Current Status and Future Applications of Cannabis Research: Unlocking the Potential

Ethan Russo, MD
Medical Director
PHYTECS

ethanrusso@comcast.net
www.phytecs.com

Copyright 2016
Cannabinoids: 3 Varieties

- **Phytocannabinoids** (Pate 1994): terpenophenolic 21-C compounds found in the genus *Cannabis* (e.g., THC, CBD)

- **Endocannabinoids** (Di Marzo 1998): natural endogenous compounds binding cannabinoid receptors (e.g., anandamide) whose functions are: “relax, eat, sleep, forget and protect”

- **Synthetic cannabinoids** (e.g., ajulemic acid) that also affect cannabinoid receptors

An internal homeostatic regulatory system of 3 components:
Endocannabinoids (anandamide, 2-AG),
CB₁, CB₂ & TRPV1 receptors,
Their regulatory enzymes

Endocannabinoids are produced on demand, travel in retrograde fashion to inhibit neurotransmitter release.

Active and “inactive” components work together in an “Entourage Effect.”
CB₁ Expression in Brain

CB₁ is highly expressed in nociceptive areas, cerebellum, limbic system, basal ganglia and reward pathways.

Although prominent in the substantia nigra and periacqueductal grey matter, it is distributed in a limited fashion otherwise in the brainstem, and not in medullary respiratory centers.
CB₁ is the most abundant G-protein-coupled receptor in the brain, with a major neuromodulatory function.

Role characterized as, “relax, eat, sleep, forget and protect.”

(Di Marzo, 1998)

Modulates pain, movement, emotion, emesis, seizure threshold, et al.

CB₂ and Inflammation

CB₂ is a mainly peripheral, immunomodulatory receptor with an important role in pain and inflammation.

CB₂ agonists also hold great promise in treatment of hepatic fibrosis and related conditions.
In addition to its anti-inflammatory and bacteriostatic effects, cannabidiol is a TRPV4 agonist that works as a sebostatic agent in acne (Olah 2014).
In addition to these systems, the ECS is active in cardiac and bone physiology.

Cannabidiol was recently demonstrated to stimulate bone fracture healing (Kogan et al. 2015)
Pentyl Cannabinoid Synthesis

Δ⁹-tetrahydrocannabinol (THC)

- Isolated and identified 1964 (Gaoni & Mechoulam)
- $K_i=53.3$ at CB₁, 75.3 at CB₂ (Felder 1995)
- Analgesic & antipruritic (Neff 2002)
- Bronchodilatory (Williams 1976)
- Neuroprotective antioxidant (Hampson 1998)
- THC has 20X A-I power of ASA, 2X A-I power of hydrocortisone (Evans 1991)
- Muscle relaxant
- Antiemetic
- Primary psychoactive component
- THC not a COX-1 or COX-2 inhibitor (Stott 2005)
- ↓ β-amyloid (Eubanks 2006)
Cannabidiol (CBD) I

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- Hardly binds CB\textsubscript{1}, but shows unique ability to antagonize the receptor in low nM range (Thomas 2007)
- Works as a negative allosteric modulator on CB\textsubscript{1} (Laprairie 2015)
- Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also antioxidant > Vitamins C and E (Hampson et al. 1998)
- Now known to be a TRPV1 agonist (like AEA) with EC\textsubscript{50} 3.2-3.5 µM (Bisogno et al. 2001)
- Inhibits uptake of the AEA, and weakly inhibits its hydrolysis (Bisogno et al. 2001)
- Alerting vs. THC in clinic (Nicholson 2004)
Cannabidiol (CBD) II

- **Anticonvulsant** (Cunha; Jones 2010)
- **Anti-anxiety** (Crippa 2010)
- Cytotoxic in breast cancer ($IC_{50}$ 6-10.6 μM) and many other cancer cell lines while being cytopreservative for normal cells (Ligresti 2006)
- Antagonist at GPR55 and GPR18 (McHugh et al. 2010)
Cannabidiol (CBD) III

- Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000)
- Not COX-1 or COX-2 inhibitor (Stott 2005)
- Displays agonistic activity at 5-HT$_{1A}$ receptor (Russo-Parker 2005), possible basis for observed anxiolysis (Resstel 2009; Soares 2010), CVA reduction (Mishima 2005), nausea (Limebeer 2009), & improvement of cognition in hepatic encephalopathy (Magen 2009).
- Enhances adenosine receptor A2A signaling via inhibition of an adenosine transporter (Carrier 2006), suggesting an important therapeutic role in various inflammatory and chronic pain states
- Prevents prion accumulation and neuronal toxicity (Dirikoc 2007)
- CBD stimulates bone fracture healing (Kogan 2015)
Misconceptions about Cannabidiol (CBD)

