The Endocannabinoid System & Marijuana: Myths and Realities

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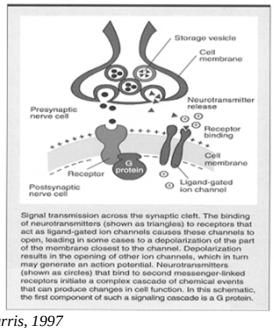
What *is* weed?

- Americans for Safe Access, a medical marijuana advocacy group, stated in its website article "Research: Definitions and Explanations" (accessed Dec. 7, 2006):
- *"...there are 483 different identifiable chemical constituents known to exist in cannabis. The most distinctive and specific class of compounds are the cannabinoids (66 known), that are only known to exist in the cannabis plant.*

  Other constituents of the cannabis plant are: nitrogenous compounds (27 known), amino acids (18), proteins (3), glycoproteins (6), enzymes (2), sugars and related compounds (34), hydrocarbons (50), simple alcohols (7), aldehydes (13), ketones (13), simple acids (21), fatty acids (22), simple esters (12), lactones (1), steroids (11), terpenes (120), non-cannabinoid phenols (25), flavonoids (21), vitamins (1) [Vitamin A], pigments (2), and elements (9).

  The very most of these compounds are found in other plants and animals and are not of pharmacological relevance with regard to the effects exerted by cannabis preparations."

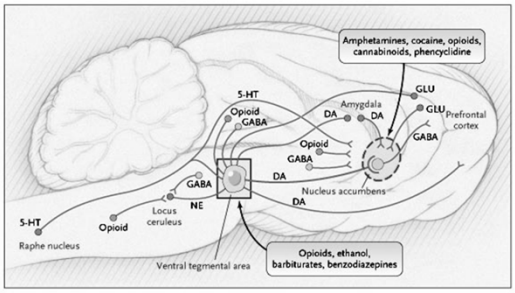
The Architecture: The Synapse



Signal transmission across the synaptic cleft. The binding of neurotransmitters (shown as triangles) to receptors that act as ligand-gated ion channels causes these channels to open, leading in some cases to a depolarization of the part of the membrane closest to the channel. Depolarization results in the opening of other ion channels, which in turn may generate an action potential. Neurotransmitters (shown as circles) that bind to second messenger-linked receptors initiate a complex cascade of chemical events that can produce changes in cell function. In this schematic, the first component of such a signaling cascade is a G protein.

- *from Mihic & Harris, 1997*

Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse



Camí, J. et al. N Engl J Med 2003;349:975-986

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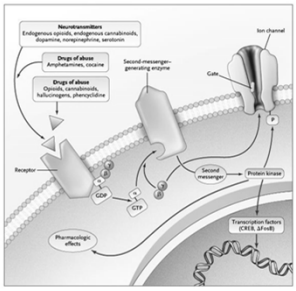
Metabotropic Mechanisms of Action of Drugs of Abuse



Camí, J. et al. N Engl J Med 2003;349:975-986

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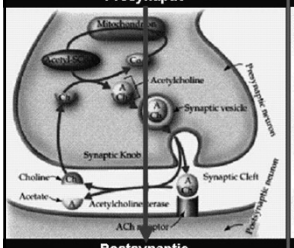
Contrast Between Classic Neurotransmission and the Endocannabinoid System

Classic Neurotransmitter: Acetylcholine (ACh)

Presynaptic

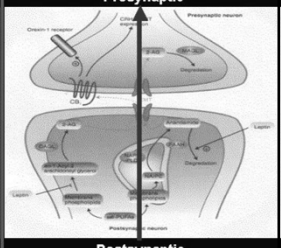


Postsynaptic

Reprinted with permission from Anaesthesia UK Website. The neuromuscular junction. At: www.frca.co.uk.

EC System

Presynaptic



Postsynaptic

Di Marzo V et al. *Nat Neurosci*. 2005;8:585-589.

