The USA Model: Uncontrolled Experiments in the Wild West

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Sativex/nabiximols is approved in 27 Countries
USA: A Patchwork of Laws  

(from mpp.org)

Light grey: medical access  
Dark grey: decriminalization  
Black: medical + decriminalization  
Blue: Legalization + medical
Oral THC (dronabinol)

- Approved in USA 1985
- Slow: 60-120 minutes or more to onset
- Loss of dose titration capability
- Too little vs. too much
- Poor therapeutic index
- 95% of THC metabolized by liver on first pass to 11-OH-THC
- Very expensive
- Lacks synergistic components
Cannabis Dosing: Smoking

- Illegal
- Provokes intoxication
- Dose titration not easily achieved
- Inefficient and wasteful of THC
- Polyaromatic hydrocarbons (PAH) produce premalignant cytological changes
- Bronchial irritation inevitable
- Can not achieve FDA approval as a prescription product
Pesticides in Smoked Cannabis

- No EPA tolerances are set for pesticides on smoked crops.
- Pesticide and growth regulator residues are frequently noted in lab testing of black market cannabis.
- ~40-70% of toxic residues persist in cannabis smoke.

The Current Study

To more fully assess the current situation, 26 distinct cannabis samples were purchased (24 concentrates, 2 cannabis inflorescence) from legal stores in Washington and passed via witnessed chain of evidence (Seattle Times) to a state certified legal licensed laboratory (Trace Analytics, Spokane, WA).

Results:

• 22/26 samples tested positively for pesticides (84.6%).

• Many harbored multiple contaminants, attaining levels in the tens or even hundreds of thousands of parts per billion (ppb), exceeding the upper limit of quantification.

• These included 24 distinct pesticide agents: insecticides, miticides, fungicides, an insecticidal synergist and growth regulators, including organophosphates, organochlorides, carbamates, neonicotinoids, etc.

## 24 Insecticides Isolated from Legal WA Cannabis

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Structure</th>
<th>Class/Usage</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaryllin</td>
<td><img src="#" alt="Structure" /></td>
<td>Fungicide</td>
<td>Questionable developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Bifenthrin</td>
<td><img src="#" alt="Structure" /></td>
<td>Insecticide</td>
<td>Questionable developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Carbaryl</td>
<td><img src="#" alt="Structure" /></td>
<td>Insecticide</td>
<td>BAD ACTOR; Cholinesterase inhibitor; carcinogenic; developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Carbendazim</td>
<td><img src="#" alt="Structure" /></td>
<td>Fungicide</td>
<td>Possible carcinogen; Questionable developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Clothianidin</td>
<td><img src="#" alt="Structure" /></td>
<td>Neonicotinoid Insecticide</td>
<td>Questionable developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Diazinon</td>
<td><img src="#" alt="Structure" /></td>
<td>Organophosphate Insecticide</td>
<td>Unlikely carcinogen; Cholinesterase inhibitor; developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Dicofol</td>
<td><img src="#" alt="Structure" /></td>
<td>Herbicide/ Photocytosis inhibitor</td>
<td>Carcinogenic; developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
<tr>
<td>Ethephon</td>
<td><img src="#" alt="Structure" /></td>
<td>Organophosphate Insecticide</td>
<td>BAD ACTOR; Carcinogenic; developmental/ reproductive toxic and endocrine disruptor</td>
</tr>
</tbody>
</table>

### Data from:
Carbaryl: a Carbamate Insecticide

BAD ACTOR
Cholinesterase inhibitor
Carcinogen;
Developmental/reproductive toxin
Suspected endocrine disruptor

Heavy Metals (Pb, Hg, Cd, Ar)

- Cannabis is a bio-accumulator
- If heavy metals (lead, mercury, cadmium, arsenic) are present in the soil or medium, they will be recruited into the plant.
- This is an advantage for growing hemp as a bioremediation technique.
- It is deleterious to ingest such material, which must be kept out of the plant for preventive public health.
Differential Vaporization

Vaporization to date has not eliminated toxic tar components or ammonia. Poses same regulatory hurdles as smoked cannabis.

Cannabis Collection II

- Illegal under federal law
- No real quality control
- No regulatory approval
- Candy is attractive to children

CBME Knock-off:
“I Can’t Believe It’s Not Nabiximols”
Victoria, BC, Canada
(photo EBR)

Only 54% of medical users had tried vaporizers, and only half, or 27% preferred them.

<table>
<thead>
<tr>
<th></th>
<th>Smoking</th>
<th>Vaporizer</th>
<th>Tea</th>
<th>Food/Tinct</th>
<th>Dronabinol</th>
<th>Nabulene</th>
<th>THC vap</th>
<th>Nabiximols</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Ever tried (N=)</td>
<td>827</td>
<td>450</td>
<td>213</td>
<td>571</td>
<td>74</td>
<td>14</td>
<td>28</td>
<td>7</td>
<td>69</td>
</tr>
<tr>
<td>b) Preference (N=)</td>
<td>599</td>
<td>225</td>
<td>23</td>
<td>75</td>
<td>17</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>c) Satisfied users (%)</td>
<td>72.4</td>
<td>50.0</td>
<td>10.8</td>
<td>13.1</td>
<td>23.0</td>
<td>7.1</td>
<td>3.6</td>
<td>57.1</td>
<td>11.6</td>
</tr>
</tbody>
</table>

**TABLE 1**

(a) Methods of Ingestion Ever Tried (Multiple Answers Possible), Most Preferred Method of Intake; (B) Expressed as Total Number of Participants; and (C) Expressed as Percentage of All Users

Only 54% of medical users had tried vaporizers, and only half, or 27% preferred them.