- A tiny amount is enough (actually more is better)
- It is a sedative (Alerting vs. THC in clinic [Nicholson 2004]), and sedation may be operative with high doses, drug-drug interactions or terpenoid effects, i.e., myrcene)
- It turns into THC in the body (Merrick 2016) (actually upregulates anandamide/ECS)
Responder Analysis (ITT) nabiximols vs. THC Extract vs. Placebo

Study GWCA0101 - Responder Analyses (ITT)

% of Patients Achieving Response Level

Odds ratios* in red are statistically significant
p-value relates to comparison of proportion of patients Sativex v Placebo

Presence of CBD in nabiximols produced clinical improvement over high-THC extract and placebo


* Odds Ratio nabiximols vs placebo.
# Fisher's Exact Test.

Results imply a markedly better therapeutic index and safety margin for nabiximols/Sativex over pure THC.

Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 163(7):1344-64, 2011

Certain cannabis terpenoids are analgesic and/or anti-inflammatory, mood enhancing, and modulate THC effects producing synergy with phytocannabinoids
Cannabis: The Species Controversy

• *Cannabis sativa* vs. *Cannabis indica* vs. *Cannabis ruderalis, Cannabis afghanica* et al.

• Morphology does not predict biochemistry!

Linnaeus vs. Lamarck: An 18th century taxonomic battle royale.

Vouchers courtesy John McPartland
www.beyondTHC.com/mcpartlands-corrected-vernacular-nomenclature/
Outline of an Ideal Cannabis Classification Scheme

• Combines shape, content and purpose
• Basic class based on primary cannabinoid (e.g. Type I for THC)
• Plant morphology (e.g., broad-leaflet, compact vs. tall, spindly)
• **Specific cannabinoid content**
• **Specific terpenoid content**
• Scent
• Taste (when vaporized)
• Uses/Effects (patient-oriented)
<table>
<thead>
<tr>
<th>Common Name</th>
<th>Terpene Super Class</th>
<th>Secondary Terpene</th>
<th>Tertiary Terpene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big Sky</td>
<td>Caryophyllene</td>
<td>Humulene</td>
<td>Limonene</td>
</tr>
<tr>
<td>Bubba Kush</td>
<td>Limonene</td>
<td>Caryophyllene</td>
<td>Linalool</td>
</tr>
<tr>
<td>OG Kush</td>
<td>Limonene</td>
<td>Caryophyllene</td>
<td>Myrcene</td>
</tr>
<tr>
<td>Purple Urkle</td>
<td>Myrcene</td>
<td>Caryophyllene</td>
<td>Pinene</td>
</tr>
<tr>
<td>Jack Herrer</td>
<td>Terpinolene</td>
<td>Caryophyllene</td>
<td>Humulene</td>
</tr>
<tr>
<td>Trainwreck</td>
<td>Terpinolene</td>
<td>Myrcene</td>
<td>Limonene</td>
</tr>
<tr>
<td>Blue Dream</td>
<td>Myrcene</td>
<td>Pinene</td>
<td>Caryophyllene</td>
</tr>
</tbody>
</table>