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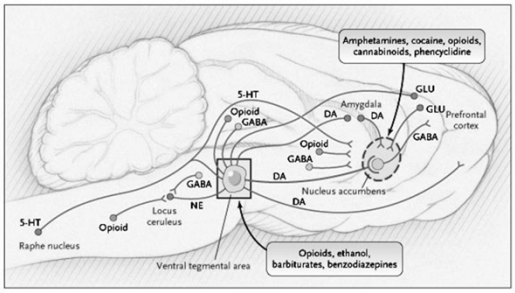
Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse



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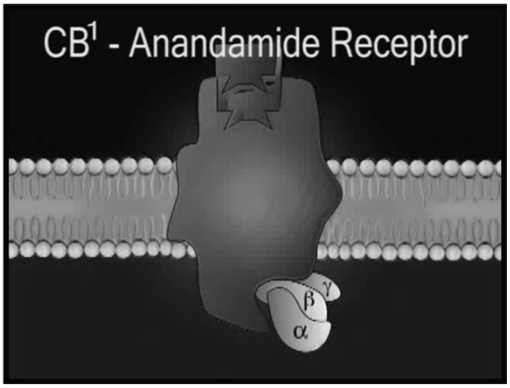
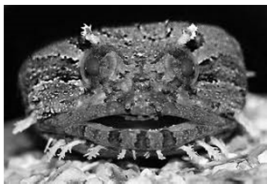


The Endocannabinoid System:
What's the connection?!?!?



Summary of Basic Endocannabinoid Biology

- The EC system is overactivated in human obesity and in animal models of genetic and diet-induced obesity
- EC system stimulation centrally and peripherally favors metabolic processes that lead to:
  - Weight gain, lipogenesis, insulin resistance, dyslipidemia, and impaired glucose homeostasis
  - CB_1 blockade reverses or ameliorates these effects in preclinical models
- Central and peripheral EC system dysfunction provides a biological basis for therapeutic CB_1 receptor blockade

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Summary of Basic Endocannabinoid Biology

- The EC system is a recently characterized physiologic system
  - 2 well-defined receptors: CB_1 and CB_2
  - 2 well-defined endocannabinoids: AEA and 2-AG
- ECs are synthesized on demand
- ECs act locally in neurons as retrograde messengers
  - Released from postsynaptic cells
  - Bind to and activate CB_1 receptors located presynaptically
  - Degrade rapidly
- In nonneuronal cells, such as adipose tissue, the EC system appears to have additional modulatory effects by influencing gene transcription of certain proteins such as adiponectin

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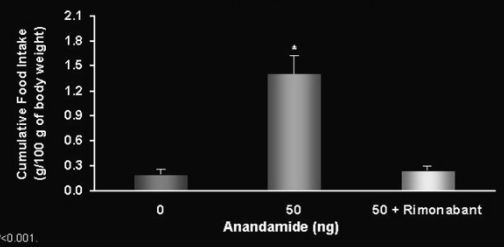
Hypothalamic CB_1 Receptor Activation by Endocannabinoids Stimulates Food Intake

Anandamide injected into hypothalamus induces hyperphagia in presatiated rats



*P<0.001.

Values are means ± SEM.

Adapted with permission from Jamshidi N et al. *Br J Pharmacol.* 2001;134:1151-1154.

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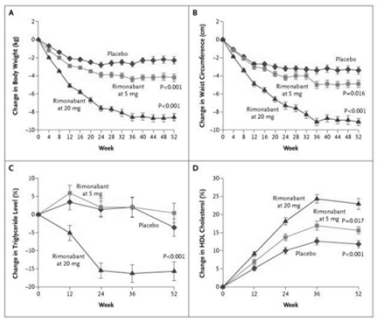
Effect of Placebo or Rimonabant for 52 Weeks on Body Weight, Waist Circumference, Plasma Triglyceride Levels, and High-Density Lipoprotein (HDL) Cholesterol Levels



Despres J et al. N Engl J Med 2005;353:2121-2134

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Endocannabinoid System: Effects of CB_1 Antagonism

Site of Action	Mechanism(s)	Clinical Implications
Hypothalamus/ nucleus accumbens	↓ Food intake	↓ Body weight ↓ Waist circumference
Adipose tissue	↑ Adiponectin ↓ Lipogenesis	↓ Visceral fat ↓ Dyslipidemia ↓ Insulin resistance
Muscle	↑ Glucose uptake ↑ O_2 consumption	↓ Insulin resistance
Liver	↓ Lipogenesis	↓ Dyslipidemia ↓ Insulin resistance
GI tract	↑ Satiety signals	↓ Body weight
Pancreas	Potential effect on insulin secretion	Potential effect on glucose/insulin metabolism

Adapted with permission from Woods SC. *Am J Med.* 2007;120:S19-S25. Juan-Pico P et al. *Cell Calcium.* 2006;39:155-162.

