Marijuana Use & Implications for Addictions

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Educational Objectives

- Increase understanding of marijuana production, pharmacology and toxicity
- Discuss endocannabinoid system and potential pharmaceutical agents
- Review medical marijuana laws
- Develop addiction treatment plan to address increased use of marijuana

Marijuana History

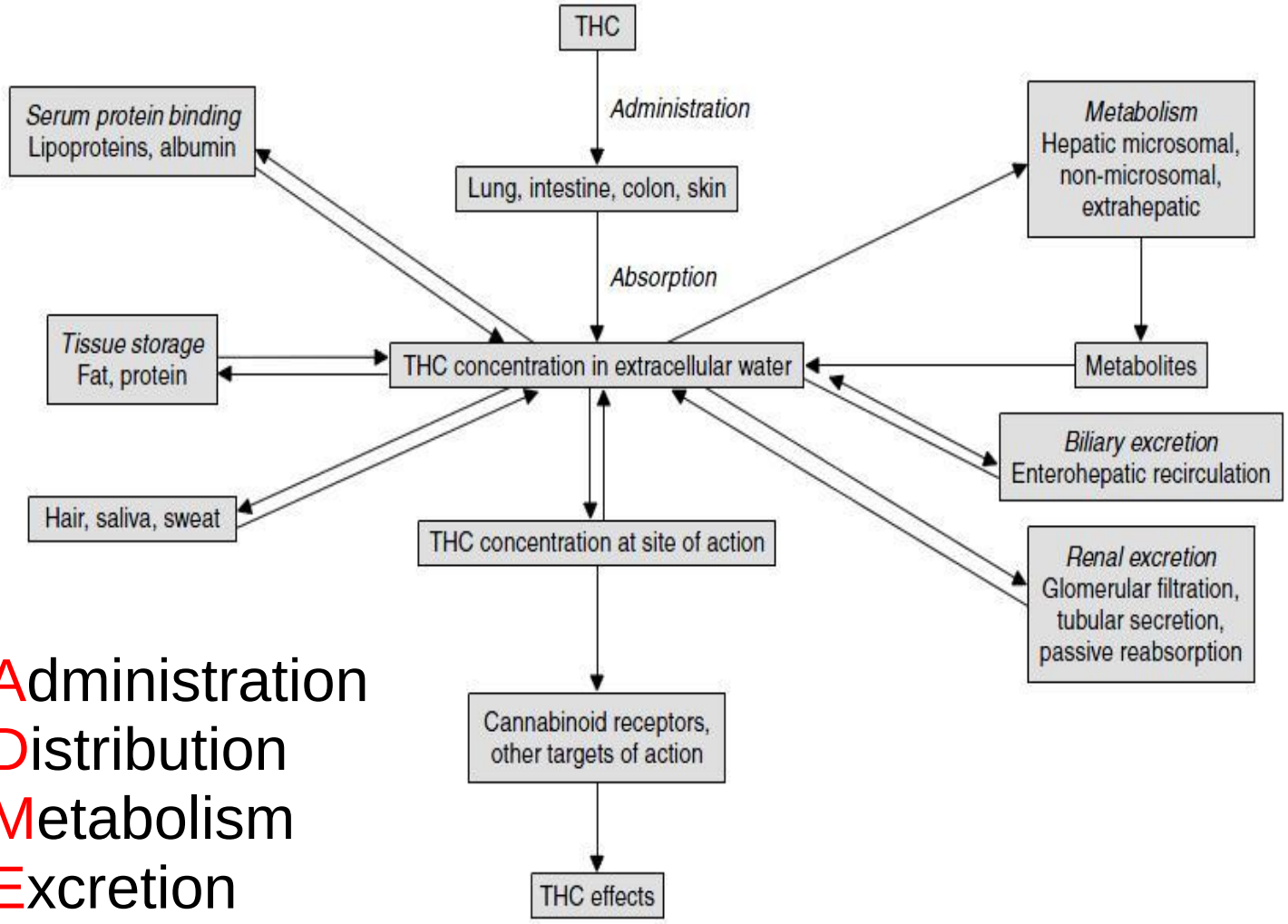
- **2373 BC:** Earliest reference by Chinese treatise on pharmacology
- **400 BC:** Its use of Cannabis in Rome
- **1765:** George Washington grew Hemp & experimented with its medical/intoxicating potency
- **1839:** Used by Professor Saughnessy as an appetite stimulant & anti-convulsant
- **1900:** Drug introduced and name reintroduced to USA by immigrant Mexican workers
- **1937:** Henry Anslinger, Commissioner of Bureau of Narcotics, campaigned against use of Marijuana
- **1937:** Federal govt. used Marijuana Tax Act & used taxes to outlaw the drug
- **Oct. 1969:** Gallup poll estimated 10 million Americans, half under the age of 21, had used the drug
- **1970:** Controlled Substance Act reported Marijuana had no potential for medical use

Pharmacology of Marijuana

- High lipid solubility (resin =oily)
  - Psychoactive effect occurs in brain = smart fat
- High potency
  - 1-2 mgs IV causes severe intoxication +hallucinations
  - Poor oral and smoking bioavailability -5%-20%
    - One joint =1-2 mg of THC x 10% = 100-200ng
- Pharmacokinetics varies by route of administration

  Street=route of administration Neighborhood=organ affected
  - Oral, often baked
    - Heat decarboxylates THC-COOH to form active THC
    - First pass metabolism of liver causes higher 11-OH THC
  - Smoked - most common
  - IV (only pure form of THC)
    - Shooting up marijuana = toxic = high fevers, shock, infection

Pharmacokinetics of THC



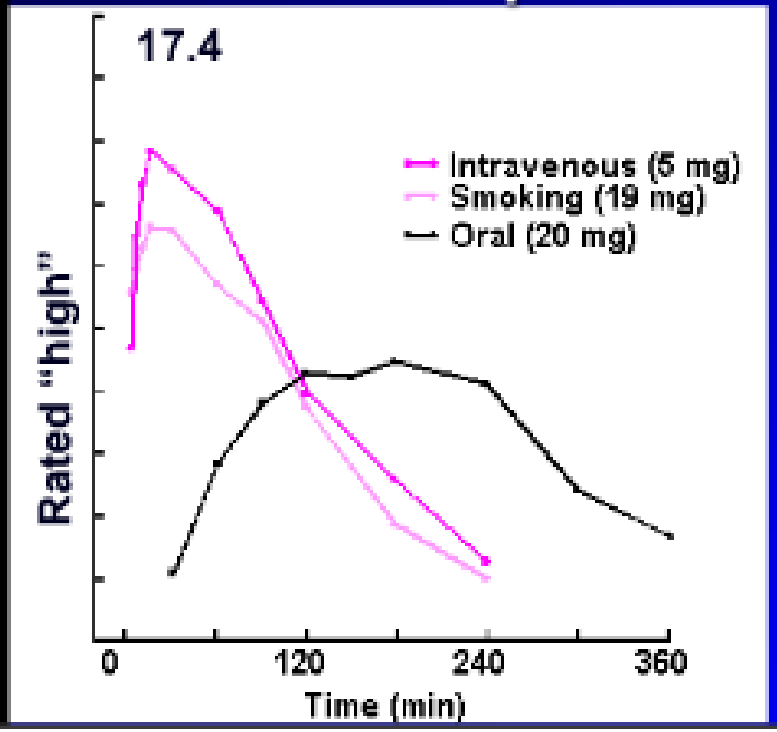
Administration
Distribution
Metabolism
Excretion

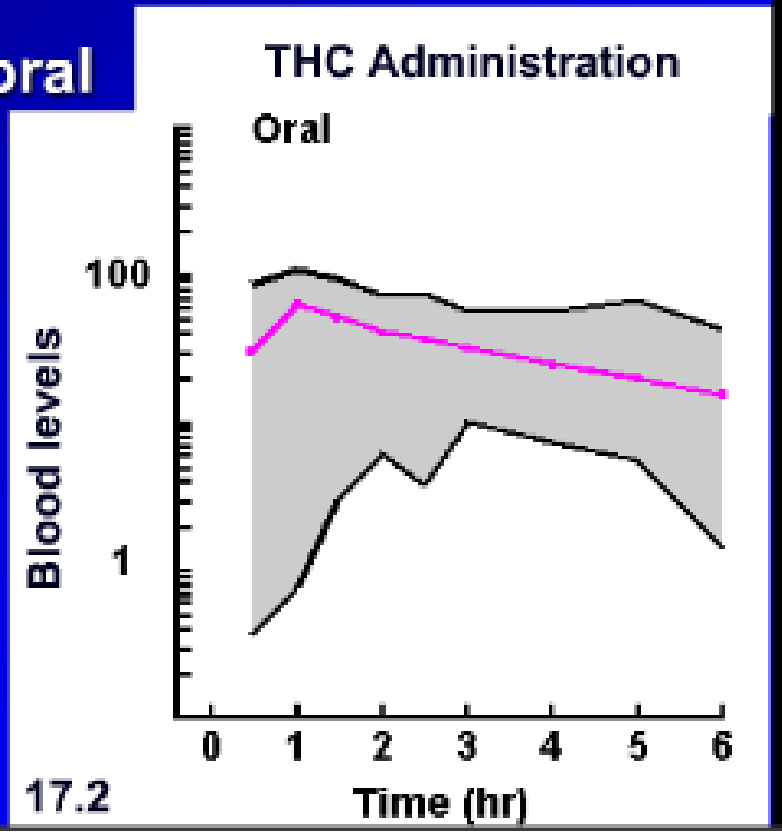
Grotenhermen , Clin Pharmacokinet (2003)

