Cannabis

- Most popular recreational drug in the US after alcohol and tobacco.
- #1 Drug in the DUI Drug Arrests and 12.6% of Friday and Saturday evening drivers test positive for use.
- Some 25 million Americans have smoked marijuana in the past year, and more than 14 million do so regularly.
- Possession and use illegal under federal law, but states have variable policies on enforcement and prosecution.

Cannabis

2700 BC - China
- Shenong pen Ts’ao ching.
  - Rheumatic pain
  - Constipation
  - Female Reproductive Problems
  - Malaria
  - Inebriant

“...Ma-fen (the fruit of cannabis) if taken in excess will produce visions of devils over a long term it makes one communicate with spirits and tightens ones body “

Zuardi, History of cannabis as a medicine: Review, Rev Bras Psiquiatr. 2006;28(2)

2000 BC - India
- Cannabis in the Atharvaveda.
  - One of the five sacred plants used medicinally and ritually.
  - Hemp (Bhanga)

“To the five kingdoms of the plants which Soma rules as Lord we speak. Darbha, hemp, barley, mighty power: may these deliver us from woe, To demons and fierce fiends we speak, to Holy Genii, Fathers, Snakes, And to the hundred deaths and one: may these deliver us from woe.”

Marijuana in Ancient History A Short Timeline. Tom Head. About.com/civil liberties
MS. 869 India Atharva-Veda Samhita, c. 1440 (Bodleian Libraries, Oriental Manuscripts)
Cannabis

700-100 BC - Scythia
- Scythians embraced cannabis for its intoxicating purposes.
- Ritual burial with cannabis seeds and leaves.
- Ritual, textile and medicinal use described by Herodotus

“The Scythians put the Seeds of this HEMP under the bags, upon the burning stones; and immediately a more agreeable vapor is emitted than from the incense burnt in Greece. The Company extremely transported with the scent, howl aloud.”

1500-1900 AD – Europe
- Widespread cultivation for fiber
- French soldiers and scientists returning from Egypt popularize hashish smoking in Europe.
- Queen Victoria’s physician, Russell Reynolds recommended its medical use for a variety of ailments and as a mild euphoriant.

“It is one of the most valuable medicines we possess”

1600-1939 AD – Americas
- Role of hemp in the US
- Medical use for rheumatism, convulsions, muscular spasms caused by tetanus and rabies.
- Recreational use by American soldiers deemed harmless.

“Marijuana as grown and used on the Isthmus of Panama is a mild stimulant and intoxicant. It is not a "habit forming" drug in the sense that the derivatives of opium, cocaine, and such drugs, are as there are no symptoms of deprivation following its withdrawal.”

1930-1970 AD – America
- U.S. Federal Bureau of Narcotics and Dangerous Drugs demonizes marijuana.
- Popularity with the artistic and literary set in the 1950’s.
- Proliferation and adoption by the Hippie culture of the 1960’s.
- Widespread use on college campuses and beyond.

“The deadly scourge that drags our children into the quagmires of degradation.”
Medical Marijuana in PA

Marijuana

Present – North America
“Nabiximols”
• Sublingual spray of THC and CBD
• 2011 GW Pharmaceuticals licensed to sell Sativex® in Canada for multiple sclerosis.
• Pending approval for cancer and neuropathic pain.
• US approval pending.

Dronabinol (Marinol®, delta-9-THC)
• Schedule III drug
Marinol has been approved by the U.S. FDA in the treatment of anorexia in HIV/AIDS patients, as well as for refractory nausea and vomiting of patients undergoing chemotherapy.

Marijuana

2000 AD- Present – America
• Currently 23 states have legalized medical use of marijuana.
• Alleged efficacy in treating:
  • AIDS (HIV) & AIDS
  • Wasting Diseases
  • Arthritis
  • Crohn’s Disease
  • Epilepsy / Seizures
  • Glaucoma
  • Migraines
  • Multiple Sclerosis / Muscle Spasms
  • Nausea of Chemotherapy
  • Pain / Analgesia

Marijuana

2000 AD- Present – The World

*Legality of cannabis for medical purposes* by Trinitresque - Own work. Licensed under CC BY-SA 3.0 via Wikipedia Commons
Cannabinoid Milestones

- 1964 Gaoni and Mechoulam identify structure of THC.
- 1984 Pfizer synthesizes CP55,940, CP47,497.
- 1986 Makriyannis describes SAR for dibenzopyrans.
- 1988 HU-210 synthesized
- 1990’s CB₁ and CB₂ are identified and characterized

Cannabinoid Pharmacology

- Endocannabinoids
  - Anandamide (AEA)
  - 2-Arachidonyl glycerol (2AG)
  - Palmitoylethanolamide (PEA)*
- Degraded by FAAH, NAAA, and MAGL

The CB-1 Receptor

- Cerebellum Movement
- Basal Ganglia Movement
- Cerebral Cortex Higher cognitive function
- Hypothalamus Appetite
- Hippocampus Learning, Memory, stress
- Medulla Nausea/vomiting, CTZ
- Spinal cord Peripheral sensation/pain

Cannabinoid Pharmacology

- Endocannabinoid-mediated depolarization-induced suppression of inhibition
  - Endocannabinoids released from the depolarized postsynaptic neuron bind to CB1 receptors in the pre-synaptic neuron and cause a reduction in GABA release.