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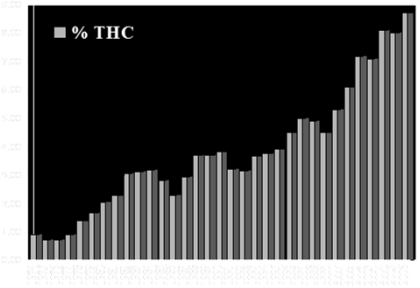
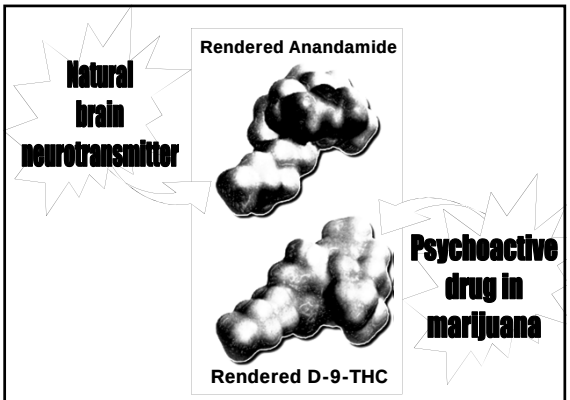
Types of Cannabis

- Three types:
  - Ruderalis (least THC)
  - Indica } (approx same THC)
  - Sativa } 1% THC : 1% CBD
- Some First People and explorers believe Sativa to be indigenous to the Americas *(Jacques Cartier, 1534).*

THC Potency 1974-2006

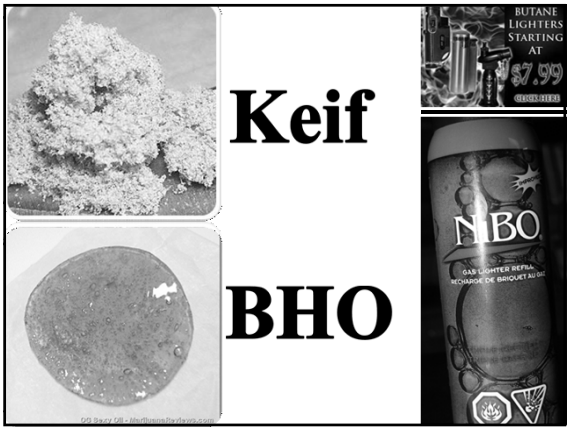


National Drug Intelligence Center,
University of Mississippi Marijuana Potency Monitoring Project (1974-2006)



Natural vs. Man made

1%THC vs. 37.2%THC
1%CBD 1-5%CBD



Marijuana Epidemiology

- National Data from NSDUHAbout 34.2%-41.9% of Americans have used marijuana (2000-2011)
- About 10.10%-11.6% of Americans have used in the past year (2000-2011)
- About 5.8%-7.1% of Americans are regular users (past month) (2000-2011)
- About 4% of marijuana users are chronic users, 5-7 days per week. (2000-2011)

SAMHSA National Survey on Drug Use and Health, 2002-2011)

National Survey on Drug Use and Health 2012 State Data Report
Eric Martin, MAC, CADC III, CPS (resource: 2010-2011 NSDUH's *n≈72,000x2 ≈ 144,000*)

Kentucky: Past 30 day marijuana use 12 and older		Kentucky: Past year marijuana use 12 and older	
Alaska	11.84%	Alaska	17.51%
Vermont	10.57%	Vermont	16.99%
Colorado	11.29%	Colorado	16.93%
Rhode Island	10.80%	D.C.	16.14%
Oregon	10.21%	Oregon	15.79%
Kentucky	**5.08%**	**Kentucky**	**8.80%**

Recent 43rd

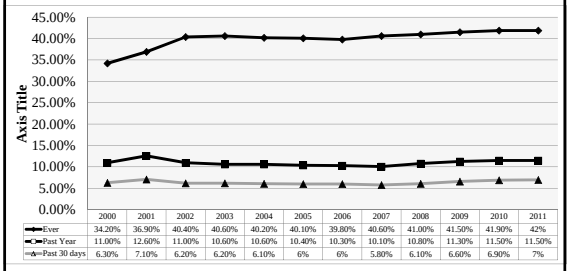
Past Year 47th

About 1 out of 20 Kentuckians 12+ in the past 30 days

About 1 out of 11 Kentuckyians 12+ In the past year

U.S. Marijuana Consumption Prevalence Rates

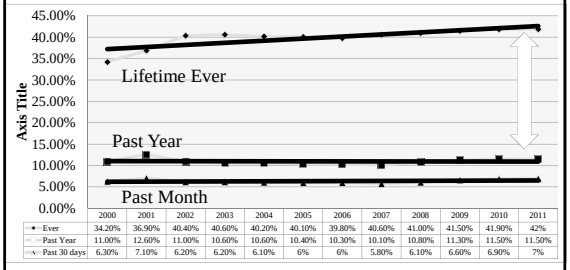
(n≈864,000 [72,000/yrX12yr])