Pharmacokinetics

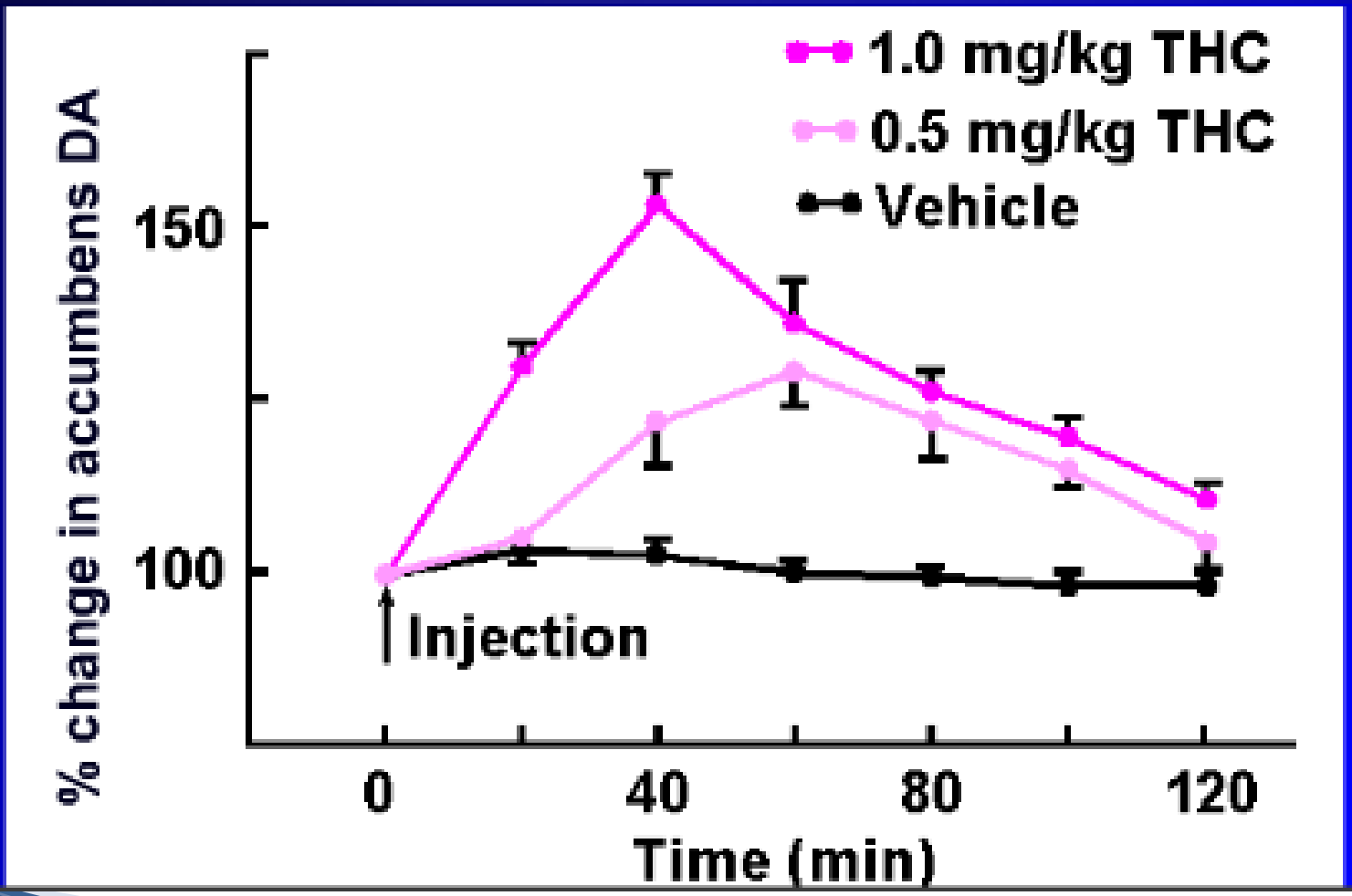
Absorption

- slow absorption with oral





Actions on DA systems

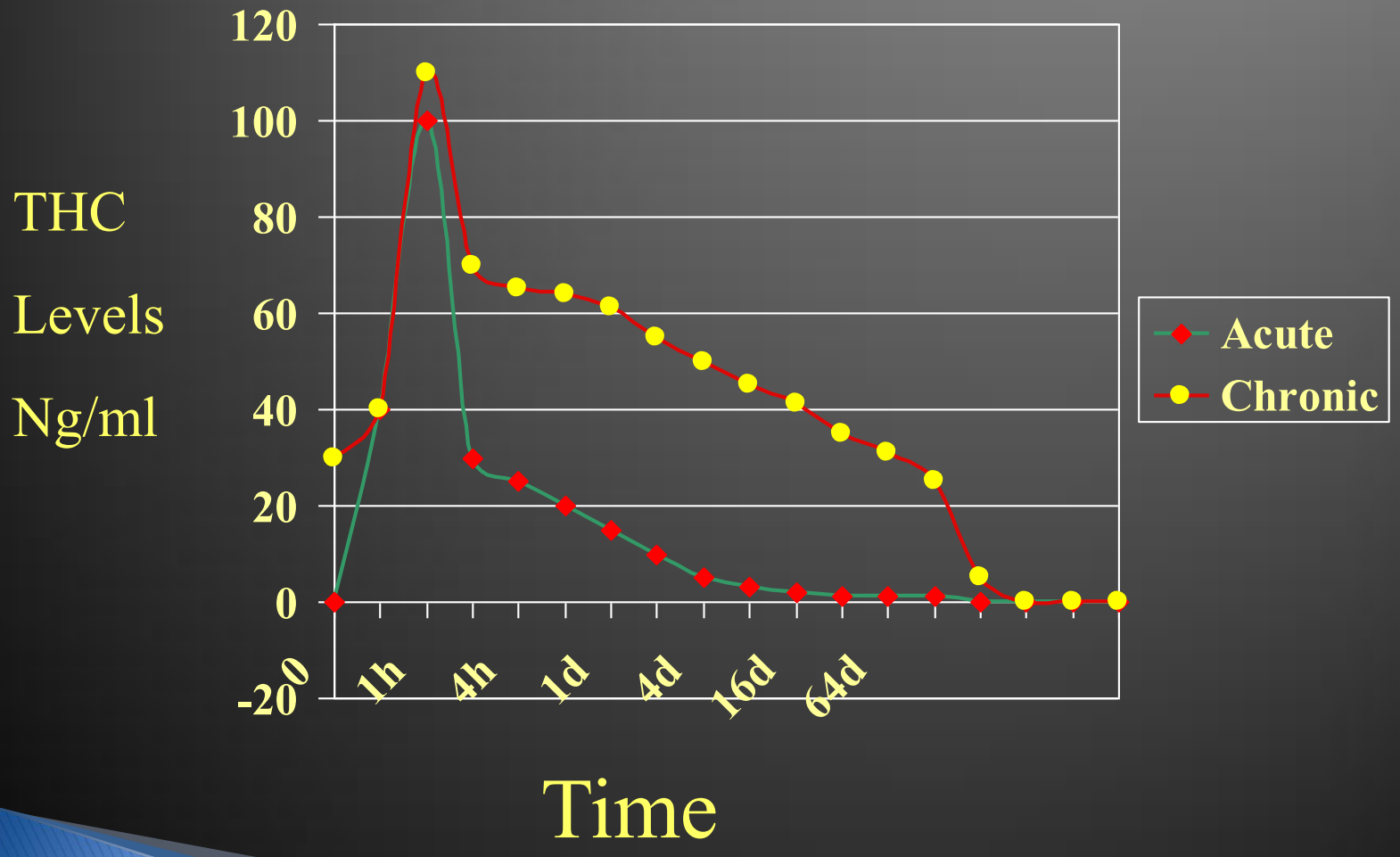


Absorption+Metabolism of Marijuana

Smoking marijuana is like having 2 drugs in one

- Fast acting and short duration of “high”
  - Smoke aerosol THC to lungs and then to brain
    - Peak effect in 5 -10 minutes because of high blood flow to brain
  - Rapid fall in levels via re-distribution to fat and muscle
    - 5-10% of peak levels occur with one hour
- Long lasting drug in body - large volume of distribution
  - 30% to 50% of THC dose is stored for 5-7 days after single dose
  - Slow release from fat stores
- Complex metabolism with long acting metabolites
  - Half life (T1/2) of THC = 20 hours
  - T1/2 of major metabolites 11-OH THC = 2-5 days
  - Inactive cannabinoid metabolites T1/2=5-10 days

THC levels in urine over time



Metabolism of Cannabinoids

CYP 2C9 – Major metabolic pathway- contributes to 18% of all P450 microsomes
CYP 3A4 and CYP 1A2 - also involved in metabolism

Greater than 50 SNP's identified – Inherited differences in metabolism

Allele frequencies(%) of CYP2C9 polymorphism

	African-American	Black-African	Pygmy	Asian	Caucasian
CYP2C9*2	2.9	0-4.3	0	0-0.1	8-19
CYP2C9*3	2.0	0-2.3	0	1.1-3.6	3.3-16.2
CYP2C9*5	0-1.7	0.8-1.8	ND	0	0
CYP2C9*6	0.6	2.7	ND	0	0
CYP2C9*7	0	0	6	0	0
CYP2C9*8	1.9	8.6	4	0	0
CYP2C9*9	13	15.7	22	0	0.3
CYP2C9*11	1.4-1.8	2.7	6	0	0.4-1.0
CYP2C9*13	ND	ND	ND	0.19-0.45	ND

Metabolic interactions with CYP2C9

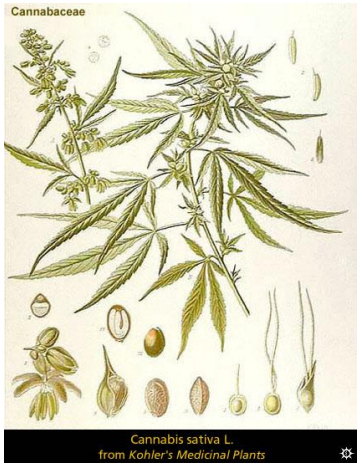
Selected inducers, inhibitors and substrates of CYP2C9

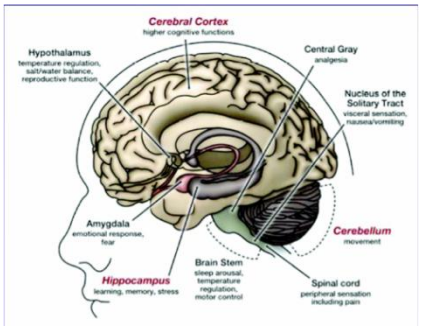
Substrates	Inhibitors	Inducers

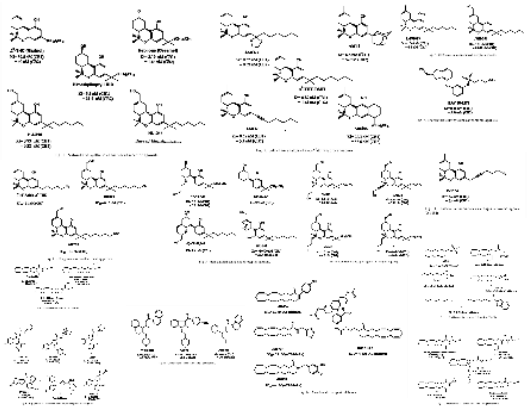
• NSAIDs (analgesic, antipyretic, anti-inflammatory)
  • celecoxib[12][13]
  • lornoxicam[12][14]
  • diclofenac[12][13]
  • ibuprofen [12][13]
  • naproxen[12][13]
  • ketoprofen[15]
  • piroxicam[12][13]
  • meloxicam[12][13]
  • suprofen[12]
• phenytoin[12][13] (antiepileptic)
• fluvastatin[12][13] (statin)
• sulfonylureas (antidiabetic)
  • glipizide[12][13]
  • glibenclamide[12][13]
  • glimepiride[12][13]
  • tolbutamide[12][12]
  • glyburide[12]
• angiotensin II receptor antagonists (in hypertension, diabetic nephropathy, CHF)
  • irbesartan[12][13]
  • losartan[12][13]
• S-warfarin[12][13] (anticoagulant)
• sildenafil[13] (in erectile dysfunction)
• terbinafine[13] (antifungal)
• amitriptyline[12] (tricyclic antidepressant)
• fluoxetine[12] (SSRI antidepressant)
• nateglinide[12] (antidiabetic)
• rosiglitazone[12] (antidiabetic)
• tamoxifen[12] (SERM)
• torasemide[12] (loop diuretic)
• ketamine
• THC
• JWH-018
• AM-2201[16]
	Strong:
	• fluconazole[12][13] (antifungal)
	• miconazole[13] (antifungal)
	• amentoflavone[17] (constituent of Ginkgo biloba and St. John's Wort[18]
	• sulfaphenazole[13] (antibacterial)
	• Valproic acid[13] (anticonvulsant, mood-stabilizing)
	• Apigenin[11]
	Moderate
	• amiodarone[12] (antiarrhythmic)
	Unspecified potency
	• antihistamines (H1-receptor antagonists)
	  • Cyclizine[19]
	  • Promethazine[19]
	• Chloramphenicol[20]
	• fenofibrate[12] (fibrate)
	• flavones[11]
	• flavonols[11]
	• fluvastatin[12] (statin)
	• fluvoxamine[12] (SSRI)
	• isoniazid[12] (in tuberculosis)
	• lovastatin[12] (statin)
	• phenylbutazone[12] (NSAID)
	• probenecid[12] (uricosuric)
	• sertraline[12] (SSRI)
	• sulfamethoxazole[12] (antibiotic)
	• teniposide[12] (chemotherapeutic)
	• voriconazole[12] (antifungal)
	• zafirlukast[12] (leukotriene antagonist)
	• quercetin[11] (anti-inflammatory)
		Strong:
		• rifampicin[12][13] (bactericidal)
		• secobarbital[12] (barbiturate)

Types of Cannabinoids

- **Organic cannabinoids →**
  - From cannabis plant
- **Endogenous cannabinoids**
  - Synthesized in brain
- **Synthetic cannabinoids →**
  - Synthesized in labs

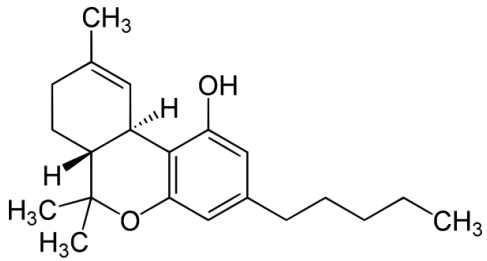




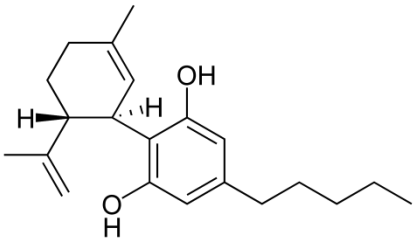


Organic Cannabinoids from Cannabis Plant

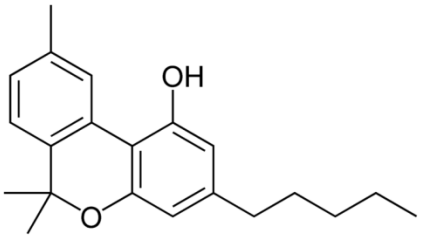
- 3 highly bioactive compounds
  - Δ^9 –tetrahydrocannabinol (THC)
    - The principle psychoactive constituent



  - Cannabidiol (CBD)
    - Most abundant organic cannabinoid after THC

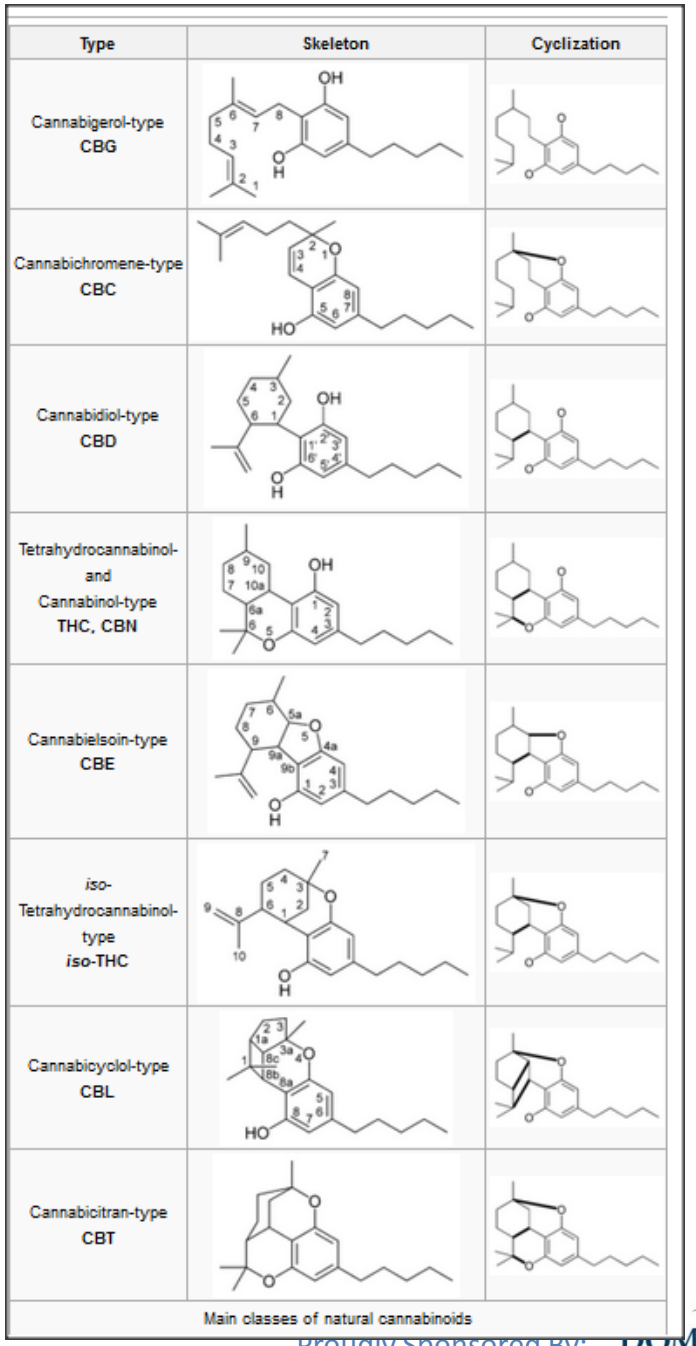


  - Cannabinol (CBN)
    - Decomposition product of THC that accumulates in aged cannabis



85 Cannabinoids in Cannabis plants

- Complex Interactions between cannabinoids
  - CBD – low affinity for CB1+CB2 receptors
  - CBD may increases CB1 receptors
  - CBD inhibit THC metabolism
  - CBD – inverse agonist of CB2
  - CBD – agonist at 5HT – antidepressant effect
  - Selective breeding can produce CBD enhanced cannabis = 15% CBD and 1% THC



Cannabinoid vs. SC

- **Phytocannabinoids**
  - Found in cannabis plant
  - THC, CBD, CBN
- **Endocannabinoids**
  - Produced within the body
  - Lipid messengers

The endocannabinoid system is a group of neuromodulator lipids and their receptors that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory

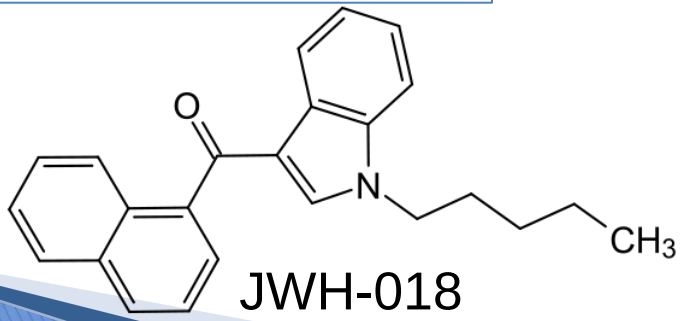
- **Synthetic Cannabinoids: 6 chemical classes**
  - Depending on synthetic compound, <u>can be anywhere from 4 times to over 100 times more potent than the THC in marijuana</u>

Synthetic Cannabinoids (SC)

