The medical science of cannabis

David Casarett MD MA
Professor of Medicine
Chief of Palliative Care
Duke University
Conflicts of interest

- SAB: Curio Wellness, Resolve Digital, Zelda Therapeutics, Evio Labs
- Senior advisor: Northern Swan
- Owner/founder: DisposeRx, Cannabis Outcomes, Dropp, MMJ.org
- No consulting or speaking for the pharmaceutical industry

Views do not reflect the opinions of Duke University or Duke Health
Focus: Medical cannabis

- Focus on medical cannabis use
- Not recreational
Marijuana: Medication or weed?
I wrote **Stoned** for Judith...
3 Surprises

• There’s a science of how cannabis works
• Cannabis has real potential benefits (and risks)
• There’s a wide gap between enthusiasm for medical cannabis and the evidence supporting it
Surprise #1: There’s a science of how cannabis works

- Tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- (And many other cannabinoids)
Ms. *Sativa*: Up close and personal
Cannabis sativa/indica: what’s the difference?

Sativa strains: Often higher THC concentrations
Indica strains: Generally lower THC and higher CBD
BUT: Species don’t really predict THC/CBD levels
Strains don’t predict chemical ingredients

<table>
<thead>
<tr>
<th>Strain Name</th>
<th>Replicates</th>
<th>Indica/Sativa/Hybrid or Unknown</th>
<th>OG or Kush</th>
<th>Average</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Generation Diablo</td>
<td>16</td>
<td>Indica</td>
<td>-</td>
<td>20.8</td>
<td>16.2</td>
<td>24.2</td>
</tr>
<tr>
<td>Afghan Kush</td>
<td>10</td>
<td>Indica</td>
<td>Kush</td>
<td>17.6</td>
<td>14.7</td>
<td>22.0</td>
</tr>
<tr>
<td>Alien OG</td>
<td>8</td>
<td>Hybrid</td>
<td>OG</td>
<td>19.7</td>
<td>14.6</td>
<td>23.8</td>
</tr>
<tr>
<td>Black Mamba</td>
<td>9</td>
<td>Indica</td>
<td>-</td>
<td>21.0</td>
<td>19.4</td>
<td>22.8</td>
</tr>
<tr>
<td>Blackberry Kush</td>
<td>11</td>
<td>Indica</td>
<td>Kush</td>
<td>16.9</td>
<td>12.5</td>
<td>18.0</td>
</tr>
<tr>
<td>Blue Dream</td>
<td>31</td>
<td>Hybrid</td>
<td>-</td>
<td>16.9</td>
<td>12.2</td>
<td>21.2</td>
</tr>
<tr>
<td>Blue Dream Haze</td>
<td>9</td>
<td>Hybrid</td>
<td>Kush</td>
<td>15.5</td>
<td>10.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Bubba Kush</td>
<td>9</td>
<td>Hybrid</td>
<td>-</td>
<td>17.4</td>
<td>13.6</td>
<td>21.0</td>
</tr>
<tr>
<td>ChemDawg</td>
<td>14</td>
<td>Hybrid</td>
<td>Kush</td>
<td>15.5</td>
<td>10.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Fire OG</td>
<td>23</td>
<td>Hybrid</td>
<td>OG</td>
<td>17.3</td>
<td>9.8</td>
<td>20.2</td>
</tr>
<tr>
<td>Girl Scout Cookies</td>
<td>19</td>
<td>Hybrid</td>
<td>-</td>
<td>16.9</td>
<td>11.2</td>
<td>23.1</td>
</tr>
<tr>
<td>Grand Daddy Purple</td>
<td>14</td>
<td>Indica</td>
<td>-</td>
<td>16.9</td>
<td>12.2</td>
<td>23.3</td>
</tr>
<tr>
<td>Green Crack</td>
<td>16</td>
<td>Sativa</td>
<td>-</td>
<td>16.4</td>
<td>11.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Harlequin</td>
<td>15</td>
<td>Sativa</td>
<td>-</td>
<td>5.0</td>
<td>2.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Headband</td>
<td>8</td>
<td>Hybrid</td>
<td>-</td>
<td>16.5</td>
<td>5.4</td>
<td>22.1</td>
</tr>
<tr>
<td>Jack Herer</td>
<td>24</td>
<td>Sativa</td>
<td>-</td>
<td>16.9</td>
<td>13.1</td>
<td>21.4</td>
</tr>
<tr>
<td>LA Confidential</td>
<td>17</td>
<td>Indica</td>
<td>-</td>
<td>15.1</td>
<td>8.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Larry OG</td>
<td>8</td>
<td>Hybrid</td>
<td>OG</td>
<td>17.1</td>
<td>6.2</td>
<td>24.3</td>
</tr>
<tr>
<td>Neptune OG</td>
<td>10</td>
<td>Indica</td>
<td>OG</td>
<td>18.0</td>
<td>12.6</td>
<td>22.8</td>
</tr>
</tbody>
</table>

