY: _____

DON'T KNOW 99

- In ou
  unde
- Use
  ques

6(b) We would like you to tell us about how you use cannabis specifically.
Please describe how you use cannabis frequently on days when you do. If you use cannabis during the night please indicate that in the "Time of day used" field;

	Time of day	Cannabis Species (Indica, Sativa, Or Hybrid)	Form of Cannabis (bud, edible, Concentrate, etc.)	Name of Product or Strain (for edibles please include concentration)	Method of Use (Smoke, Vaporize, Water Pipe, Eat or Drink, etc.)	Amount Used (a Puff, a Few Puffs, a Bowl, a Bite etc)	Reason for Use (Sleep, Nausea, Pain, Recreation, etc)	Dispensary (Name, private, home grow, etc)	Other comments
First use	10Am	All	Bud	Blue Dream SourDiesel KoslerKush	Smoke + Vape	joint	Anxiety	livwell	
Second use	8 Am	All	Bud + Concentrate	" "	Smoke + Vape	joint	Anxiety	livwell	
Third Use	12pm	Both + Hybrid	Bud + Conc.	" "	Smoke	joint	" "	livwell	
Fourth Use	2pm	Indica	Bud	" "	Smoke	joint	" "	livwell	
Fifth Use	4pm	Indica	Bud	" "	Smoke	joint	" "	livwell	
Sixth Use	6pm	Indica	Bud	" "	Smoke	joint	" "	Livwell	
Seventh Use	7pm	Indica	edible + Bud	" " Sweet Grass	Smoke + EAT	joint + 10-30mg	" "	livwell	
Final Use of the Day	8pm – 12mn	Indica	edible + Bud	" " Sweet Grass	Smoke + EAT	joint + 10-30mg cookie	" "	livwell	

Cannabis Self-Titration

Recreation vs Medical differ in the target result of the exposure, being high/calm/sedated/relaxed vs achieving a therapeutic effect such as control of pain or anxiety but they have things in common

Self-Titration is complex and is effected by many factors;

- What is used
  - Strain; cannabinoid composition, other molecular factors
  - Form; bud, concentrate, other forms
- How is it used
  - Temperature effects the exposure so method of use effects exposure
  - smoke vs filtering through liquid vs vape vs eat vs tincture vs dab vs….
- Route of exposure
  - lungs vs skin vs digestion

Cannabis and Self-Titration

In the real world

A convenience sample of 121 current and former cigarette smokers surveyed, participants in a lung health study in Denver at NJH. 33 reported cannabis use >1 day per month the number of uses per day and the reason for that use.

Uses Per Month	Uses Per Day	Reason For Use
2	1	sleep, rec, pain, relax
2	1	rec
2	2	sleep, nausea, pain, rec
3	1	pain
5	1	pain
6	1	sleep, pain
6	1	rec
10	1	pain
10	1	anxiety, rec
10	1	pain
10	1	rec
11		sleep, pain, rec
13	1	sleep, pain
15	1	pain
15	1	pain
15	1	rec
15	1	sleep, anxiety
15	2	rec
17	3	rec
20	1	pain, rec
20	1	sleep, pain
20	2	relax, appetite, pain
20	3	rec
25	3	pain
26	3	sleep, rec
29	1	pain
30	1	pain
30	2	sleep, pain
30	3	pain, PTSD
30	3	sleep, appetite, relax
30	4	sleep, nausea, stress, anxiety, appetite
30	4	pain
30	5	pain, cancer, sleep

Cannabis Pharmacokinetics

- Smoking turns ~50% of the THC into smoke that is inhaled
  - Remainder lost to heat an smoke that isn't inhaled
- ~50 of smoke that is inhaled is exhaled
- The bioavailability of THC is between 10% and 25%
- Serum THC levels rise immediately and fall rapidly back to baseline ~3 hours later
- Edible bioavailability is 5-20%
- Serum THC peaks after edible consumption between 1 and 3 hours later

Dosage – industry http://www.cheebachews.com

- Each Cheeba Chew is cut within precise weight tolerances, ensuring consistent medicinal effects every time for patients. We have perfected our process to consistently make the safest pharmaceutical grade cannabis extract possible, while activating 98%+ of the available cannabinoids. Every single batch of extract is tested for THC, CBD, and CBN content. We also test with edibles on a monthly basis to ensure that we are sticking to our promise of making the most potent and consistent cannabis edible on the market.