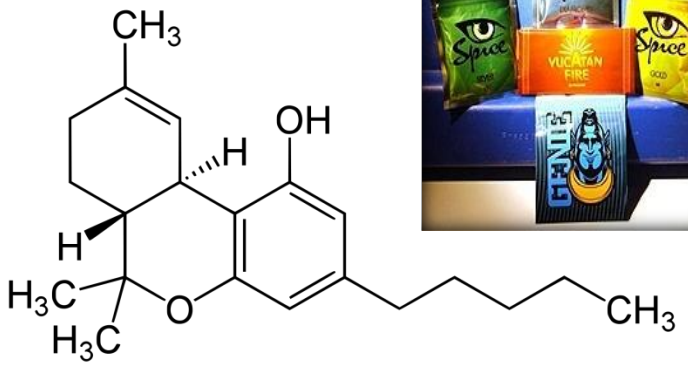
- Developed for research
  - JWH-018 & JWH-073
  - JWH-250, CP-47, 497
  - HU-210

- Dr. John W. Huffman, Clemson University professor, synthesized many novel cannabinoids as part of research for National Institute for Drug Abuse (NIDA) on endogenous cannabinoid receptors - but never tested on humans nor approved by FDA. "*Apparently someone picked it up, I think in Europe, on the idea of doping this incense mixture with the compound and smoking it*" –Dr. Huffman

THERE ARE OVER 100 KNOWN SYNTHETIC CANNABINOIDS



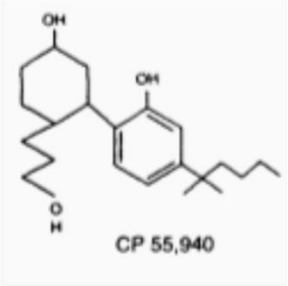
JWH-018

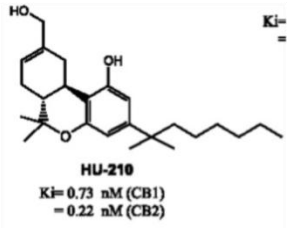


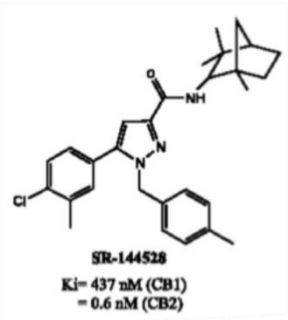
Δ^9-THC

Synthetic Cannabinoids

- Other notable synthetic cannabinoids.
  - CP-55, 940 : Produced in 1974; 40-60 times as potent as THC.
  - HU-210: 100 - 800 times as potent as THC.
  - HU-211: Also called dexanabinol, is now undergoing phase III clinical trials for treating traumatic brain injury. (has no binding affinity).
  - SR-144528: Used to distinguish between CB_1 and CB_2 receptors. (Binds almost exclusively to CB_2 receptor – exhibits a 700-fold selectivity)
  - Many more . . .







CANNABINOIDS IN MEDICAL CANNABIS

ENDOCANNABINOIDS
Anandamide(AEA)

PHYTOCANNABINOIDS
THC, CBD, CBN, ettc

SYNTHETIC CANNABINOIDS
THC Only(Marinol)

ENDOCANNABINOID RECEPTORS

(Brain Receptors)

CB1, CB2, etc

The Endocannabinoid System(ECS) is involved in regulating a variety of phycological processes including appetite, pain and pleasure sensation, immune system, mood and memory

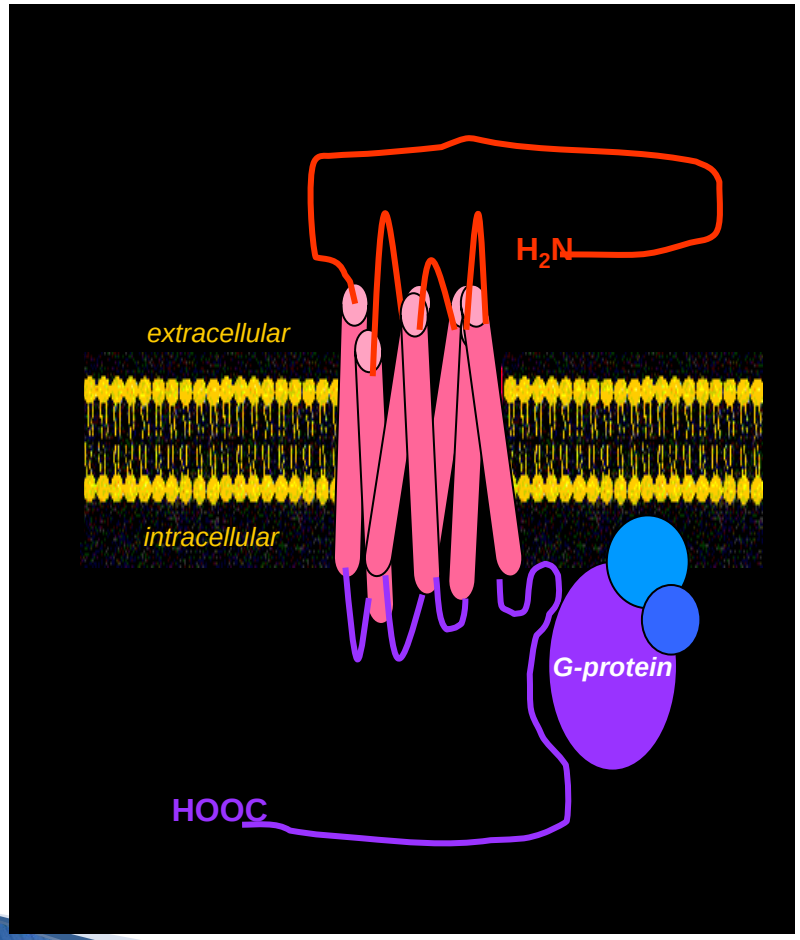
Types of Cannabinoid Receptors

- History of THC research
  - 1986 Synthetic cannabinoid CP 55,940 discovered
    - 10-100x potent as THC
    - Allowed for identification of THC receptors
  - 1988 Howlett, Devane identified cannabinoid receptor
    - Type 1 - CB1, located in specific areas in brain
    - Type 2 - CB2, located in peripheral sites
- Development of cannabinoid antagonist
  - SR141716
  - Trade name = rimonibant

What Normally Binds to Receptors

- If receptors are present normally, what is their function and what normally binds to them
  - Endogenous ligand = substance that binds to receptor = anandamide (sanskrit word for bliss)
    - Inside our brain normally acting marijuana like substance
  - Role of anandamide in normal brain functioning =
    - Control and modulation of mood and memory
    - Serve as link which transmit, transform, translate objective and subjective events into perceptions and emotions
      - Aging causes loss of neurons in the hippocampus and relates to memory loss of aging and Altheimer's disease

Human cannabinoid receptors



- CB1 receptors
  - Present mainly in brain and spinal cord
- CB2 receptors
  - Present in spleen and immune cells

- **both types are 7-helix transmembrane receptors, coupled to G-proteins**

Cannabinoid Receptors

- Why is marijuana so non-toxic
  - Location of CB1 receptors determines effect of THC
    - No CB1 receptors in medulla-no effect on centers that control respiration and blood pressure - No lethal dose known
      - Development of cannabinoids as analgesics, compared to opiates, pain control without risk of Cardiopulmonary suppression
    - Lots of CB1 receptors in cerebellum and basal ganglia
      - Development of antispasmotic drugs for MS, stroke
  - Major effect of cannabinoids is on regulation of mood
    - Effect on hippocampus gates information during memory consolidation

CB_1 Receptors

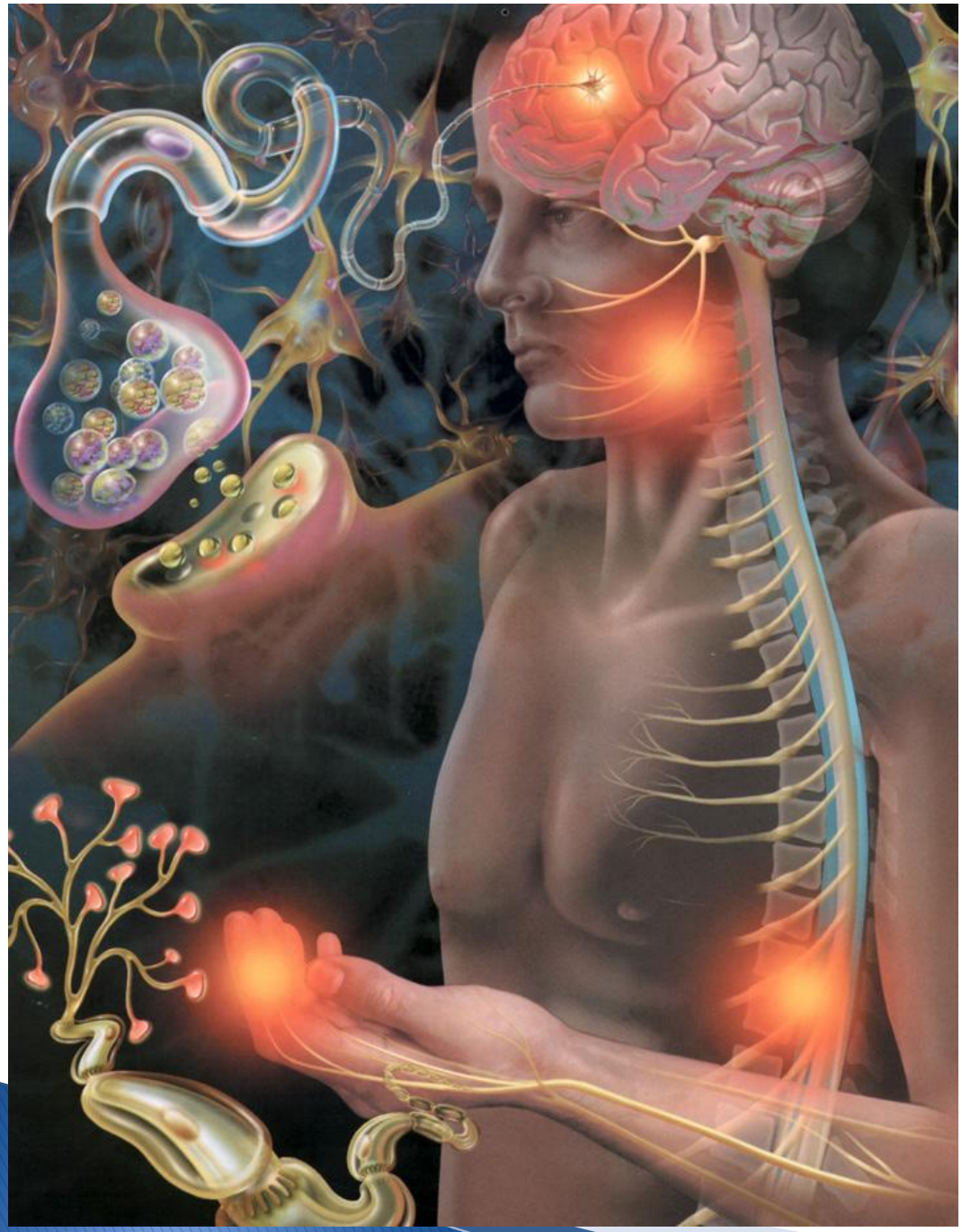
- Short-term activation: responsible for most of the cognitive and intoxicating effects caused by THC.
  - Activation for seconds inhibits presynaptic N-type calcium channels and activates inwardly rectifying potassium channels, reducing neurotransmission (retrograde signaling).
- Long-term activation: can change gene expression.
  - Activation for minutes or hours can induce expression of neuroprotective proteins like brain-derived neurotrophic factor (BDNF) which is known to counteract cell damage.

CB_2 Receptors

- Expressed in the PNS by immune cells (Most notably the B-cells and Natural killer cells).
- THC and CBN bind to this receptor as partial agonists.
- Leads to reduced inflammation by inducing apoptosis of immune cells, and by inhibiting the ability of macrophages to process antigens and prime helper T cells.

Mechanism of Action-Cannabinoids

- Binding of cannabinoids to receptors-CB1
  - Modulation of GABA
    - Increased dopamine in reward circuitry by GABAergic pre-synaptic inhibition of dopaminergic neurons=increased firing in reward circuitry
- Increased opiate levels
  - If block opiates from increasing, then no “high” from cannabis
    - Knock out gene in mice - no high if given THC
    - Naltrexone stops high
- Endocannabinoid system facilitates forgetting of irrelevant or maladaptive behaviors or aversive memories
- Presynaptic attenuation of Glutamate
- Alteration of prostaglandins
- Inhibition of Calcium uptake by synaptasomes
- Induction of sleep by increasing adenosine levels
- CB1 activation has anticonvulsant effects