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Ever	34.20%	36.90%	40.40%	40.60%	40.20%	40.10%	39.80%	40.60%	41.00%	41.50%	41.90%	42%
Past Year	11.00%	12.60%	11.00%	10.60%	10.60%	10.40%	10.30%	10.10%	10.80%	11.30%	11.50%	11.50%
Past 30 days	6.30%	7.10%	6.20%	6.20%	6.10%	6%	6%	5.80%	6.10%	6.60%	6.90%	7%

U.S. Marijuana Consumption Prevalence Rates

(n ≈ 864,000 [72,000/yrX12yr])



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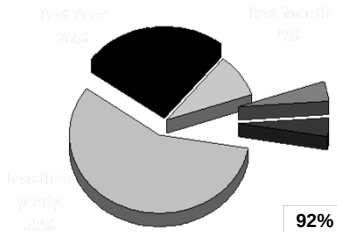
Past Year	11.00%	12.60%	11.00%	10.60%	10.60%	10.40%	10.30%	10.10%	10.80%	11.30%	11.50%	11.50%
Past 30 days	6.30%	7.10%	6.20%	6.20%	6.10%	6%	6%	5.80%	6.10%	6.60%	6.90%	7%

Of the 42% of Americans who smoke marijuana

(approx. 113 million Americans, 12 and older)



92% of marijuana users consume marijuana less than weekly

What percentage of the population develops Marijuana Addiction, Abuse, Dependence, etc..

- NORML reported that "approximately 8% of marijuana users develop a pattern of abuse and dependence problems".

- 8-9% meet diagnostic criteria for cannabis dependence, Cannabis Dependence: Its Nature, Consequences and Treatment, Marlatt, 2006

NORML, recorded testimony to Congress 1999
Cannabis Dependence: Its Nature, Consequences and Treatment, Marlatt, 2006

Are there valid medical uses for endocannabinoid drugs?

Marinol

- *"Marinol (dronabinol) is the only cannabinoid with approval for marketing in the United States....*
- *Marinol is manufactured as a capsule containing THC in sesame oil; it is taken orally. It was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA approved marketing of dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS. The preclinical and clinical research on THC that culminated in the FDA's 1985 approval was supported primarily from the National Cancer Institute (NCI), whose research support goes back to the 1970s....*
- *Marinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps needed for purification. The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10-20% of an oral dose reaches the systemic circulation.*
- *The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing. In contrast, inhaled marijuana is rapidly absorbed....*
- *Marinol's most common adverse events are associated with the central nervous system (CNS); anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality."*

- http://medicalmarijuana.procon.org/view.answers.php?questionID=000089

Other scientific trials

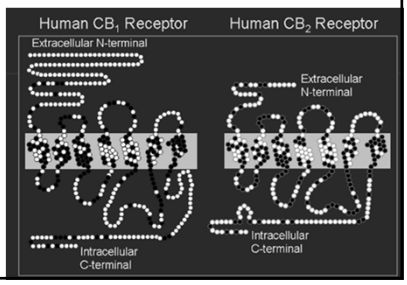
- Rimonabant improves tobacco cessation and blocks inhibition produced by alcohol in amygdala projections
- Modulation of CNR1 gene receptor reduces cocaine dependence and IV drug use
- Stimulation/blockade of EC systems modulates GABA, glutamate and dopamine systems

More scientific studies

- "Knockout" of CB1 receptors blocks social withdrawal in PCP-induced schizophrenic activity in mice
- Chronic stimulation of CB2 liver receptors results in regression of fibrosis in cirrhosis
- High incidence of Q63R polymorphism of the CB2 gene in Japanese alcoholics and depressed subjects