Elzinga et al. Natural Products Chemistry and Research; 2016.
The science of cannabinoid receptors

THC: CB1 and CB2 receptors, mostly in the brain, plus reproductive system

CBD: Other receptors, mostly in the immune system, plus microglial cells in the brain

Other cannabinoids... Other receptors...
Cannabis is nature’s way of hacking the endocannabinoid system

- Anandamide, the “Bliss Molecule”
- 2-AG
- Many more
Surprise #1B
There’s a science of how to use marijuana
Absorption and metabolism

• Concentration (THC)
  – flower=2-10%
  – hash>30%
  – shatter>80%

• Bioavailability
  – PO=10-20%; Inhaled=30-50%
  – BUT: Wide (10-fold) inter-individual variability (inhaled)
Advantage of smoking: fast uptake

Figure 13-1 Mean Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) concentrations during smoking of a 3.55% THC cigarette. Each arrow indicates a single puff on the cannabis cigarette, demonstrating the rapid increase in THC concentrations. Note that concentrations peak before the end of smoking.
William O’Shaughnessy, goats, and tinctures
Edibles
The future of cannabis delivery systems?

What We Know About Vaping-Related Lung Illness
Doctors, officials urge people to stop vaping as they investigate six deaths, hundreds of potential cases of pulmonary illness
Surprise #2: Cannabis does have real medical benefits (and risks)
“The best medicine the drug companies don’t want you to know about.”
-Dispensary owner in San Diego
Potential uses in state laws in the US:

• Nausea
• Chronic pain
• Anxiety
• PTSD
• Anorexia/weight loss
• Insomnia
• Pediatric epilepsy
• And many more...
PAIN, PAIN GO AWAY
FREE MEDICAL CANNABIS CARD
1-833-CARD-4-FREE
How much evidence is there of medical benefit?
Answer: Not as much as we’d like

• **Moderate** evidence:
  – Neuropathic pain
  – Spasticity

• **Weak** evidence:
  – Nausea
  – Weight gain in the setting of chronic, serious illness (AIDS, cancer)
  – Sleep
National Academy of Sciences guidance:

- Conclusive/Substantial:
  - Chronic pain
  - CINV
  - Spasticity in MS

- Moderate
  - Improved sleep (in OSA, fibromyalgia, chronic pain and other conditions)

- Limited:
  - Improved outcomes after TBI or intracranial hemorrhage
“Conclusive or substantial evidence for chronic pain”
“Approximately 1 in 5 patients will benefit”
“Risks outweigh benefits”

Cannabis products for adults with chronic neuropathic pain

Published:
7 March 2018

Authors:
Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

Bottom line

There is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain.

Background
Blinding: The Achilles heel of medical cannabis research

- Among patients assigned first to “active” marijuana, 14/15 (93%) guessed correctly
Curating the emerging evidence
[Cannabis doesn’t cure cancer]
“Risks? Marijuana doesn’t have any risks—it’s a flower. Not like morphine.”

- Dispensary owner in Denver
A Toxicologic View of Marijuana

Marijuana is acutely, and probably chronically, toxic. Its potential dangers need further investigation.

LOUIS J. CASARETT, Ph.D., and RANDALL C. BASELT, B.S., Honolulu
Risks?

**Known risks**
- Driving impairment
- Addiction
- AYA brain development
- Hyperemesis syndrome
- Psychotic episodes

**Possible risks**
- Myocardial infarction**
- Stroke*
- Schizophrenia*
- Long-term cognitive dysfunction**

- NOT: Cancer, lung disease
(Pulmonary risks)

- Very minor PFT changes
  - Increased FVC
  - Decreased FEV1 and FEV1/FVC for very heavy users
  - No cancer risk

(Tashkin, Annals ATS, 2013)
Driving

• Slow reaction times
• Distraction
• Lack of focus
• Poor salience detection
• Field sobriety test not helpful
Contaminants
Risks

• A few risks are known
• Many are speculative
• Everyone has an axe to grind
• Case reports are common and can be misleading
So...Medication or weed?

• Significant benefits
• Real risks

“What is a weed? A plant whose virtues have never been discovered.”

-Ralph Waldo Emerson
The medical marijuana enthusiasm-evidence gap
How much evidence of benefit and safety is enough?

For patients and physicians:
- One or two small studies
- Ideally a controlled trial
- Anecdote

For researchers and policymakers:
- Multiple large controlled trials
- Placebo controls
- Rigorous blinding
- Large-scale safety studies
If enthusiasm for medical marijuana has outstripped the evidence supporting its use, that’s often because people are dissatisfied with the medical care they’re receiving.