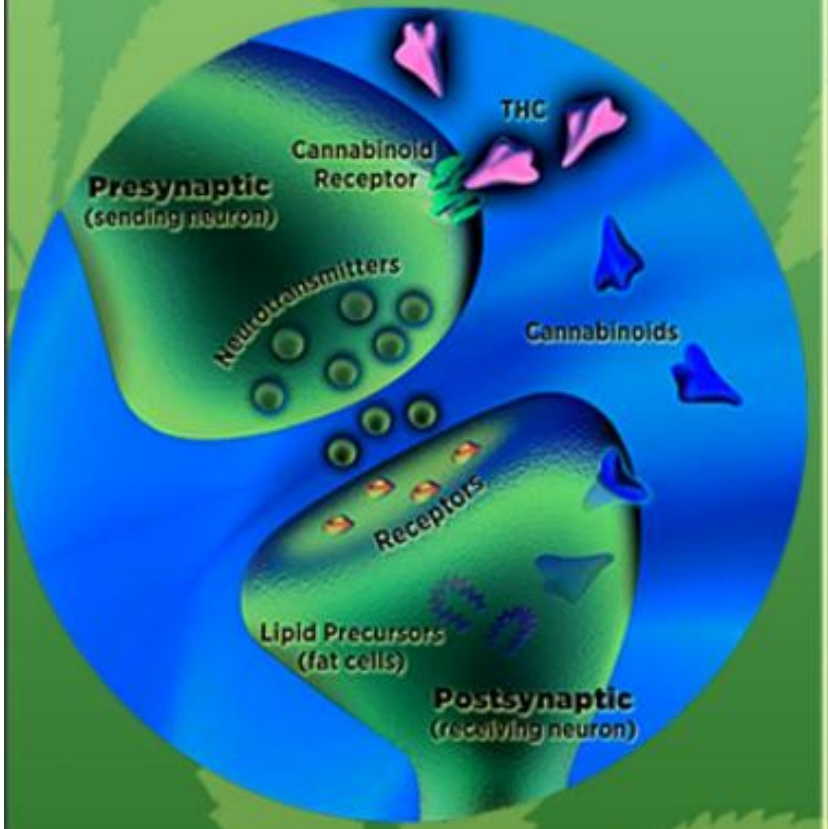
Cannabinoid Sites of Action

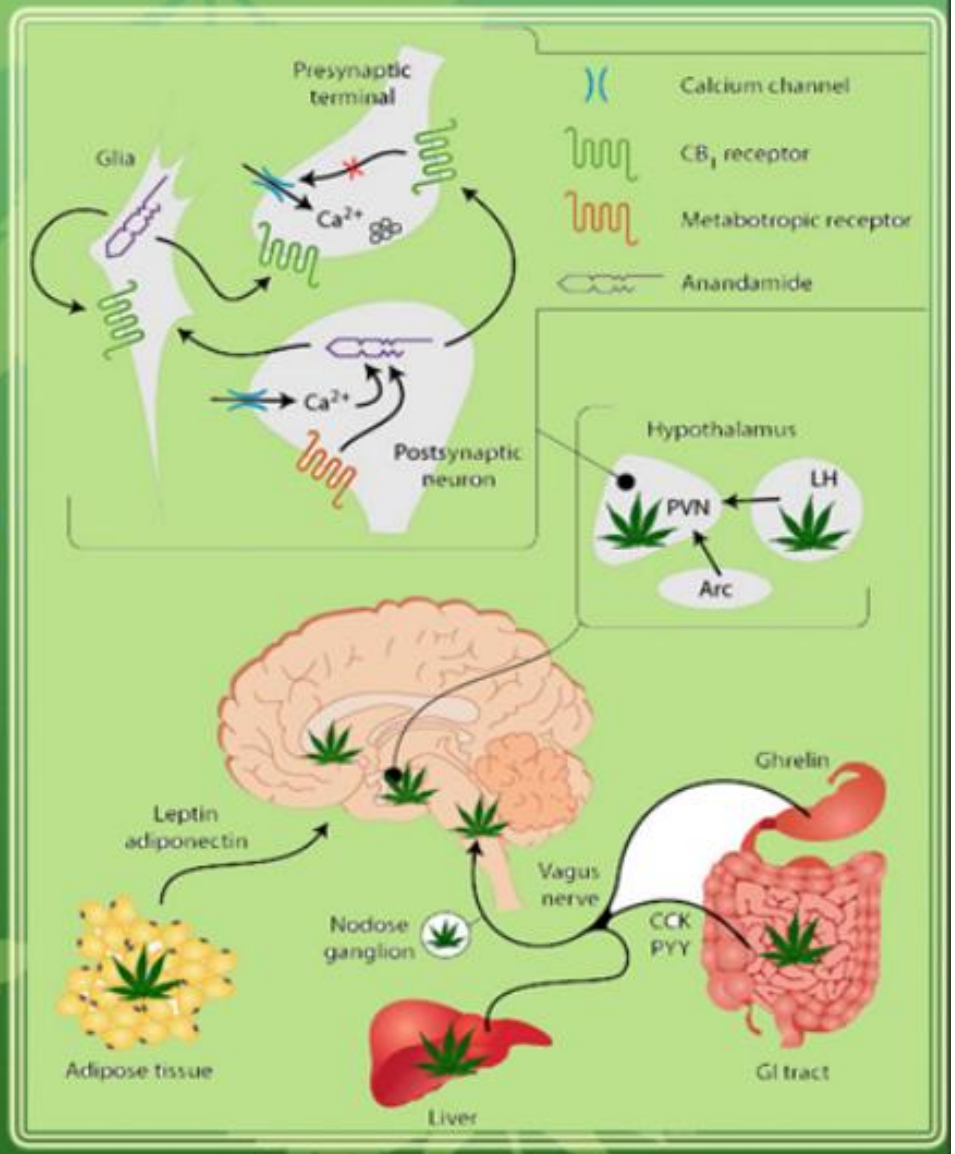
Supraspinal descending inhibition

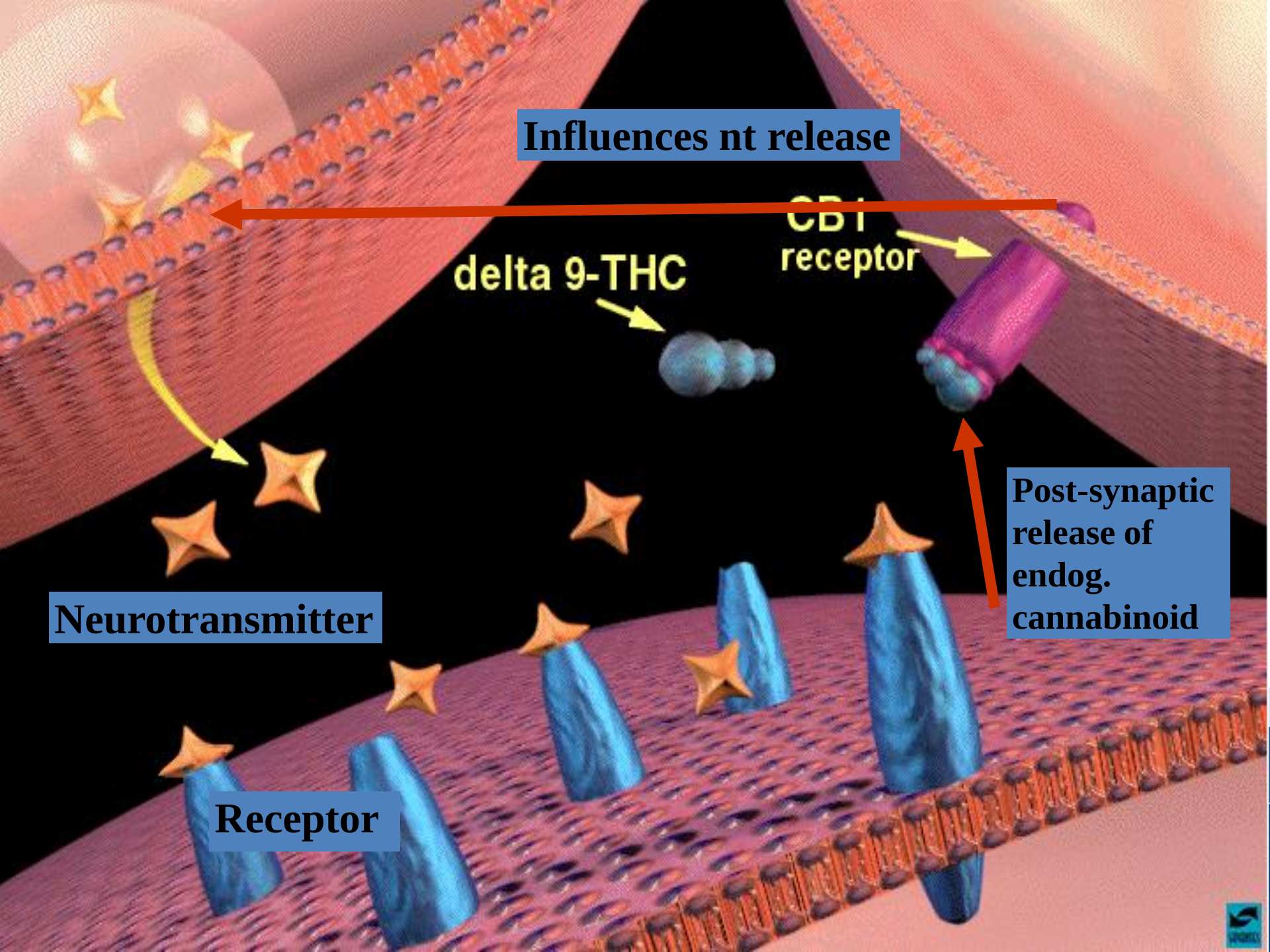
Spinal

Peripheral

ENDOCANNABINOID SYSTEM






Influences nt release
CB1
receptor
delta 9-THC
Post-synaptic
release of
endog.
cannabinoid
Neurotransmitter
Receptor

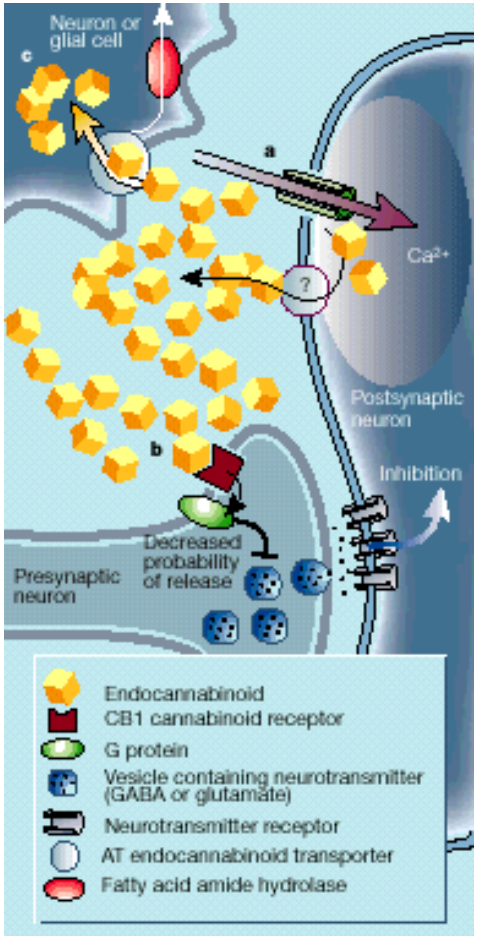
Neurobiology

Editorial, Nature

Cannabinoids act backwards

MacDonald J. Christie and Christopher W. Vaughan

(Wilson & Nicoll, 2001; Ohno-Shosaku et al., 2001; Kreitzer & Regehr, 2001)



- Cannabinoids are able to function as retrograde synaptic messengers
- Endocannabinoid synthesized and released from postsynaptic neurons
- Travels backwards across synapse activating CB1 on the presynaptic axon
- Resulting in supression of neurotransmitter release

Spectrum of Pharmacological Effects

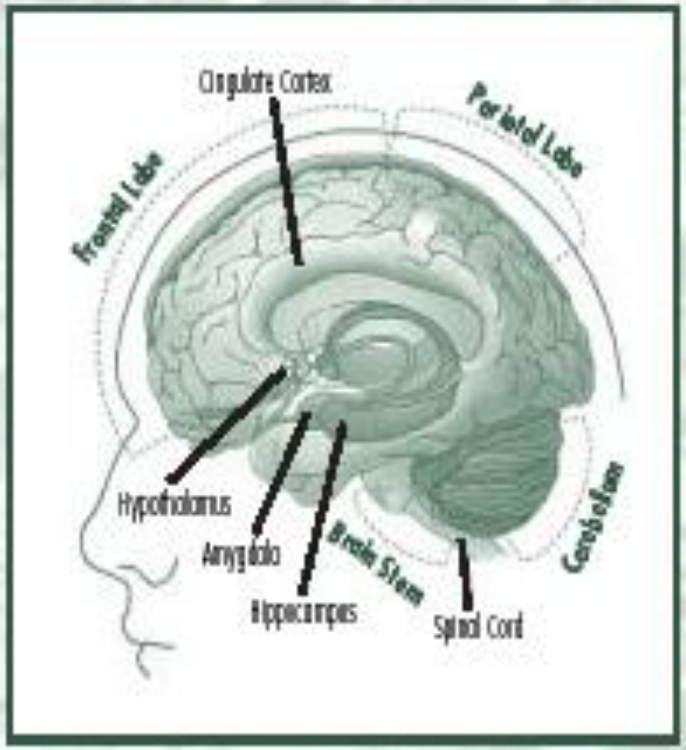
- Disruption in mechanism of attention
- Impairs short term memory
- Altered interpretation of sensory info
- Analgesia
- Decrease control of motor movement
- Immunosuppressant
- Ptosis
- Increased heart rate
- Sleepiness
- Decreased skin temperature
- Relaxation
- Increased appetite
- Paranoia

Desired Effects of Marijuana

Most pronounced when drug levels are on the rise

- Sense of well being
- High
- Feeling of relaxation
- Altered perception of time and distance
- Intensified sensory experiences
- Excessive laughter
- Talkativeness
- Increased sociability
- Escape from problems
- Decreased worry
- Sleep induction
- Decrease boredom
- Attention to details
- Dream like state
- Impaired memory
- Difficulty concentrating
- Impaired goal directed mental activity

Marijuana's Effects on the Brain

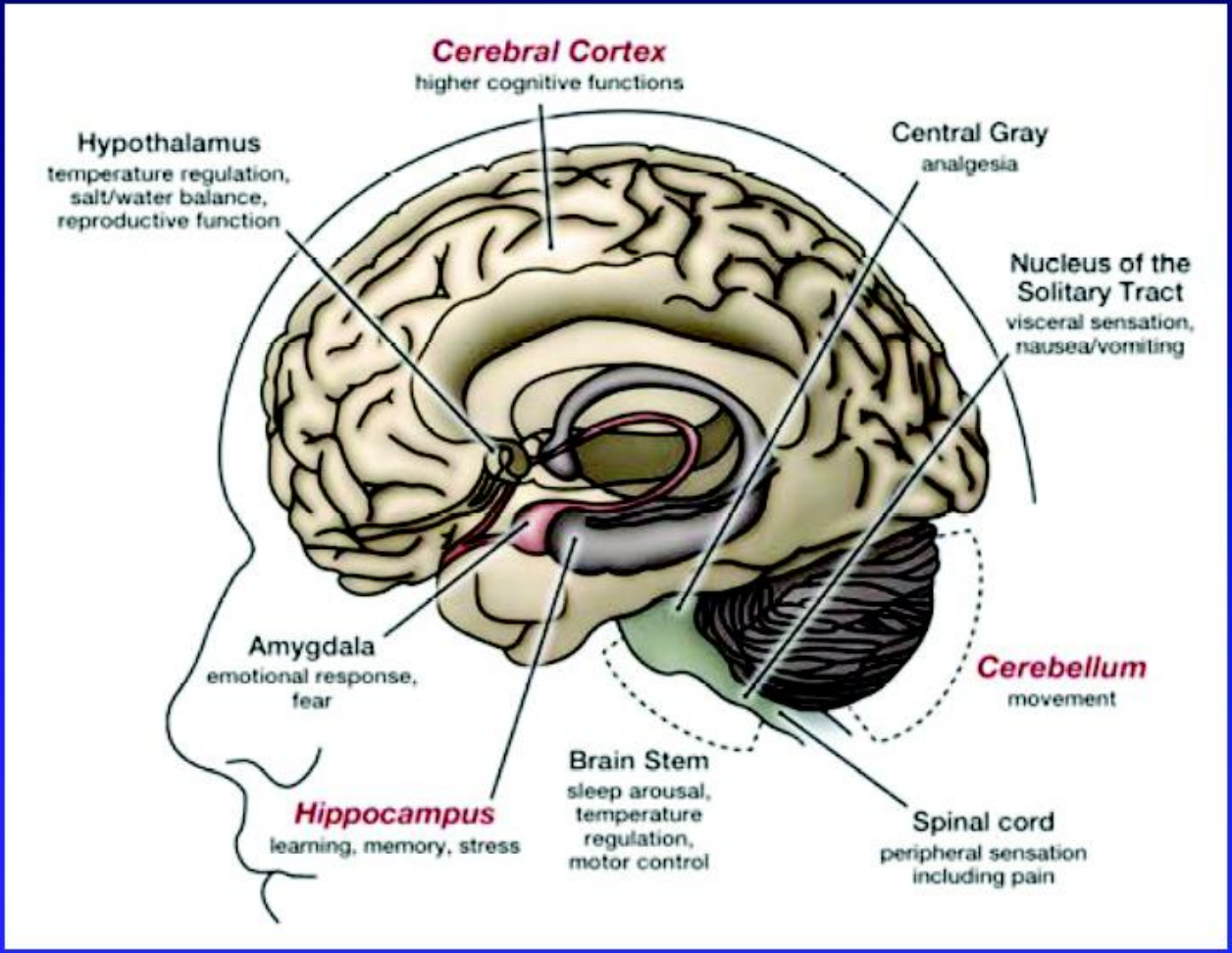


When marijuana is smoked, its active ingredient THC travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

Brain Region	Functions Associated With Region
Brain regions in which cannabinoid receptors are abundant	
Cerebellum	Body movement coordination
Hippocampus	Learning and memory
Cerebral cortex, especially cingulate, frontal, and parietal regions	Higher cognitive functions
Nucleus accumbens	Reward
Basal ganglia Substantia nigra pars reticulata Entopeduncular nucleus Globus pallidus Putamen	Movement control
Brain regions in which cannabinoid receptors are moderately concentrated	
Hypothalamus	Body housekeeping functions (body temperature regulation, salt and water balance, reproductive function)
Amygdala	Emotional response, fear
Spinal cord	Peripheral sensation, including pain
Brain stem	Sleep and arousal, temperature regulation, motor control
Central gray	Analgesia
Nucleus of the solitary tract	Visceral sensation, nausea and vomiting

Some Brain Regions Containing CB_1 Receptors

Red = abundant CB_1 receptors Black = moderately abundant CB_1 receptors



Adapted from Joy JE, et al, eds. *Marijuana and Medicine*. 1999.