*PEA does not bind to cannabinoid receptors
Cannabinoid Pharmacology

**Endocannabinoid Neurobiology**
- Memory
- Appetite
- Energy Balance and metabolism
- Stress Response
- Autonomic Nervous System
- Immune Function
- Female Reproduction
- Analgesia
- Thermoregulation
- Sleep

**Acute Physiological Effects**
- Tachycardia
- Conjunctival injection
- Xerostomia
- Increased appetite
- Analgesia
- Vasodilation
- Bronchodilation
- Decreased respiratory rate

**Acute Psychoactive Effects**
- Euphoria
- Relaxation/Stress Reduction
- Enhanced Perception
  - Music, Humor, Arts
  - Increased Creativity/Abstract Thinking/Sensuality
- Illusions/Pseudohallucinations
- Time Distortion
- Ataxia
- Anxiety, Paranoia, Illusions, Depersonalization

**Cannabinoid Pharmacokinetics**

*Smoked THC Time-Concentration Curve*

- THC Concentrations peak within minutes of last inhalation, and fall rapidly as the drug distributes.

*Background Images:*
- "Bloodshot EyeBall" by Psychonaught - Own work. Licensed under Public Domain via Commons

*Images courtesy of:*
- Marilyn Huestis, Borkenstein Drug Course, 2012

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barry.logan@nmslabs.com
Cannabinoid Pharmacokinetics

Smoked THC Time-Concentration Curve

• THC concentrations fall:
  • To about 60% of their peak within 15 minutes after the end of smoking.
  • To about 20% of their peak 30 minutes after the end of smoking.

Courtesy Marilyn Huestis, Borkenstein Drug Course, 2012

Factors Affecting Peak/Concentration

• Dose
  • Potency of marijuana
  • Amount smoked
  • Duration and frequency of smoking/inhalation
  • Depth of inhalation/breath holding

• Tolerance
  • Frequency and pattern of use

• Body Fat

• Co-ingestion with alcohol or other drugs

• Time between smoking and blood draw

Cannabinoid Pharmacodynamics

Smoked THC Time-Concentration Curve

• There is substantial inter-subject variability in peak THC concentration based on smoking technique, body fat, metabolism

Courtesy Marilyn Huestis, Borkenstein Drug Course, 2012

Visual Analog Scale Composite Stoned, High, Strength (n=63)
Cannabinoid Pharmacodynamics

Feel-Drug Visual Analog Scale

![Graph showing Feel-Drug Visual Analog Scale](image)

Cannabinoid Pharmacokinetics

Oral THC Time-Concentration Curve

- No ability to titrate dose
- THC concentrations peak at 2-4 hours
- Longer Effect Profile
  - 6-10 hours or greater
- Active Metabolite 11-OH-THC contributes to effects

Cannabis and Health

**Physical Health**

- **Respiratory:** Marijuana smoke causes respiratory inflammation and increased risk for bronchitis and COPD.
- **Cancer:** Marijuana smoke contains many of the same carcinogenic chemicals as tobacco smoke but cancer rates are comparable to controls.
- **Cardiac:** Heart attack patients smoking marijuana displayed a 5-fold greater risk of heart attack than non-users in the hour following smoking – equivalent to the risk from exercise.


Cannabis and Health

**Physical Health**

- **Reproductive:** Endocrine disrupting effects of marijuana show subtle but significant effects on fertility and sperm production, egg implantation, embryonic development, and fetal growth.
- **Perinatal:** Marijuana use during pregnancy or breast feeding is linked with the following outcomes: Low birth weight; developmental delay; and behavioral problems, but other factors confound.

Cannabis and Health

Psychosocial Health

- Dependence: 9%-18% of regular marijuana users report compulsive use with higher rates in adolescents.
- Mental Health: Increased rates of depression and anxiety are reported among regular marijuana users, although the direction of causality is not established.
- Marijuana use can precipitate schizophrenia and psychosis in predisposed individuals.

http://www.csam-asam.org/adverse-effects-marijuana-healthcare-professionals

Cannabis and Impairment

Acute Cognitive Effects:
- Concentration and sustained attention/vigilance.
- Fatigue, sleepiness, lethargy, memory problems.
- Reaction time
- Difficulty in thinking and problem-solving.
- Difficulty in registering, processing, and using information.