- *Dosage Information (these are estimates for an average tolerance, effects can vary greatly from one person to another)*
- Single Dose (17.5mg THC) – 1-2 bowl hits
- Double Dose (35mg THC) – 3-4 bowl hits
- Quad Dose (70mg THC)- Joint to yourself
- Deca Dose (175mg THC) – High Tolerance Patients Only

- If it's your first time trying a Cheeba Chew we recommend 17.5mg THC/single dose, or 1/4 of a Quad Dose Chew. We never recommend consuming a whole Quad Dose your first time taking Cheeba Chews. With the correct dose, effects typically last between 2 – 6 hours.

- Time for Cheeba Chews effects to be felt vary greatly from one patient to another. Most will start to feel the effects around 30mins, but sometimes it can take 3hrs. This is dependent on how your individual body reacts to Cannabinoids. What you ate, and the amount of cannabis you smoked/consumed during the past 24 hours play a major role. Every patient is different.

Topics

- Background
  - History, Advocacy & Legislative Action
- Cannabinoids
  - Endocannabinoid system
  - Exogenous cannabinoids
- Cannabis Biology
  - Cannabis as a consumable product
- Cannabis as a potential Therapeutic Agent

What is a therapeutic agent;
a therapeutic agent is a compound with a beneficial and desirable effect when used in some way.

19. The above-named patient has been diagnosed with and is currently undergoing treatment for the following chronic, debilitating medical condition **or** has a chronic, debilitating disease or medical condition that produces one or more of the following:

☐ a. Cancer ☐ b. Glaucoma ☐ c. HIV or AIDS positive
☐ d. Cachexia* ☐ e. Severe nausea* ☐ f. Seizures*
☐ g. Persistent muscle spasms* ☐ h. Severe pain*

20. Etiology is required for medical conditions with an asterisk (*), if known.
Etiology: _____ **or** ☐ Etiology unknown.

Potential Negative Associations

- Addiction potential; heavily investigated and published broadly
- Pulmonary effects; primarily symptomatic (e.g. cough and phlegm) and not functional (e.g. FEV_1 ,FVC or FEV_1/FVC) or causative for emphysema outside of cigarette smoking
- Cardiovascular; evidence to show a negative effect of overstimulation of the endocannabinoid system (opposing effects of CB-1 vs CB-2 in cardiac tissue possibly associated with exogenous cannabinoids)

Nausea and Appetite

- Cancer chemotherapy related nausia
- HIV/AIDS related cachexia

Pain

- Neuropathic pain (RTC trials of cannabis)
  - Diabetic neuropathy
  - HIV/AIDS
  - Post-traumatic injury
  - Cancer
  - Dental
  - Multiple Sclerosis

Muscle

- Multiple Sclerosis spasticity and tremors
- Parkinson’s Disease tremors

Gastrointestinal

- The gut is strongly effected by the endocannabinoid system making diseases effecting the gut potential targets of endocannabinoid modulating medications or exogenous cannabis
  - Crohn’s Disease
  - Celiac Disease
  - Inflammatory Bowel Disease

Sleep

- Many studies, trials and observational measures of cannabis users mention altered sleep, many positive (sleep onset), some negative (sleep quality).
- Our study is investigating sleep in people using cannabis specifically to effect their sleep.

Neurological effect

- CBD decreased risk for impairment due to stroke in CB-1 ablated animals
- CB-2 receptor stimulation may provide neural anti-inflammatory effects
- CBD may be neuroprotective through other pathways outside of directly binding CB-1 and CB-2 (e.g. other endocannabinoid triggers and receptors)
- These effects are altered by tolerance and “the psychoactive effects of cannabis may be prohibitive for neuroprotection “
- Cannabis impairs cognition and its use in people with existing cognitive impairment may not be warranted

In summary

- Cannabis is a botanical that is very complicated and we have a long way to go to understand how the hundreds of molecules in the plant interact to generate effects in humans
- The endocannabinoid system is very complex and some drugs attempting to access it have failed due to cardiovascular and other adverse effects
- Self-titration of cannabis exposure in people is complex and subject to change due to tolerance
- Edible exposure can vary by person

Questions?