Adverse Effects of Marijuana

- Anxiety and Panic
- Paranoia
- Depression
- Sedation + confusion
- Altered sense of time
- Impaired short term memory
- Amotivational syndrome
- Dry mouth
- Impaired coordination
- Increased heart rate
- Slow gastric emptying
- “Blind munchies”
- Lightheadedness
- Coughing
- Headaches

Health Consequences of Marijuana

- Acute (present during intoxication)
  - Impairs short-term memory
  - Impairs attention, judgment, and other cognitive functions
  - Impairs coordination and balance
  - Increases heart rate
- Persistent (lasting longer than intoxication, but not permanent)
  - Impairs memory and learning skills
- Long-term (cumulative, potentially permanent effects of chronic use)
  - Can lead to addiction
  - Increases riskof chronic cough, broncithits, and emphysema
  - Increases risk of cancer of the head, neck, and lungs

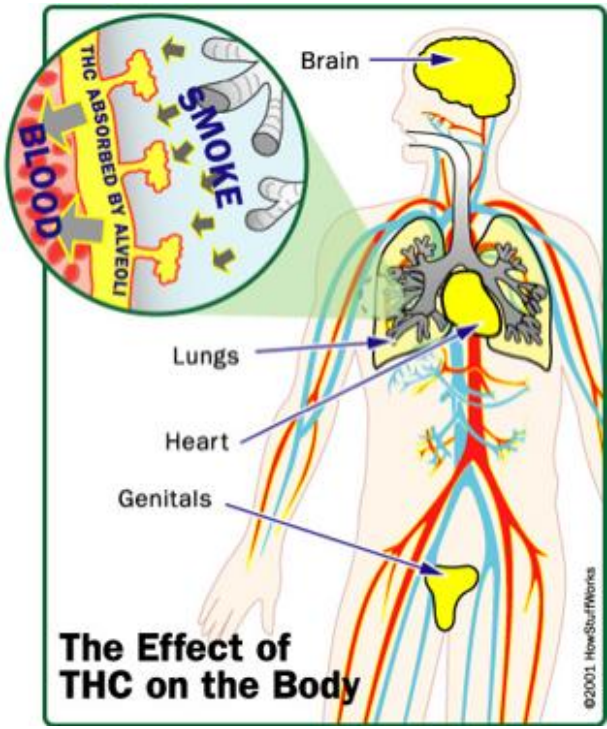
Effects Of THC On The Body

Cardiovascular System

- Increased heart rate & blood pressure
- Higher incidence of heart attacks in smokers > 50 years old
- Blood vessels in cornea dilate (bloodshot)
- Increased appetite, dry mouth, dizziness, slight nausea
- Respiration depression is **not** observed
- Dangerous physical reactions are almost never seen

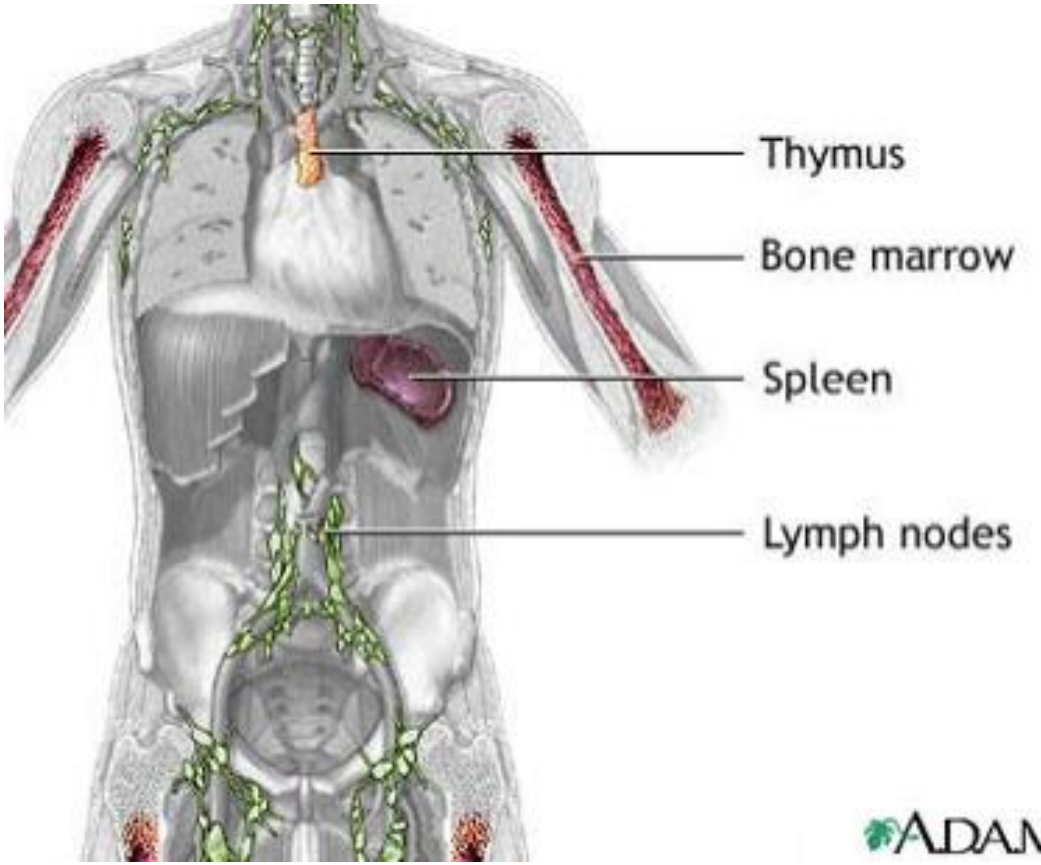
Pulmonary Effects of Marijuana

- Short lived bronchodilation
- Chronic bronchitis
- Acute and chronic sinusitis
- Increased frequency of pulmonary infection
- Long term use can damage lung tissue
  - Large airway dilation
  - Cellular inflammatory changes
  - Marijuana smoke contains 50-70% more carcinogens than cigarettes
  - Produces high levels of enzyme that converts hydrocarbons into their carcinogenic forms



Effects Of THC On The Body

- Cannabinoid receptors are found primarily in the immune system
- Long-term use is associated with immunosuppression



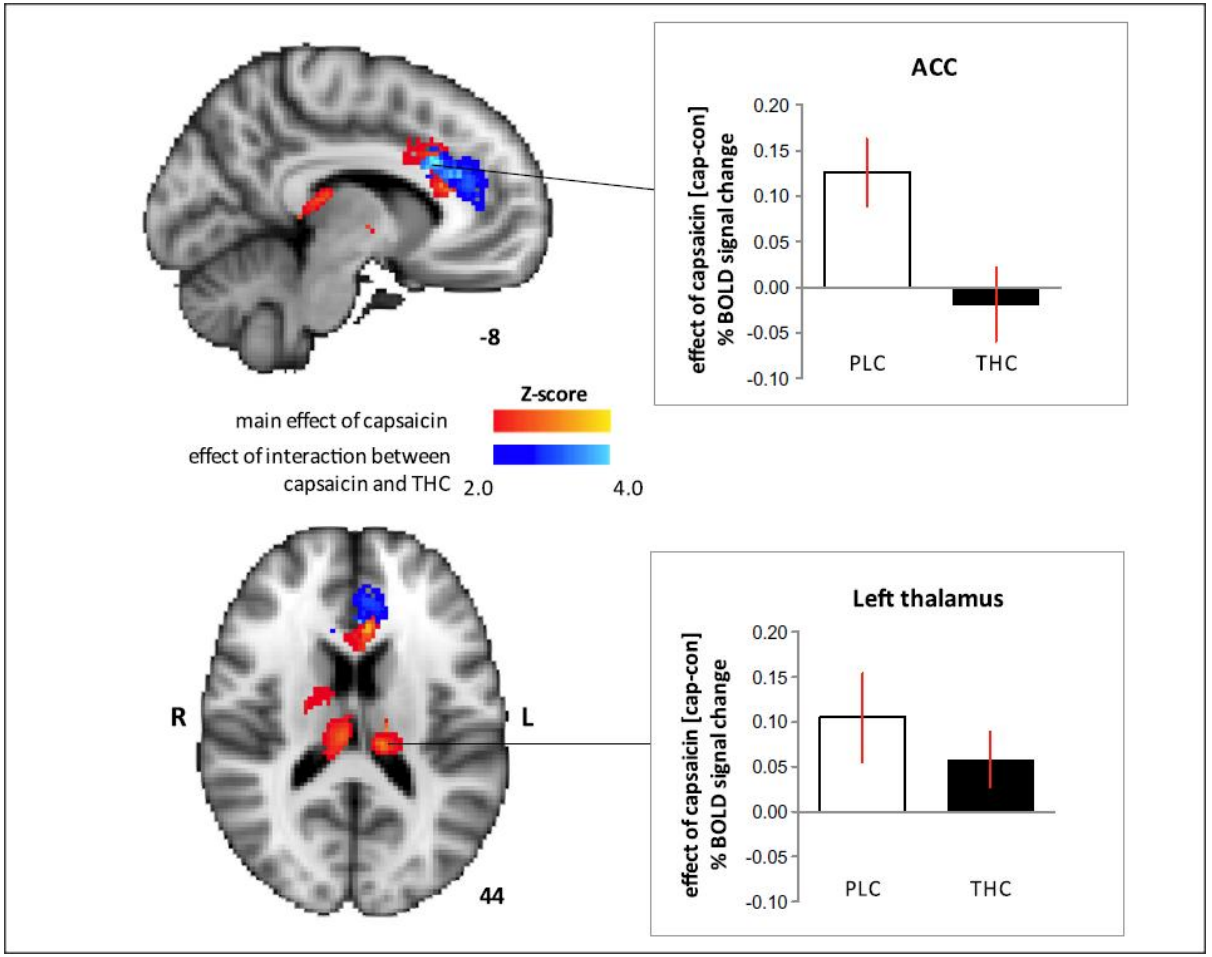
Immune Effects of Marijuana

- **Impaired cell mediated immunity**
  - Interfere with macrophage
  - Suppress antibody formation, cytokine production, leukocyte migration and natural killer cell activity
- **Decreased host resistance to bacterial and viral infection**
  - Warning re: chemotherapy – immunosuppression may increase risk of infections (fungal) – not protected from vaporization
- **Potentially useful as immunosuppressant**
  - Multiple sclerolisis
  - Complex for liver fibrosis/cirrhosis – THC worses fibrosis, CBD may decrease fibrosis

Endocrine Effects of Marijuana

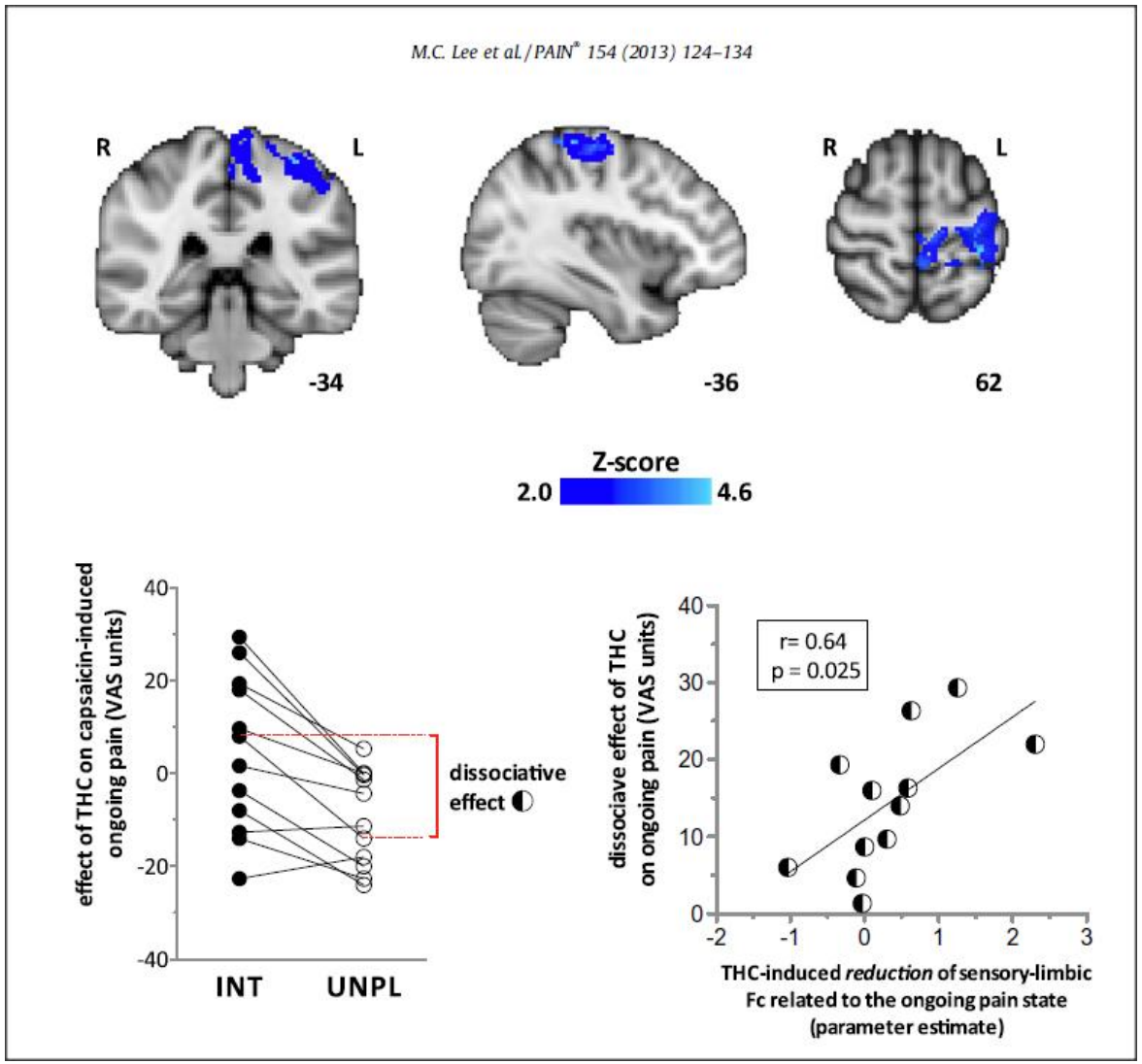
- **Sperm Counts**
  - MJ use causes decline in sperm count and concentration and decrease sperm motility and increased sperm morphology
  - THC binds to CB1 receptor on spermatozoa
    - Inhibits acrosome reaction