Smoking predominates!
The Quest for Higher THC

Cannabis Concentrates, or “Dabs”

- Cannabis is extracted with polar solvents
- Many are flammable and potentially explosive
- THC (and contaminants) are highly concentrated by the process
- “Naphtha” in RSO and butane are often contaminated and leave toxic residues
- Even dab users acknowledge greater tolerance and withdrawal (Loflin, 2014)
- >50% of legal sales in Washington State
- How high does a patient need to be to have symptom relief?

“Vaporization” of “Wax” (or Burning?)

E-cigarettes use propylene glycol and glycerol as propellants.

Under heat, up to 2% of this mixture forms **formaldehyde**, a Group 1 carcinogen (International Agency for Research on Cancer-IARC).

Risk is as much as 15X that of chronic cigarette smoking.

Problems in Cannabis Laboratory Analysis

• Hampered by illegality: Lack of Schedule I permits (USA)
• Lack of uniformity in methodology
• Poor application of due diligence, “dry-lab results”
• Dearth of cannabinoid standards
• Cannabinoids are tough to assay properly
• Terpenoids are even tougher
National Pain Report: Survey of >1300 Fibromyalgia Patients, April 2014

http://nationalpainreport.com/marijuana-rated-most-effective-for-treating-fibromyalgia-8823638.html

Rates of opioid overdose mortality increased over time, but always less in cannabis states, with a plateau near the end of the study period.

States with medical cannabis laws had a 24.8% lower overdose mortality (p=0.003), and figures improved annually the longer the policy was in effect. These policies were estimated to have saved 1729 lives in 2010.

“If the relationship between medical cannabis laws and opioid analgesic overdose mortality is substantiated in further work, enactment of laws to allow for use of medical cannabis may be advocated as part of a comprehensive package of polices to reduce the population risk of opioid analgesics.” (p. 1672)
The Four Pillars of True Medicine

1) Efficacy
2) Safety
3) Standardization
4) Accessibility

- **Quality**
  - Product Composition
  - Characterization
  - Quantification of components
  - Standardization / Consistency
  - Stability / Storage

- **Safety**
  - Animal data, including:
    - Carcinogenicity
    - Reproductive toxicology
    - Chronic toxicology
    - Genotoxicology
    - Safety pharmacology
  - Clinical data
    - Several hundred patient-years of data required
    - Reports of all adverse events (mild/moderate/severe – related and unrelated)
    - Immediate regulatory notification of SAEs

- **Efficacy**
  - Multiple Phase II & Phase III placebo-controlled clinical trials for indication

What’s Wrong with Current Herbal Cannabis Clinical Trials?

• They are too short in duration.
• They are too small in size.
• Use of unstandardized cannabis preparations renders the results unreproducible.
• Blinding has been largely inadequate.
• They do not advance the regulatory process (i.e., approval as a pharmaceutical) at all in the USA.
Cannabis Efficacy: Where Are We Now?

- Solid clinical trial proof for cannabinoid therapy exists for cannabis, THC and CB₁ agonists:
  - Nausea and vomiting
  - Anorexia associated with chemotherapy, HIV/AIDS
  - Spasticity in multiple sclerosis and other neurological conditions
  - Neuropathic pain, whether peripheral or central
  - Cancer pain
  - Lower urinary tract symptoms (LUTS)

- For cannabidiol (CBD):
  - Intractable epilepsy
  - Schizophrenia, positive and negative symptoms
Clinical Research Priorities

• Pain and Inflammation, particularly unstudied conditions
• Arthritis, both rheumatoid and osteoarthritis
• Inflammatory bowel disease (Crohn, ulcerative colitis)
• Metabolic syndrome/insulin resistance
• Dermatology: acne, psoriasis, contact dermatitis
• Neuroprotection in dementia, TBI, CVA
• Optimizing ECS health
• Lifestyle and nutritional research

Reduce cannabis need
Prospective Cannabis Research

What is needed:

1) Standardized GMP cannabis with appropriate cannabinoid & terpenoid profiles
2) Genuine Phase II and III clinical trials meeting FDA standards for pharmaceutical development

What is not needed:

1) More case-studies
2) More surveys
3) Additional NIDA-supplied studies that cannot be reproduced or advance therapeutics
4) Wasted public funds
Conclusions

• Cannabis has proven medical potential, and has led to discovery of the ECS, a major physiological homeostatic regulatory system

• Cannabis, in the proper formulation, can become an approved pharmaceutical meeting necessary criteria of safety, efficacy and consistency.