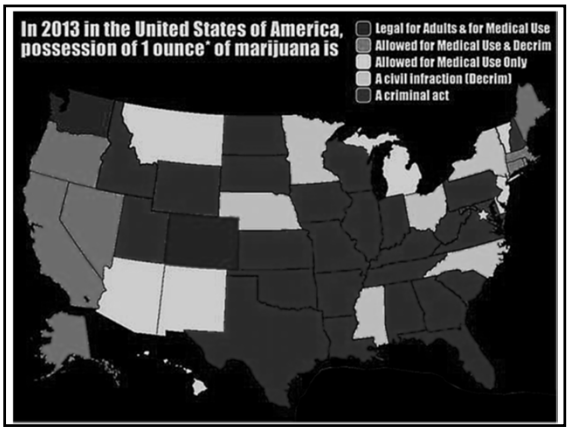
CB2 and pain

- CB2 agonists (AM1241) inhibit nociception without producing CNS effects
  - The effects do not cross-over to morphine effects
- CB2 appears to modulate:
  - Acute pain
  - Pain associated with nerve injury
  - Chronic inflammatory pain
  - Post surgical pain
  - Cancer pain



Sativex®

- Cannabis extract 1:1 THC:CBD; also terpenes, flavonoids, etc.
- Approved in Canada for adjunctive treatment of MS neuropathic pain and for cancer pain;
- US advanced clinical trials in cancer pain began Nov. 2007
- Oromucosal spray
- Intermediate onset of action, 15-40 minutes
- Allows patients to titrate their dose



NEW MEXICO DEPARTMENT OF HEALTH

Purpose of the Program

The Lynn and Erin Compassionate Use Act:

"The purpose of the act is to allow the beneficial use of medical cannabis in a regulated system for alleviating symptoms caused by debilitating medical conditions and their medical treatments"

Established July 2007

New Mexico Medical Cannabis Program

Building A HEALTHY New Mexico!

Qualifying Conditions

Original Conditions

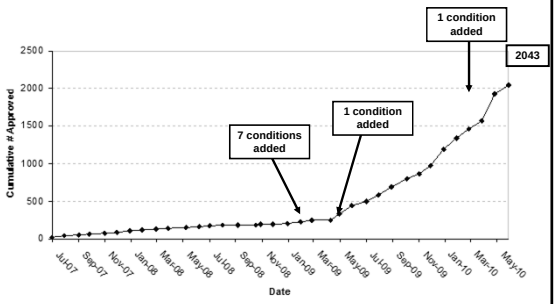
- Cancer
- Glaucoma
- HIV/AIDS
- Multiple Sclerosis
- Epilepsy
- Spinal Cord Damage with Intractable Spasticity
- Patients in hospice care

Conditions Added

- Painful peripheral neuropathy
- Intractable nausea/vomiting
- Severe anorexia/cachexia
- Hepatitis C infection *currently receiving antiviral treatment*
- Crohn's disease
- Post-traumatic Stress Disorder
- Amyotrophic Lateral Sclerosis
- Severe Chronic Pain
- Autoimmune mediated inflammatory arthritis

Building A HEALTHY New Mexico!

Numbers of Licensed Patients



Building A HEALTHY New Mexico!

The 7% Solution to the Recession!!!

- Currently before the NM State legislature is a proposal to apply a 7% "gross receipts" tax on producer revenues
- Indistinguishable from tobacco or alcohol taxes
- Similarly "addictive" as a State policy
- *About as medically scientific as chewing chicona bark to get the antimalarial effect of quinine.*

Considerations not given in the original "compassionate use" strategy

- Effect of chronic smoke inhalation on pulmonary function
  - Pletcher et al., 2012, JAMA 307: 173-181
- Higher incidence of testicular germ cell tumors in adolescent males with chronic use
  - Daling et al., 2009, **Cancer 115:**1215–1223
- Impairment of driving and other "safety sensitive" functions
  - Schwope et al., 2012, J. Analytical Toxicology 36:405–412
  - Bosker et al., 2012, Addiction 107: 1837-44
- Lack of standards for interpretations of levels and "DUID"
  - State by State variations

State-by-State January 2011

So, Dr. Adair, what do you really think?

- Medical marijuana programs do disservice to patients by providing a mix of drugs and toxins without standards.
- The politics distract from potentially valid medical uses for endocannabinoid agonists/antagonists by not funding research, especially on the CB2 system.
- Potentially valid uses are trumped by the known addictive properties of CB1 activation.

Options for Second Opinions

Options for Second Opinions

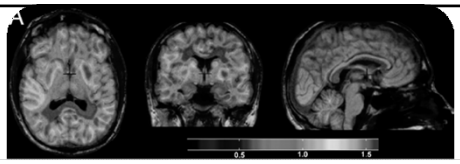
What about the illegal, nonmedical synthetics?