fMRI : THC effect on emotional pain



M.C. Lee et al. / PAIN 154 (2013) 124–134

THC: Effect on Functional Connectivity



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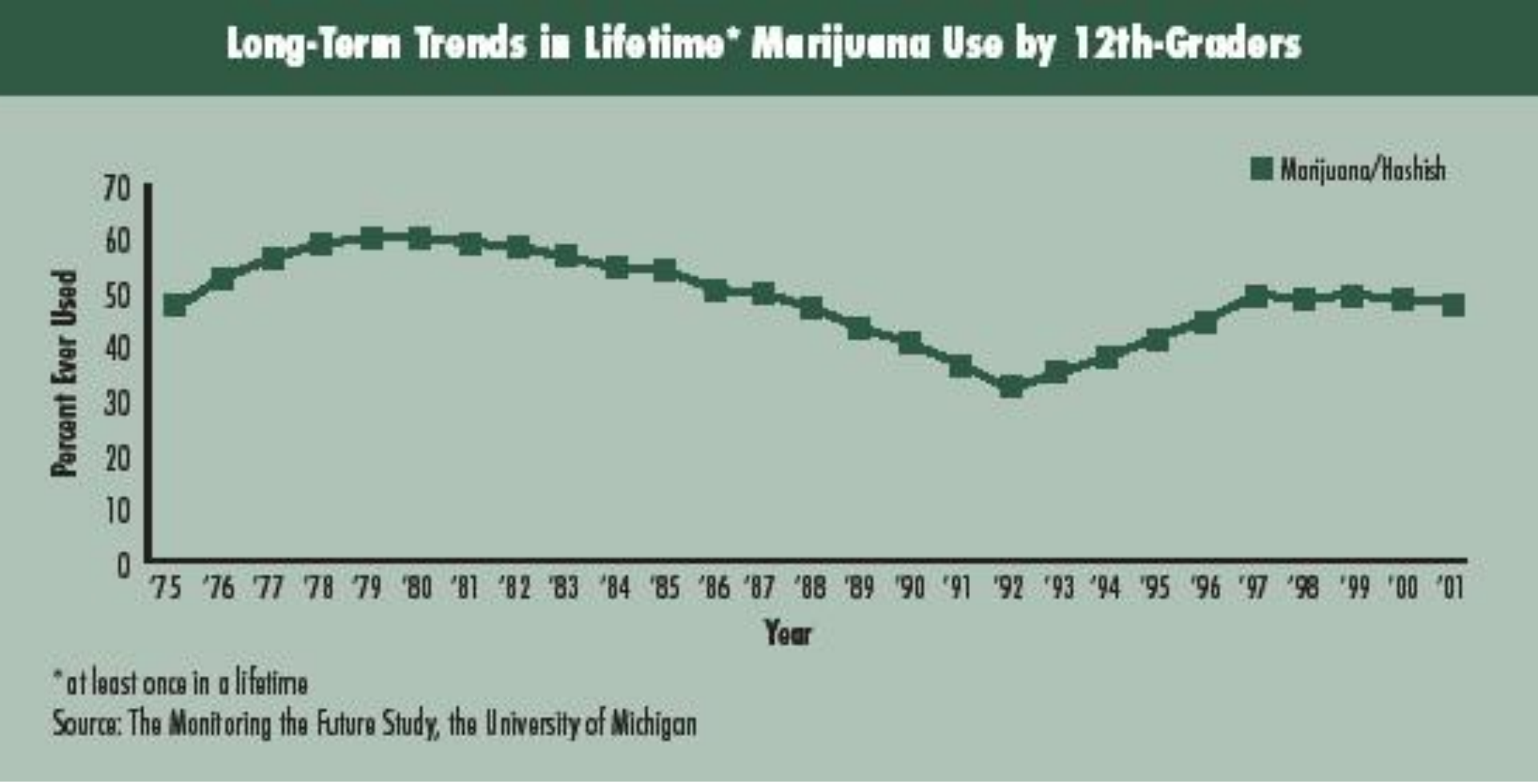


Marijuana is most commonly used illict drug

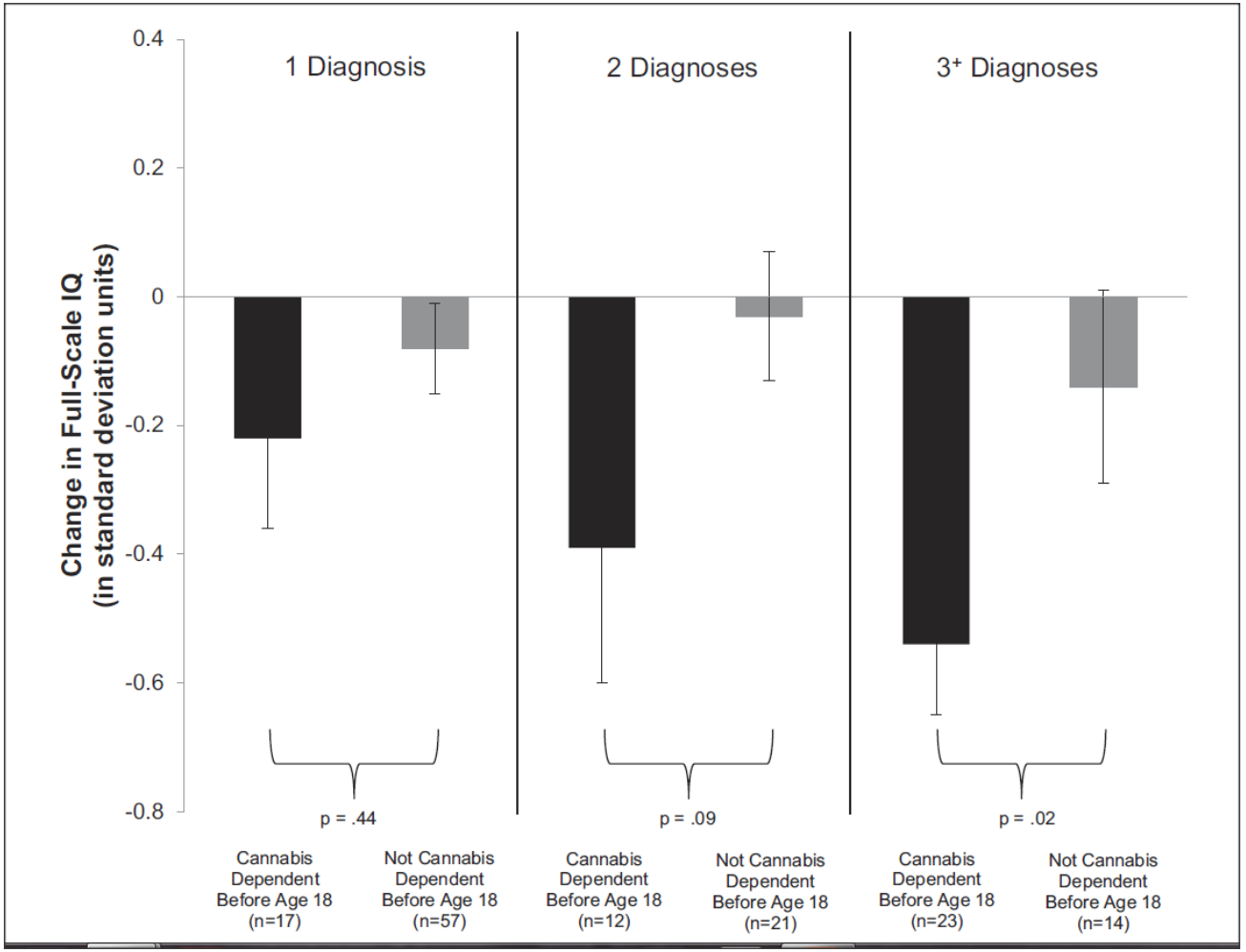
Marijuana contributing factor in greater than 110,000 ER visits in 2001

39% of males, 26% of females adult arrestees tested positive for marijuana in 1999 (data from NIDA Arrestee Drug Abuse monitoring program, ADAM)

Effects of Marijuana on Learning and Behavioral Functioning

- Effect on memory, concentration and learning
  - 129 college students- daily smokers (27 of preceding 30 days)
    - Significant impairment in memory, attention and learning even if not used in 24 hours
    - Heavy users (compared to infrequent users, 3 out of 30 previous days) had more trouble sustaining and shifting their attention , and in registering, organizing, and using information
    - Ability to recall words from a list was impaired one week after cessation of smoking, but returned to normal within 4 weeks
- Effect on performance of life functioning (likelihood of being loser)
  - Impairment in critical life skills
    - Researchers gave students a battery of tests measuring problem solving and emotional skills in 8th grade and repeated again in 12th grade
      - Heavers users started out slightly behind non-using peers, but by senior year were significant worse
      - Marijuana use (independent of alcohol use) reduced capacity for self-reinforcement, a group of skills that enable individual to maintain confidence and persevere pursuit of goals.

Persistent Neuropsychological Decline: Age Onset of Cannabis Use



Persistent cannabis users show neuropsychological decline from childhood to midlife. Meier et al:www.pnas.org/lookup/suppl/doi:10.1073/pnas.1206820109/-/DCSupplemental.

Effects of Marijuana on Performance in School and at Work

- Effect on work productivity
  - Studies reviewing marijuana smoking and job problems
    - Increased absenteeism, tardiness and job turnover
    - Increased frequency of accidents and worker compensation claims
    - Municipal employees who smoked on or off the job reported more “withdrawal behaviors”
      - Leaving work without permission, daydreaming, spending work time on personal matters, and shirking tasks
- Effect on personal problems
  - Marijuana use causes more problems in daily life or inteferes with ability to cope with one’s personal problems
    - Higher doses of marijuana interfere with learning and memory
      - Fall behind in accumulating intellectual, job or social skills
      - Persistence of impairment can last weeks after last use, long past feeling of being high
      - Lack of motivation and acceptance of sub-optimal situations allow someone to stay in job or relationship for longer than they intended

Tolerance

- Tolerance to *Cannabis sativa* occurs by 2 separate mechanisms:
  1. desensitization of brain cannabinoid receptors
  2. rapid receptor internalization followed by agonist binding & receptor activation

Symptoms of Marijuana Withdrawal

- Nausea and anorexia
- Tremor and salivation
- Sweating
- Altered sleep/wake cycles
- Insomnia & dreaming – REM
- Restlessness / agitation
- Irritability
- Depressed Mood

Table 1. The cannabis withdrawal scale.

Not at all						Moderately						Extremely	Negative Impact on daily activity (0–10)
1	The only thing I could think about was smoking some cannabis	0	1	2	3	4	5	6	7	8	9	10	
2	I had a headache	0	1	2	3	4	5	6	7	8	9	10	
3	I had no appetite	0	1	2	3	4	5	6	7	8	9	10	
4	I felt nauseous (like vomiting)	0	1	2	3	4	5	6	7	8	9	10	
5	I felt nervous	0	1	2	3	4	5	6	7	8	9	10	
6	I had some angry outbursts	0	1	2	3	4	5	6	7	8	9	10	
7	I had mood swings	0	1	2	3	4	5	6	7	8	9	10	
8	I felt depressed	0	1	2	3	4	5	6	7	8	9	10	
9	I was easily irritated	0	1	2	3	4	5	6	7	8	9	10	
10	I had been imagining being stoned	0	1	2	3	4	5	6	7	8	9	10	
11	I felt restless	0	1	2	3	4	5	6	7	8	9	10	
12	I woke up early	0	1	2	3	4	5	6	7	8	9	10	
13	I had a stomach ache	0	1	2	3	4	5	6	7	8	9	10	
14	I had nightmares and/or strange dreams	0	1	2	3	4	5	6	7	8	9	10	
15	Life seemed like an uphill struggle	0	1	2	3	4	5	6	7	8	9	10	
16	I woke up sweating at night	0	1	2	3	4	5	6	7	8	9	10	
17	I had trouble getting to sleep at night	0	1	2	3	4	5	6	7	8	9	10	
18	I felt physically tense	0	1	2	3	4	5	6	7	8	9	10	
19	I had hot flashes	0	1	2	3	4	5	6	7	8	9	10	

Instructions: This version of the CWS asks about symptoms experienced over the last 24 hours, and can be administered by an interviewer OR by self report. The following statements describe how you have felt over the last 24 hours. Please **circle the number** that most closely represents your personal experiences for each statement. For each statement, please rate its negative impact on normal daily activities on the same scale (0 = Not at all to 10 = Extremely), writing the number in the right hand column.