Ongoing Studies in Colorado

Project title	Primary investigator
Do Adolescents and Young Adults with **Inflammatory Bowel Disease** Benefit from Use of Marijuana?	Edward J. Hoffenberg, University of Colorado School of Medicine at the Anschutz Medical Campus, Children's Hospital Colorado
A Randomized, Double-blind, Placebo-controlled Crossover Study of Tolerability and Efficacy of Cannabidiol (CBD) on **Tremor in Parkinson's** Disease	Maureen A. Leehey, Department of Neurology, University of Colorado School of Medicine at the Anschutz Medical Campus
Treating **PTSD** with Marijuana: Clinical and Functional Outcomes	Marcel O. Bonn-Miller, Dept. of Psychiatry, University of Pennsylvania, and VA National Center for PTSD
Cannabidiol (CBD) and **Pediatric Epilepsy**	George Sam Wang, Department of Pediatrics, University of Colorado School of Medicine at the Anschutz Medical Campus and Children's Hospital Colorado
Medical Marijuana in the **Pediatric Brain Tumor** Population (palliative care)	Nicholas Foreman, Dept. of Pediatrics, Pediatric Neuro-oncology, Children's Hospital Colorado
Use of Medicinal Cannabinoids as Adjunctive Treatment for Medically Refractory Epilepsy (**pediatric epilepsy**)	Kelly Knupp, Dept. of Pediatrics, Children's Hospital Colorado and University of Colorado School of Medicine at the Anschutz Medical Campus
Placebo-controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment- Resistant Post Traumatic Stress Disorder (**PTSD**)	Marcel O. Bonn-Miller, University of Pennsylvania and VA National Center for PTSD
A Double Blind, Placebo-Controlled Cross Study Comparing the **Analgesic Efficacy** of Cannabis versus Oxycodone	Emily Lindley, Dept. of Orthopedics, University of Colorado School of Medicine at the Anschutz Medical Campus
Colorado Cannabis Cohort: Efficacy, Safety, and Usage Patterns of Medical Marijuana for **Sleep**	Russell Bowler, National Jewish Health Gregory Kinney University of Colorado CSPH

CDPHE and Retail Marijuana (C.R.S. 25-1.5-111 & SB-13-283)

Retail Marijuana Public Health Advisory Committee

An appointed panel of scientists and health care professionals with expertise in cannabinoid physiology to monitor emerging health effects and other information.

- Systematically review the scientific literature
- Review public health surveillance data
- Recommend public health related policies
- Recommend public health surveillance activities
- Identify research gaps important to public health

COLORADO
Department of Public Health & Environment

CDPHE Goal
Translate Science into Public Health

- Develop consensus statements that convey the quality and quantity of scientific evidence behind a finding
- Translate consensus statements into plain language statements in a standardized way
- Guide the development of evidence-based prevention campaigns
- Analyze surveillance data using high quality methods

Potential targets of medical marijuana research

- Positive effects:
  - Stroke recovery
  - Glaucoma
  - Pain management
  - Nausea reduction for chemo patients
  - Muscle relaxant for spastic muscles
  - Seizure control

- Negative effects:
  - Drugged driving
  - Impaired brain development from long
    term use in teenagers
  - lung damage from the smoke
  - ER visits for children consuming edibles

What can we learn from this natural experiment?