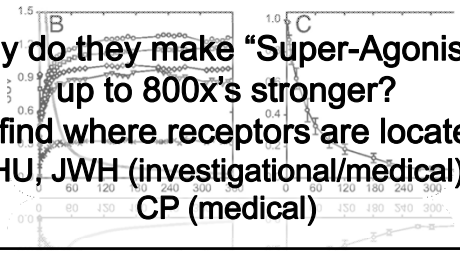
Nearly 100 Synthetic Cannabinoids

- AM-087
- AM-1221
- AM-1241
- AM-2201
- AM-2233
- AM-4030
- AM-411
- AM-630
- AM-679
- AM-694
- AM-855
- AM-905
- AM-906
- AM-919
- AM-938
- AM251
- AM404
- AMG-1
- AMG-3
- AMG-36
- AMG-41
- JWH-007
- JWH-015
- JWH-018
- JWH-019
- JWH-030
- JWH-051
- JWH-073
- JWH-081
- JWH-098
- JWH-122
- JWH-133
- JWH-147
- JWH-161
- JWH-164
- JWH-167
- JWH-171
- JWH-182
- JWH-193
- JWH-198
- JWH-200
- JWH-203
- JWH-210
- JWH-249
- JWH-250
- JWH-251
- JWH-307
- JWH-359
- JWH-398
- JWH-424
- A-40174
- A-41988
- BAY 38-7271
- BAY 59-3074
- BML-190
- HU-211
- HU-243
- HU-308
- HU-320
- HU-331
- HU-336
- CP-47
- CP-50
- CP-55

Including Oleamide…

*McDonald, RG. et al (2008). "Bioactive Contaminants Leach from Disposable Laboratory Plasticware". Science **322** (5903): 917.*





Why do they make "Super-Agonists" up to 800x's stronger?

To find where receptors are located.

HU, JWH (investigational/medical)

CP (medical)

- **Spice**
- **K2**
- **Genie**
- **Yucatan Fire**
- **Skunk**
- **Sence**
- **Smoke**
- **ChillX**
- **Earth Impact**
- **Gorillaz**
- **Galaxy Gold**
- **Space Truckin**
- **Solar Flare**
- **Moon Rocks**
- **Blue Lotus**
- **Aroma**
- **Scope**
- **Sky**
- **OG Potpourri**

Our K2 Blends Our Now 100% Legal Everywhere!
D.E.A. Compliant. All products comply with current and proposed legislation.
- new packaging -
View our entire collection as low as $7/gram
Make sure to try BLACK MAMBA the strongest k2 ever made
BUY NOW!
INTRODUCING BLACK MAMBA
THE STRONGEST K2
INCENSE EVER MADE!
As featured on...
& other countless publications
FOX NEWS

Booze in case she starts to come down
The world's biggest lighter
K2
Buy Now

Assignment

- In groups at your table,
- Make a list of all the “Quit-Talk” (quittin’ soundin’ stuff) that you heard.

How well did you listen?

What “Quit-talk” or “Consequences” did he present?

- PROS:
- CONS:

Inability to control consumption is – “loss of control” or, in other words an impulse control disorder or problem

MTP Sx in Diagnostic Assessment

(n=450 daily marijuana users, multi-site)

DIAGNOSTIC CRITERIA	%+
Persistent desire or one or more unsuccessful attempts to cut down or control use.	**96%**
Continued use despite knowledge of a physical or psychological problem cause or exacerbated by marijuana use	**95%**
A great deal of time spent in activities necessary to get, use, or recover from the effects of marijuana	**83%**
Withdrawal	**78%**
Marijuana taken in larger amounts or over a longer period than intended	**77%**
The need for markedly increased amounts of marijuana to achieve the desired effect (tolerance)	**68%**
Important social, occupation or recreational activities given up because of marijuana	**64%**

MTP Sx Client Checklist

MARIJUANA HAS CAUSED YOU …	%+
…to feel bad about your use	**90.2%**
…to have lower energy	**86.0%**
…to procrastinate	**86.0%**
…to experience Memory loss	**76.4%**
…to have lower productivity	**75.1%**
…to have lower self-esteem	**74.2%**
…to lack self-confidence	**68.4%**
…withdrawal symptoms	**61.1%**
…to experience problems with partner	**58.0%**
…to have financial problems	**48.9%**
…to have difficulty sleeping	**46.0%**
…to have problems with family	**44.4%**
…to neglect family	**38.7%**
…to have medical problems	**33.6%**
…to experience problems with friends	**26.4%**

Now, if nothing else, you understand……..

The "munchies"

Thank you!!!