Score by summing each items value to a maximum withdrawal score of 190 (you can derive two scores from the scale: one for withdrawal intensity and one for the negative impact of withdrawal – each separate score has a theoretical maximum of 190).

doi:10.1371/journal.pone.0044864.t001

Cannabinoid Antagonist

- SR141716 blocks anandamide at CB1 receptors
  - Marijuana blocker given to volunteers prior to smoking marijuana and asked to rate "high" and
    - 40% to 75% less drug effect than control group
    - Less dose of blocker produces less reduction in "high"
- SR141716 blocks increases in heart rate produced by marijuana

SR141716 may produce worsening of marijuana withdrawal if given to regular marijuana smokers who still have marijuana within their systems

Risk of Addiction

- Lifetime prevalence of addiction in general population is 3%-16%.
- 20% of MJ smokers in CO consume 80% of MJ sold
  - Regier, Meyers, & Kramer, 1984

Risk of Addiction When Treating Pain

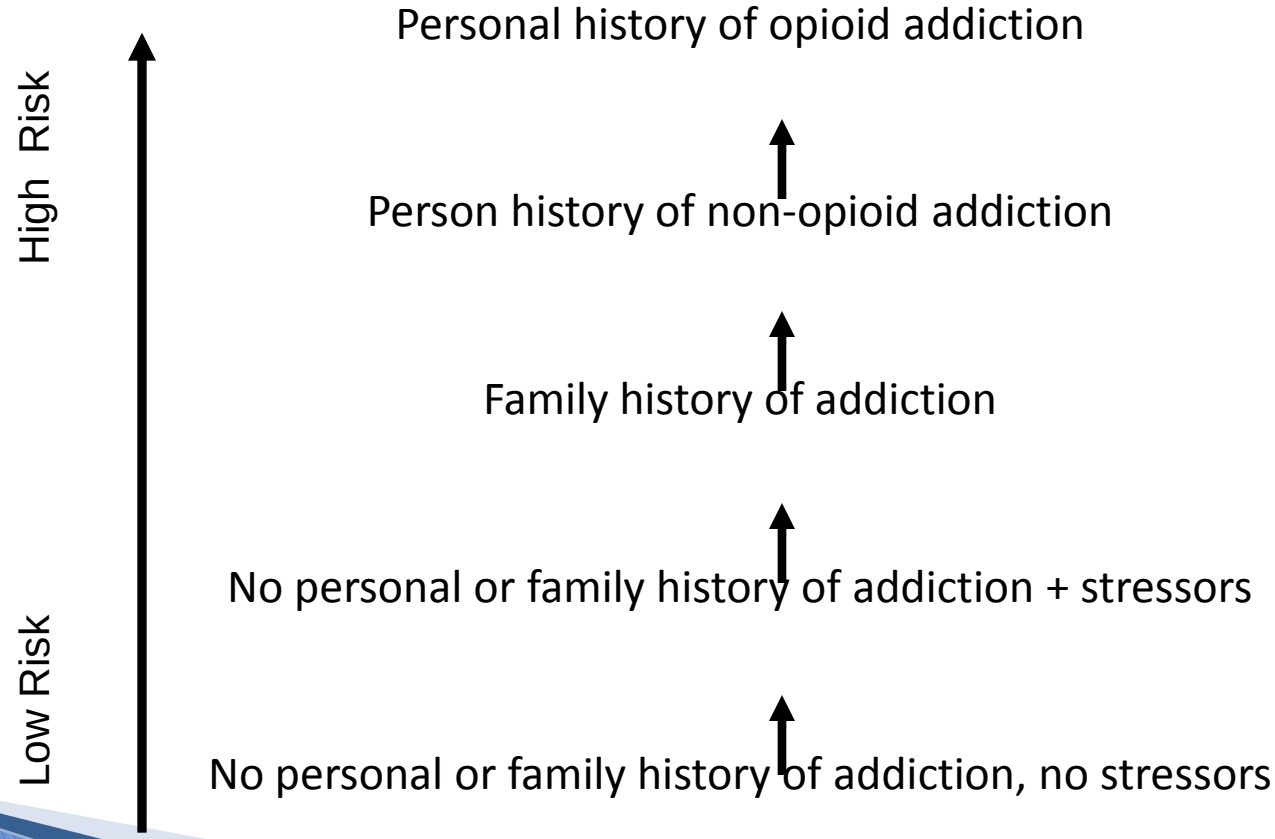
- Acute Pain — Low Risk of Addiction
- Chronic Pain — Up to 50-70%

- Living with Pain
  Richard L. Reilly, D.O.

Adapted from Don Kurth, MD-Non Narcotic Pain Management-Common Threads Conference 2002

Hierarchy of Risk to Addiction

Risk to becoming addicted to therapeutic opioids depends upon interaction between personal and family history and environmental stressors



Is Patient Using Drugs Addictively?

- What is the nature of the relationship between patient and drug?
  - Did they want to take more?
    - If one is good, two is better
  - Did the thought of stopping increase desire for the drug?
    - Loss of supply requires awareness of “special relationship”
  - Is there awareness of the need to cut down or control use?
    - Awareness of cutting down or controlling use = problem
  - Is the use resulting in negative feelings toward use
    - Feeling guilty about using and continuing to use = use despite consequences
    - Social users and adequately dosed pain patients aren’t guilty about use
  - Are any family members or friends giving feedback to them about their use?
    - Usually adequate treatment does not result in others worrying about use
    - When someone is annoyed at feedback, then they have a problem

Risk of Addiction

- Increased potency can increase risk of addiction and adverse side effects
  - Average THC potency over last 30 years increased from 1.7% to 13%
- Adolescents at increased risk for poly substance abuse and psychosis
  - Decreased perception of harm and increased use
- Increased numbers of “card carrying” patients entering treatment (either as caregivers or patients)
- Increased numbers seeking anxiety and depression relief rather than other indications (pain vs suffering)
- Most applicants for medical marijuana cards are experienced cannabis users seeking legal immunity and do not have adequate documentation of medical indications or have inadequate treatment

Co-Occurring Disorders

Conditions with a higher association with substance use disorders

- Positive status for HIV
- AIDS
- Hepatitis C
- Severe, debilitating, chronic Pain

Therapeutic Uses

Historical & Current Medical Uses for Marijuana

Treat Insomnia
Calm anxiety
Treat venereal disease
Calm coughs
Control spasms
Relieve childbirth pain
Calm migraine headaches
Relieve glaucoma
Control pain & nausea
Induce weight gain

Status of Medical Marijuana Laws

- 14 States decriminalize use of cannabis for medical use
- Patient or caregiver can grow
- Distribution by dispensaries
- All states require physicians as “gatekeepers”
- Prescribe vs. recommend use
- Laws do not create new rights – provide affirmative defense against possession and other criminal offenses
- Perceived permissiveness of Obama administration caused rapid growth of dispensaries and physicians practices exclusively based upon issueing cannabis recommendations

Medical Marijuana Program (MMP)

- Indicated Conditions for Eligibility for MMP
  - Cancer
  - Glaucoma
  - Positive status for HIV
  - AIDS
  - Hepatitis C
  - Chronic debilitating disease or condition
    - Cachexia or wasting syndrome
    - Severe, debilitating, chronic pain
    - Severe nausea
    - Seizures
    - Severe and persistent muscle spasms, including but not limited to, those characteristics of multiple sclerosis or Crohn's disease
    - Agitation related to Alzheimer's Disease

Medical Marijuana: Patient Diagnoses

Diagnosis	Count		Percent	
2010	2012	2010	2012	
Cancer or Treatment	214	354	5.87%	4.00%
Glaucoma or Treatment	37	85	1.02%	1.00%
Positive Status for HIV or Treatment	97	107	2.66%	1.00%
AIDS or Treatment	38	39	1.04%	0.00%
Hepatitis C or Treatment	209	291	5.74%	4.00%
Chronic or Debilitating* Disease or Condition		1419		38.94%
Cachexia/Wasting Syndrome	100	265	2.74%	3.00%
Chronic Pain*		711		
Seizures	24	125	0.66%	2.00%
Muscle Spasms	585	1393	16.05%	17.00%
Agitation of Alzheimer's	3	8	0.08%	0.00%
Severe Nausea	207	858	5.68%	11.00%
Severe, Debilitating Chronic		3504		44%
Other**		1015		13%

Medical Marijuana Program (MMP)

Physician's Attestation Signature

- I certify that I
  - Am licensed to practice in RI
  - Have a patient-physician relationship with qualifying patient
  - Have completed a full assessment of this patient's medical history
- The patient has been diagnosed with above conditions
- Marijuana used medically may mitigate the symptoms or effects of the patient's condition
- It is MY PROFESSIONAL OPINION
  - That the potential benefits of the use of medical marijuana would likely outweigh the health risks for this patient

Medical Marijuana Program (MMP)

For the Patient who is a Minor

- I certify that I am the custodial parent or legal guardian
- The patient's attending physician has explained the risks and benefits of medical use of marijuana
- I consent to use of marijuana for medical purposes
- I agree to serve as patient's designated primary caregiver
- I agree to CONTROL the acquisition of marijuana and the DOSAGE and FREQUENCY of use by the patient

Functional Status and Time

Patients with HIV, AIDS, Hepatitis C

- No specification of severity of illness
- No objective guidelines for functional status
- Could live years in asymptomatic state

- Patients with non-malignant chronic pain
  - Have high prevalence of anxiety, depression and other mood difficulties
  - Are likely to be exposed to other potentially addictive drugs – opioids and benzodiazepines

Physician Responsibility

- Does long term use of marijuana complicate the diagnosis or management of underlying condition
  - Sedation from marijuana may be interpreted as side effect of other prescribed medications
  - Physicians may adjust prescribed medications dosage or change to more powerful and dangerous medications when not aware of contribution that marijuana to side effects or lack of efficacy
- Worsen depression and anxiety
- Create lower motivation for non-drug related activities
- Interfere with cognitive processing, balance, memory and motor skills placing patient at higher risk for behavioral toxicity
- Interfere with job functioning secondary to memory and learning problems
- Precipitate relapse to other addictive medications

Ethical, Professional and Licensing Issues

- Ethical and professional responsibilities
  - How can physician safely recommend cannabis when there is unknown or inadequate information about composition, dosage, side effects, or therapeutic targets
- Medical Licensing Boards require same standard of care as prescribing or recommending other treatments
  - History and physical examination, review of past medical treatments, development of treatment plan, follow up and oversight
  - Failure to comply may result in licensing actions of unprofessional conduct, license suspension or revocation
  - Malpractice carriers may restrict coverage of claims involving cannabis recommendations

Recommendations to Attending MD

Screen for abuse and addiction and Mood Disorders

- Clinical interview
- Standardized instruments – CAGE, AUDIT, DAST, MAST, BDI, Hamilton
- Urine Drug Testing

Monitor and manage underlying condition

- Continue to ask about use of marijuana as a form of self-prescribing
- Contact pharmacy about other prescribed medications
- Inquire about potency of marijuana
- Inquire about use of alcohol and other addictive drugs
- Order frequent urine drug testing
  - Relapse to more powerful drugs and absence of prescribed opioids

Monitor for development of side effects and behavioral toxicity

- Sedation and cognitive problems
- Frequency of “breakthrough pain”
- Worsening of mood symptoms
- Problems with impaired judgment, personality changes, motivational status
- Problems with motor control – ability to operate machinery, driving, complex skills

Obtain Consultation and refer to treatment

- Refer to Addiction Medicine Specialist or Addiction Psychiatrist
- Obtain psychiatric or psychological consultation

Potential Legal Liability

Risk of causing an addictive problem "iatrogenic addiction"

- Could you create cannabis dependence by OK'ing its chronic use if you have not appropriately screened for the presence of known associated conditions and measured the presence of other drugs of abuse by ordering urine drug testing

Failure to Diagnose

- If you miss an underlying addictive disorder and the patient's use of marijuana become problematic, are you responsible for the recommendation
- What if patient uses marijuana, relapses to other drugs and suffers complications, did you contribute to the risk for and the development of cross addiction

Improper management of diagnosed condition

- If patient's co-existing disorders worsen, are you responsible for not asking about their self-prescribing and administration of marijuana
- If the patient relapses to alcohol and their hepatitis C liver condition worsens, are you responsible if you don't recommend stopping medical marijuana and recommending treatment for addiction

Legal liability in civil court proceding

- If patient had a MVA and you did not give them proper informed consent or overlooked behavioral impairment without addressing the issue of medical marijuana, can you be help responsible?
- If your patient was being prescribed high dose opioids for pain, and had an adverse consequence, how would you prove that it was the medical marijuana and NOT your prescribed medications?

ASAM White Paper : Medical Marijuana

- "Medical Marijuana" does not follow modern scientific method
  - Lack of quality control and standardization
    - Standardization by identify, purity, potency and quality
    - Provide adequate directions for use
    - Risk/Benefit profiles defined by well-controlled clinical trials
  - All major medical organization support FDA approval process
  - AMA and most medical organizations reject state legislative enactments to determine whether a medical should be made available to patients
  - Federal law prohibits distribution of cannabis by dispensaries

ASAM White Paper : Medical Marijuana

- New Drugs including botanicals must go through FDA regulatory process
  - Possible contamination with pesticides and fungi
  - Does not assure patients a reliable and reproducible dose
  - Increased cannabis potency heightens risk of adverse events, especially among niave users
  - Increased risks of abuse and dependence, especially among adolescents
  - Risk management measures to prevent diversion inadequate
  - Funding for such enforcement is lacking

ASAM White Paper : Quality Control

Contamination with microbes

- Aflatoxins are not destroyed by heat (smoking or vaporization)
- Increased risk of neurological toxicity from pesticides
- Increased risk of aspergillosis
- Immuno-suppressed patients vulnerable to infections
- Heavy metals and pesticides
  - Recent samples in CA - >170x permitted for herbals
- No inspections of producers, growers, distributors
- Patients injured by harmful products have no legal recourse

ASAM White Paper : Quality Control

Lack of labeling (required by law for medical products)

- Content information
- Warnings
- Instructions for proper use
- Unlicensed and untrained dispensary personnel offer medical advice concerning efficacy or appropriateness of various products

- Lack of physician supervision
  - Gatekeeper physician controls access yet has little reliable information and data to assess treatment efficacy, safety, etc
  - Unknown information about contraindications, drug interactions, genetic variability in metabolisms,

ASAM Recommendations

- Cannabis, cannabis based products and cannabis delivery devices should be subject to same standards that are applicable to other prescription medications and medical devices and should not be marketed until approved by FDA
- Smoking is not a safe drug delivery mechanism
- ASAM recognizes supremacy of federal regulatory standards for drug approval and distribution
  - ASAM accepts that states can enact legislation that is more restrictive, but rejects concept that states can enact more permissive regulatory standards
- ASAM rejects a process whereby State and local ballot initiatives are being decided by individuals not qualified to make such decisions

ASAM Recommendations

ASAM recommends that physicians reject responsibility for providing access until approved by FDA

For those states that have placed physicians in a gatekeeper role, ASAM has an obligation to help licensing authorities assure that physician who choose to discuss the medical use of cannabis products

- Adhere to established professional standards of proper patient care
- History and good faith examination of the patient
- Development of treatment plan with objectives
- Provision of informed consent, including discussion of side effects
- Periodic r3eview of the treatment efficacy
- Consultation as necessary
- Proper record keeping that supports decision to recommend the use of cannabis

- Have a bona fide physician-patient relationship
- Ensure that the issuance of “recommendations” is not a disproportionally large (or exclusive) aspect of their practice
- Not issue a recommendation unless the physician has adequate information regarding the composition and dose of the cannabis product
- Have adequate training in identifying substance abuse and addiction

Med MJ Treatment Agreement 1

Patients seeking treatment at Meadows Edge for substance abuse who use medical marijuana will agree to the following:

- Will present a valid medical marijuana card at the time of intake, which will be copied and placed within the medical record.
- Will be required to sign a release of information to the physician recommending the medical marijuana. Clients who refuse to allow this communication will not be allowed the use of medical marijuana and will be treated as other clients who use marijuana despite claims for medicinal use.
- Will agree to regular urine drug testing that will quantify marijuana levels, allowing for monitoring of treatment adherence over time.
- Will agree to psychological and neuropsychological testing to determine the extent of potential interference with neurological functioning and its impact on addiction treatment and recovery.

Med MJ Treatment Agreement 2

- Will be willing to share the evaluation results with the attesting physician in an ongoing manner. Refusal of such a release of information during the course of treatment will be evaluated by our medical director and may result in changes to treatment planning, including potential discharge from our program and transfer to another facility or provider.
- Will be willing to stop marijuana use during treatment at Meadows Edge, whether the marijuana was obtained legally within the medical marijuana program, or through illegal means.
- Will be willing to repeat testing to demonstrate changes in any impairments to document improvement with abstinence.

Med MJ Treatment Agreement 3

- Will be willing to follow the recommendations of the Meadows Edge staff regarding the use of medical marijuana after discussion with the attesting physician. If there is disagreement between the recommendations of our addiction medicine staff and the attesting physician, then Meadows Edge reserves the right to discontinue treatment and refer management to the attesting physician.