Giese, M. et al., submitted for publication 2014
*Journal of Association of Official Analytical Chemists*
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>Pesticide</th>
<th>Structure</th>
<th>Class/Usage</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoxystrobin</td>
<td></td>
<td>Fungicide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Bideconazole</td>
<td></td>
<td>Miticide</td>
<td>Slight acute toxicity; potential ground water contaminant, questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Boscalid</td>
<td></td>
<td>Fungicide</td>
<td>Possible carcinogen; questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Carbaryl</td>
<td></td>
<td>Carbamate/Insecticide</td>
<td>BAD ACTOR: Cholinesterase inhibitor; carcinogen; development/developmental/toxic; suspected endocrine disruptors</td>
</tr>
<tr>
<td>Carbendazim</td>
<td></td>
<td>Fungicide</td>
<td>Possible carcinogen; questionable ground water contaminant, questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td></td>
<td>Neonicotinoid</td>
<td>Questionable developmental/reproductive toxic; questionable endocrine disruptors</td>
</tr>
<tr>
<td>Diazinon</td>
<td></td>
<td>Organophosphate/Insecticide</td>
<td>Unlikely carcinogen; cholinesterase inhibitor; developmental/reproductive toxic; suspected endocrine disruptors</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td></td>
<td>Herbicide/Photosynthesis Inhibitor</td>
<td>Carcinogen; developmental/reproductive toxic; suspected endocrine disruptors</td>
</tr>
<tr>
<td>Ethiphos</td>
<td></td>
<td>Organophosphate/Insecticide</td>
<td>BAD ACTOR: Carcinogen; cholinesterase inhibitor; potential ground water contaminant, questionable developmental/reproductive toxic; questionable endocrine disruptors</td>
</tr>
<tr>
<td>Etoxazole</td>
<td></td>
<td>Miticide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Fenpyroximate</td>
<td></td>
<td>Insecticide/ Miticide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td></td>
<td>Neonicotinoid/Insecticide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Malathion</td>
<td></td>
<td>Organophosphate/Insecticide</td>
<td>Cholinesterase inhibitor; possible developmental/reproductive toxic, suspected endocrine disruptors</td>
</tr>
<tr>
<td>Myclobutanil</td>
<td></td>
<td>Triazole/Fungicide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Permethrin</td>
<td></td>
<td>Pyrethroid/Insecticide</td>
<td>BAD ACTOR: Moderate acute toxicity; Carcinogen; potential ground water contaminant, questionable developmental/reproductive toxic, suspected endocrine disruptors</td>
</tr>
<tr>
<td>Pyriproxyfen</td>
<td></td>
<td>Pyridine/Pesticide</td>
<td>Questionable developmental/reproductive toxic and questionable endocrine disruptors</td>
</tr>
<tr>
<td>Pyraclostrobin</td>
<td></td>
<td>Fungicide</td>
<td>Questionable developmental/reproductive toxic and questionable endocrine disruptors</td>
</tr>
<tr>
<td>Pyrimethanil</td>
<td></td>
<td>Pesticide</td>
<td>Possible carcinogen; questionable developmental/reproductive toxic; suspected endocrine disruptors</td>
</tr>
<tr>
<td>Trifluralin</td>
<td></td>
<td>Herbicide/Photosynthesis Inhibitor</td>
<td>Carcinogen; developmental/reproductive toxic; suspected endocrine disruptors</td>
</tr>
<tr>
<td>Trifloxystrobin</td>
<td></td>
<td>Fungicide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Tritonalex</td>
<td></td>
<td>Fungicide</td>
<td>Questionable developmental/reproductive toxic and endocrine disruptors</td>
</tr>
<tr>
<td>Xanamide</td>
<td></td>
<td>Fungicide</td>
<td>Questionable developmental/reproductive toxic and questionable endocrine disruptors</td>
</tr>
</tbody>
</table>

Pesticides encountered in 26 cannabis samples in Washington State.


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.

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?)

Vape Pens, Propylene Glycol & Formaldehyde

E-cigarettes use propylene glycol and glycerol as propellants.

Under excessive 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.

• Smoked NIDA cannabis in 50 subjects TID for **5 days**
• **All required to have previous cannabis smoking experience**
• **Results**
  – decreased daily pain ($p=0.03$)
  – hyperalgesia ($p=0.05$)
  – 52% with >30% pain reduction vs. placebo ($p=0.04$)
• **AEs in smoking group (psychoactive effects) were prominent**

<table>
<thead>
<tr>
<th></th>
<th>Cannabis, mean (95% CI)</th>
<th>Placebo, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety‡</td>
<td>0.25 (0.14, 0.44)</td>
<td>0.10 (0.05, 0.22)</td>
</tr>
<tr>
<td>Sedation†</td>
<td>0.54 (0.36, 0.81)</td>
<td>0.08 (0.04, 0.17)</td>
</tr>
<tr>
<td>Disorientation‡</td>
<td>0.16 (0.07, 0.34)</td>
<td>0.01 (0.00, 0.04)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>0.13 (0.03, 0.45)</td>
<td>0.04 (0.01, 0.14)</td>
</tr>
<tr>
<td>Confusion†</td>
<td>0.17 (0.07, 0.39)</td>
<td>0.01 (0.00, 0.06)</td>
</tr>
<tr>
<td>Dizziness†</td>
<td>0.15 (0.07, 0.31)</td>
<td>0.02 (0.01, 0.05)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.11 (0.04, 0.30)</td>
<td>0.03 (0.01, 0.14)</td>
</tr>
</tbody>
</table>

Side effects were rated three times daily on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

* $p < 0.05$; † $p < 0.001$.  