- Large population
- Long term self titration of treatment
- Consistent patterns of treatment aimed at therapeutic benefit
- Broad public communication

Potential Weaknesses

- Tolerance
- Abuse
- Exposure of at risk populations
- Difficulty moving beyond anecdotal data

Table 1. Effects of regular use of marijuana alone on chronic respiratory symptoms and lung function in comparison with nonsmoking control subjects

Symptoms
Increased prevalence of chronic cough or sputum (17, 18, 20–22), wheezing (17, 18, 20–22), and shortness of breath (20)
Increased incidence of acute bronchitic episodes (17) or clinic visits for acute respiratory illness (19)
Lung Function
No difference in FEV_1 or FVC (17, 20, 21)
Increase in FVC (23, 27, 29)
Increase in FEV_1 (23)
Decrease in FEV_1/FVC (18, 20)
No difference in single-breath nitrogen washout measures (17, 25)
No differences in FRC, TLC, or RV (17, 21)
Increases in FRC, TLC, and RV (27)
Increase in Raw and decrease in SGaw (17, 25, 27)
No difference in D_{LCO} (17, 21, 27)

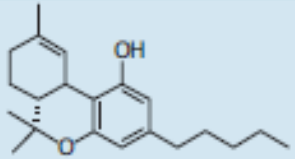
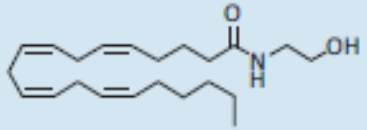
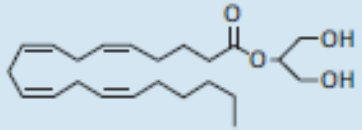
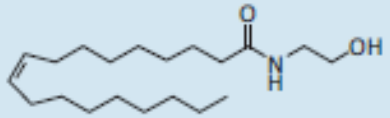
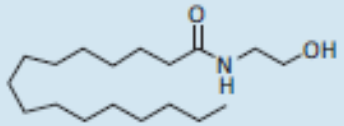
Definition of abbreviations: D_{LCO} = single-breath diffusing capacity for carbon monoxide; FRC = functional residual capacity; Raw = airway resistance; RV = residual volume; SGaw = specific airway conductance; TLC = total lung capacity.

Tashkin Marijana Annals of ATS 2012

Research Gaps

- Research studies on all outcomes should evaluate **occasional users**, separate from **regular** or **heavy users**.
- Research studies on all outcomes should include **former users** and **continuing users** with comparable prior use frequency and age of onset to help separate **long-term effects** from the effects of **current use**.
- Additional studies with more varied **time periods of abstinence** are needed to assess the duration of **cognitive impact** of marijuana use.
- Studies evaluating the potential psychological outcomes of marijuana use should have separate evaluations of **males and females**.
- More studies are needed to assess the risk of increasing use or becoming addicted for occasional users, based on **age of onset**.