- Will be willing to share all data with any other regulatory agencies about marijuana use involved in your care. RI law does not allow for continued use of medical marijuana when criminal activity or sanctions (such as after DUI or drug possession charges) or on the grounds of facilities abiding by the drug free workplace act. Refusal to allow or restriction communication with involved regulatory authorities will be referred to the medical director for evaluation and may result in treatment transfer or termination.

- Will sign a medical marijuana treatment agreement (see attached) and abide by its conditions and expectations.

Nausea and Vomiting

- Marinol (dronabinol (delta-9-tetrahydro cannabinol; **Δ**9-THC)) is approved in Canada in 2.5mg and 5mg capsules

- It is indicated for severe nausea and vomiting associated with cancer chemotherapy

Nausea and Vomiting

- Cannabinoids present clear advantages over placebo in the control of CINV
- Evidence from randomized trials shows cannabinoids to be clinically only slightly better than conventional dopamine D2-receptor antagonist anti-emetics
- In some cases, patients appeared to prefer the cannabinoids over conventional therapies despite increased incidence of side effects such as drowsiness, dizziness, and hallucinations.
- For certain patients, a degree of sedation and euphoria may be perceived as beneficial during chemotherapy

Oral Cannabinoid Preparations

- Dronabinal (Marinol®) - synthetic Δ-9 THC
  - Approved in 1985 for chemotherapy induced nausea and vomiting and 1992 for anorexia and appetite stimulation
  - Efficacy compared to early anti-emetics but no recent comparison to newer more effective anti-emetics
  - Comparable efficacy to ondansetron for delayed chemotherapy induced nausea and vomiting
  - Cannabis extract (2.5 THC/1 CBD), Dronabinol and placebo comparison – no difference in appetite, weight gain and quality of life
  - Marinol® effective for central neuropathic pain in MS
  - Marinol® no to little objective effectiveness for spasticity in MS, but significant subjective improvements in spasticity, spasm, pain, tiredness and sleep

Therapeutic Uses

Dronabinol synthetic THC:

- Used as an appetite stimulant in AIDS patients
- Used in treatment of nausea & vomiting associated with chemotherapy
- Potential use to reduce muscle spasms & pain of multiple sclerosis
- Can reduce intraocular pressure of glaucoma

Nausea and Vomiting

- Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing and common adverse event associated with cancer treatment
- It is widely recognized that smoked cannabis relieves CINV
- Cannabinoid CB1 and CB2 receptors have been found in areas of the brainstem associated with emetogenic control. CB1 receptors are found in large quantities in the cerebral cortex, hippocampus, basal ganglia and cerebellum.
- Animal studies suggest that anti-emetic properties of cannabinoids are most likely related to their agonistic actions at CB1 receptors
- An *in vitro* study has shown that THC also antagonizes the 5-HT3 receptor raising the possibility that cannabinoids may exert their anti-emetic action through more than one mechanism

Oral Cannabinoid Preparations

- Cannador® - oral cannabis extract with 2:1 ratio of THC to CBD
  - No differences between appetite or quality of life compared to THC
  - No objective improvement in spasticity in MS, but subjective improvement in spasticity, spasm, pain and sleep
  - Modest dose –dependent decrease in rescue analgesia in post op pain

- Cesamet® (Nabilone) – synthetic cannabinoid analogue more potent than THC.
  - Approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond to available antiemetics
  - Possible reduced spasticity related pain in patients with upper motor neuron syndrome

Phyto-Cannabinoids Medication

Sativex®

Botanical Medication Development : 3 Stages

Botanical Raw Material (BRM)

- Fresh or processed (cleaned, frozen, dried, sliced)

Botanical Drug Substance (BDS)

- Prepared from BRM by-pulverization, decoction, expression, aqueous extraction, ethanolic extraction
- Available in multiple forms – powder, paste, liquid, juice, gum, syrup or oil

Botanical Drug Product (BDP)

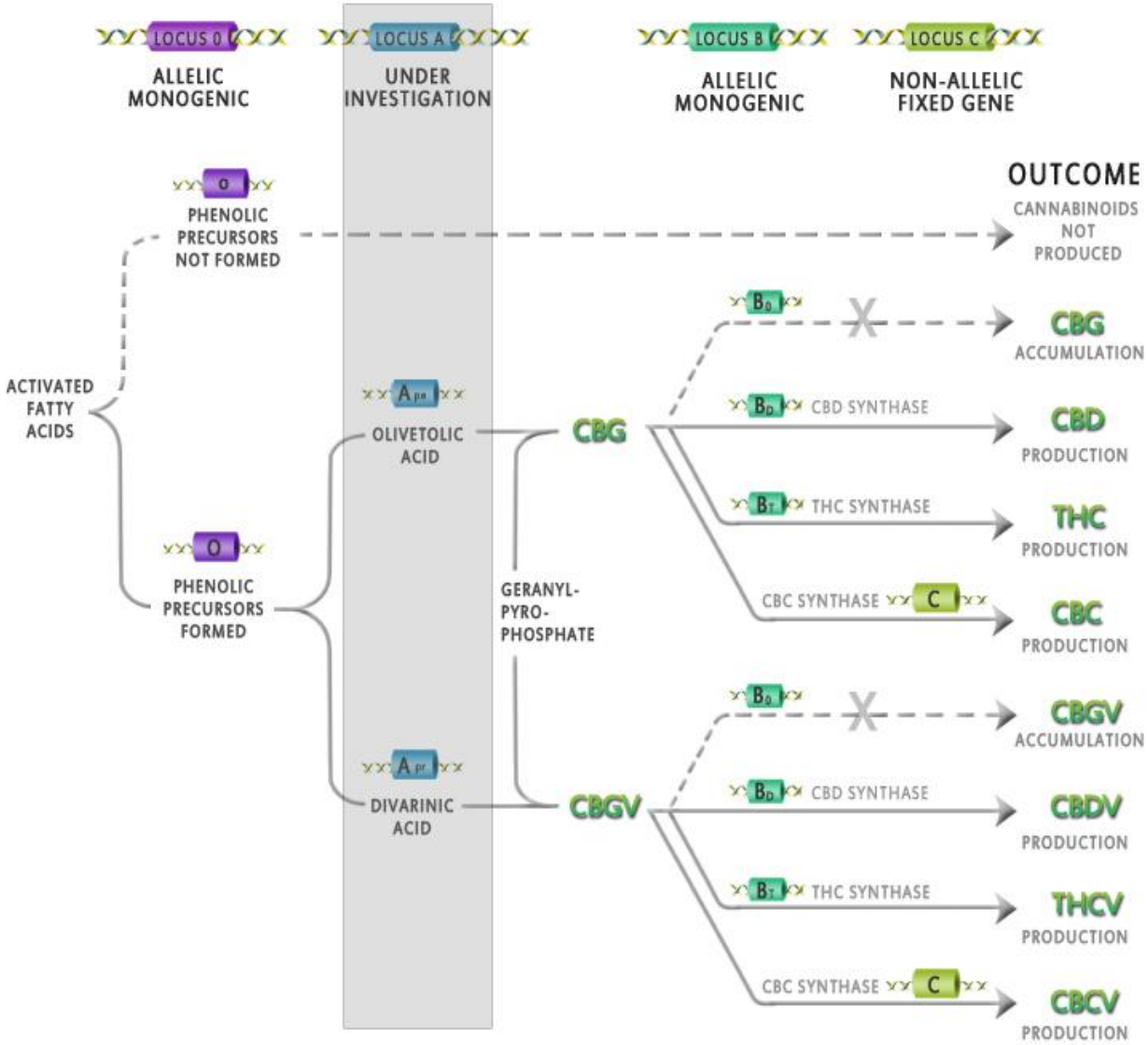
- Finished drug product prepared from BDS
- Solutions, teas, powders, tablets, capsules, elixirs, oropharyneal sprays, topicals

Cannabinoid Botanical Medicines

- Breeding and cultivation of cannabis plant varieties
  - Varieties bred for content of selected cannabinoid molecules
  - Strict control of growing environment
    - Controlled breeding of cloned plants
    - Computer-controlled glasshouses
    - Strict quality control procedures
- Standardised whole plant extracts (GMP extraction)
- Formulation into non-smoked drug delivery systems
- Full commercial pharmaceutical development programme including pre-clinical and clinical research
- Submission and approval from regulatory authorities

Data must provide robust evidence for Quality, Safety, Efficacy

Genetic Manipulation of Cannabinoid Content



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Sativex: Public Health Rationale

Sativex® emphasises the importance of pharmaceutical solution

- Required to meet standards of modern medicine: quality, safety, efficacy
- Standardized for composition and dosage
- Non-smoked; delivered like other pharmaceutical products
- Maintains integrity of physician-patient relationship
- Clinical studies ensure physicians have appropriate prescribing information
- Prescription only; patients obtain only through monitored health care sources, i.e., pharmacy
- Reimbursed by health insurance
- Eliminates physician liability for recommending unapproved drug
- Legal; no patient stigma
- Remove patients from the broader controversy over marijuana

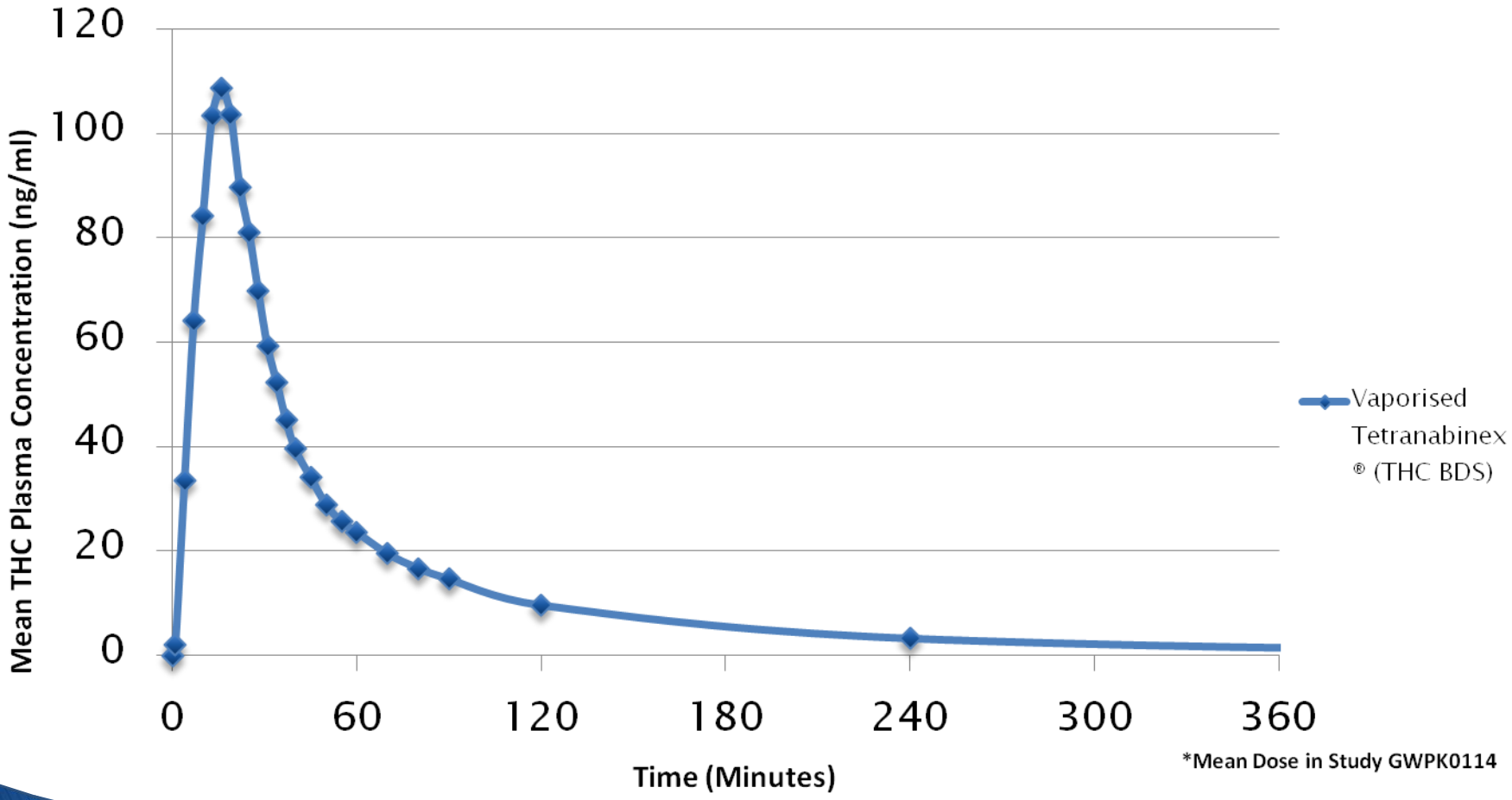
Product Portfolio

PRODUCT	INDICATION	Pre-clin	Phase I	Phase II	Phase III	Submit	Approval
Sativex	Multiple Sclerosis						
THC:CBD	MS Pain						
(1:1 ratio)	MS Spasticity						
	MS Bladder						
	Peripheral Neuropathic Pain						
	Allodynia						
	Diabetic Neuropathy						
	Central Neuropathic Pain						
	MS						
	Brachial Plexus						
	Spinal Cord Injury						
	Cancer Pain						
High CBD	Rheumatoid Arthritis						
ratios	Inflammatory Bowel Diseases						
	Neurogenic Symptoms						
	Psychotic Disorders						
	CNS (Epilepsy / Neuroprotection)						
High THC	Post-operative Pain						
	Chronic Pain						
THC-V	Neurotherapeutics						
Methadone	Drug Dependency						
Diamorphine	Drug Dependency						

Oromucosal/Sublingual Cannabis

- Sativex® (nabiximols) is botantically derived cannabis extract with 1:1 ratio of THC to CBD
  - Positive results for brachial plexus avulsion, neuropathic pain from MS, spasticity in MS, rheumatoid arthritis, peripheral neuropathic pain.
  - Better analgesic effect when compare pure THC to 1:1 ratio of THC/CBD for pain
  - Little cognitive impairment
  - Approved in Canada for neuropathic pain in MS and pain associated with advanced cancer
  - Currently in phase 3 clinical trails in USA for advanced cancer pain not relieved by high potency opioids

THC plasma levels following administration of 6.65mg* of vaporised THC



*Mean Dose in Study GWPK0114

Conclusions : Impact on Addiction Treatment

- Marijuana use is increasing
- Medical marijuana will only confuse situation
- Legalization may not improve public health – see project SAM
- Knowledge of cannabinoids will assist addiction treatment professional in helping patient sort through mis-information
- Treatment indications for Med MJ have multiple contraindications – education of patient in risk/benefit ratio
- Long term side effects + public health impact are not known
- Risk for addiction in genetically vulnerable : gateway brain
- Marijuana causes and complicates addiction treatment
- Approval of new medications will lower need for Med MJ
- Unlikely that legalization will have significant impact on crime, gangs, jail or organized drug distribution