Cannabis and Health

Chronic Cognitive Effects

- Chronic marijuana use causes changes in brain function, as demonstrated by measures of cerebral blood flow, glucose metabolism, electrophysiology, and structural anatomy.
- Functional imaging studies have shown less activity in brain regions involved in memory and attention in chronic marijuana users than in non-users, even after 28 days of abstinence.
- Adolescents are most at risk.

http://www.csam-asam.org/adverse-effects-marijuana-healthcare-professionals

Cannabis and Impairment

Psychomotor Aspects

- Decreased motor coordination
- Slurred speech
- Dizziness
- Impairment in reaction time and tracking.
Cannabis and Driving

Driving Deficits
- Attention
- Vigilance
- Arousal
- Weaving
- Impulsivity
- Reaction Time

Cannabinoids and Driving

• Experimental Evidence
  - THC’s impairing effects increase with task complexity.
  - Unexpected circumstances and choice during otherwise monotonous driving exhibit increased risk for errors over non-cannabis using controls.
  - Reaction time, road tracking, weaving, steering wheel variability, and brake latency all increase with recent cannabis exposure.
  - THC effects on cognitive performance following smoking include immediate recall, executive functioning, working memory and attention.
  - Crash risk results are mixed

Cannabis and Driving

Mean change in weaving in the Road Tracking Test after incremental doses of THC alone.

Equivalent effect of BAC (g/100ml)

Courtey Jan Ramaekers, Borkenstein Drug Course, 2012
Cannabis and Driving

Driving Deficits
- Attention
- Vigilance
- Arousal
- Weaving
- Impulsivity
- Reaction Time

Effects of a user-preferred THC dose are comparable to 0.05-0.07g/100mL alcohol.

Cannabis, Alcohol and Driving

• There is no good evidence linking specific THC thresholds in blood to a degree of impairment
  • Blood samples are typically collected 45 minutes to 2 hours after alleged impaired driving.
  • THC concentrations change dramatically over 30 minutes, and can’t reliably be extrapolated to the time of driving.
  • Blood concentrations do not approximate the concentrations in the brain, especially after oral ingestion
  • A threshold of 1, 2, or 5ng/mL is not evidence of impairment at the time of driving
Cannabinoid Concentrations

<table>
<thead>
<tr>
<th></th>
<th>% Subjects with THC &gt;1ng/mL</th>
<th>% Subjects with THC &gt;2ng/mL</th>
<th>% Subjects with THC &gt;5ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Cannabinoid</td>
<td>79.5%</td>
<td>60.3%</td>
<td>29.6%</td>
</tr>
<tr>
<td>+ Cannabinoid + Alcohol - Other Drug</td>
<td>90.51%</td>
<td>78.9%</td>
<td>49.3%</td>
</tr>
<tr>
<td>+ Cannabinoid + Alcohol + Other Drug</td>
<td>79.4%</td>
<td>56.8%</td>
<td>23.5%</td>
</tr>
<tr>
<td>+ Cannabinoid + Alcohol + Other Drug</td>
<td>74.6%</td>
<td>55.5%</td>
<td>28.6%</td>
</tr>
<tr>
<td>+ Cannabinoid + Alcohol + Other Drug</td>
<td>71.9%</td>
<td>47.8%</td>
<td>19.0%</td>
</tr>
</tbody>
</table>

Percentage of arrested drivers (n=4,799) with THC concentrations above various statutory thresholds (1ng/mL (PA); 2ng/mL (OH, NV); 5ng/mL (WA, CO, MT).

To Legalize or Not?

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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</thead>
<tbody>
<tr>
<td>The public are increasingly demanding access as an option</td>
<td>The scientific evidence for treating more than a few specific conditions is weak</td>
</tr>
<tr>
<td>A significant segment of the population believes it is beneficial</td>
<td>Its negative effects are an additional burden to regulate and administer</td>
</tr>
<tr>
<td>The evidence for health risks show few major risks, and high risk populations can be regulated or educated</td>
<td>Vulnerable populations are most at risk and don’t need additional exposure to this risk</td>
</tr>
<tr>
<td>A legitimate market will reduce the illicit market</td>
<td>Increased availability will lead to increased use</td>
</tr>
<tr>
<td>Prohibitions around driving under the influence will offset the risks to the public</td>
<td>Technology for screening for recent marijuana use is immature and science doesn’t support limits</td>
</tr>
</tbody>
</table>

Logan, Kacinko, Beirness, AAAFTS in press, 2015

Questions

barry.logan@nmslabs.com