Table 1. Major (endo)cannabinoids and the main metabolic enzymes of the ECS

Name	Chemical structure
THC	
AEA	
2-AG	
OEA	
PEA	

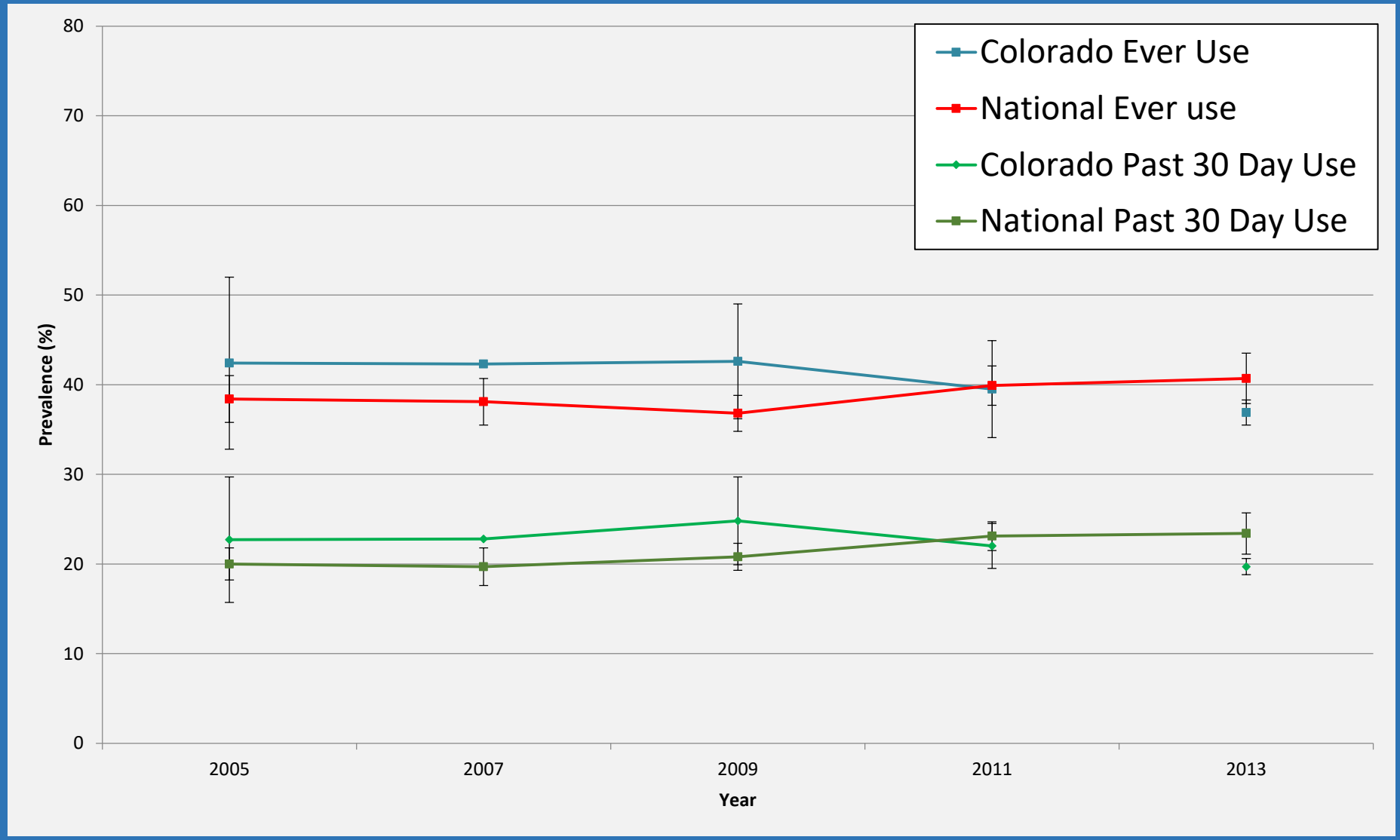
Endocannabinoid signaling at the periphery: 50 years after THC
Mauro Maccarrone, Itai Bab, Tamás Bíró, Guy A. Cabral, Sudhansu K.Dey, Vincenzo Di Marzo, Justin C. Konje, George Kunos, Raphael Mechoulam, Pal Pacher, Keith A. Sharkey, Andreas Zimmer, Trends in Pharmacological Sciences Volume 36, Issue 5, May 2015

Spinal Pain Pilot Data

- Asked 150 participants in a spinal pain clinic whether they used cannabis for pain management, 35 reporting cannabis use for pain management
  - 45% had a red card
  - 90% reported smoking, 45% eating and 29% vaporizing
  - 81% reported “cannabis is more effective than narcotics”
  - 89% reported “cannabis is more effective than NSAID”
  - 88% reported “cannabis is more effective than nerve targeted pharmaceuticals”

Emily Lindley, University of Colorado Denver

Healthy Kids Colorado Survey



THC vs. THCa

Marijuana flower is often said to contain THC, but this is not technically true. The plant contains "THCa", which is not psychoactive in its natural state. THC is created through decarboxylation.

Decarboxylation is the process of heating THCa, which naturally occurs in cannabis plants, to activate THC that can be absorbed in the body through ingestion. In the process, the THCa loses carbon and oxygen molecules, and about 12.3 percent of its weight.

This weight reduction is calculated using the molecular weight of THCa and THC.

Although the report authors refer to both THC and THCa throughout the report, the reader can interpret the terms as synonomous.

https://www.colorado.gov/pacific/sites/default/files/MED%20Equivalency_Final%2008102015.pdf