Nabiximols Oromucosal Extract

• 1:1 combination from two clonal cannabis chemovars yielding a high THC extract and a high CBD extract.
• A botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch.
• USAN: nabiximols (accepted as a unitary formulation)
• THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids, terpenoids (most GRAS), and other minor components (also GRAS).
• each 100 μL pump-action spray provides 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol, propylene glycol excipients, and peppermint as flavoring/masking agent.

• Intermediate onset
• Allows dose titration
• Acceptable to patients
GWP Good Agricultural Practice (GAP)

- Grown in organic compost ("leaf mold")
- Female clones from mother plant assure biochemical consistency
- Fertilization prevented
- Climate-controlled (temperature, light cycles, humidity)
- Integrated Pest Management (IPM)
Thin Layer Chromatography of Cannabis Resin vs. nabiximols
Biochemical Fingerprinting of nabiximols

Overlay of cannabinoid chromatographic profiles from 25 batches of nabiximols over 9 years
(courtesy of Peter Gibson, PhD, GW Pharmaceuticals)
## Nabiximols Efficacy: Multiple Sclerosis Clinical Trials

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Study Details</th>
<th>Key Efficacy Result</th>
<th>P-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase II (Randomised, Double-Blind, Placebo Controlled Studies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GWN19902</td>
<td>Symptoms of MS and other nervous system conditions (n=25)</td>
<td>Improvement in Spasticity (VAS)</td>
<td>(&lt;0.05)</td>
<td>Wade DT et al. Clin Rehab. 2003</td>
</tr>
<tr>
<td>GWMS0001</td>
<td>MS Symptoms (n=160)</td>
<td>Improvement in Spasticity (VAS)</td>
<td>0.001</td>
<td>Wade DT et al. Multiple Sclerosis 2004</td>
</tr>
<tr>
<td><strong>Phase III (Randomised, Double-Blind, Placebo Controlled Studies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>X</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GWCL0403</td>
<td>MS, Spasticity (n=337)</td>
<td>Improvement in Spasticity (NRS)</td>
<td>0.22</td>
<td>Collin C et al. Neurol Res. 2010</td>
</tr>
<tr>
<td>GWMS0106</td>
<td>MS, Spasticity (n=189)</td>
<td>Improvement in Spasticity (NRS)</td>
<td>0.048</td>
<td>Collin C et al. Eur J Neurol. 2007</td>
</tr>
<tr>
<td>GWSP0604</td>
<td>MS, Spasticity (n= (A) -572, (B) -241)</td>
<td>Improvement in Spasticity (NRS)</td>
<td>(p=0.0002)</td>
<td>Novotna J et al. Eur J Neurol 2011</td>
</tr>
<tr>
<td>GWSP0702</td>
<td>MS, Spasticity (n=36) Randomised Withdrawal Study Design</td>
<td>Time to treatment failure (NRS)</td>
<td>(p=0.013)</td>
<td>Notcutt W et al. Multiple Sclerosis 2011</td>
</tr>
<tr>
<td>GWSP1172</td>
<td>MS Spasticity (n=121) 12 month RCT</td>
<td>GIC</td>
<td>(P&lt;0.0001)</td>
<td>ECTRIMS 2013</td>
</tr>
<tr>
<td><strong>Long Term Extension Studies (Open Label)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GWMS0001</td>
<td>Open label extension study (n=137)</td>
<td>Long term efficacy(NRS)</td>
<td>N/A</td>
<td>Wade DT et al. Mult Scler 2007</td>
</tr>
<tr>
<td>GWEXT0102</td>
<td>Open label extension study (n=507)</td>
<td>Long term efficacy(NRS)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
### Randomized Controlled Trials of nabiximols in Pain

<table>
<thead>
<tr>
<th>N</th>
<th>Indication</th>
<th>Duration/Type</th>
<th>Outcome/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Neurogenic pain</td>
<td>Series of 2-week N-of-1 crossover blocks</td>
<td>Improvement with high-THC extract and nabiximols on VAS pain vs. placebo (p&lt;0.05), symptom control best with nabiximols (p&lt;0.0001) [Wade et al. 2003]</td>
</tr>
<tr>
<td>24</td>
<td>Chronic intractable pain</td>
<td>12 weeks, series of N-of-1 crossover blocks</td>
<td>VAS pain improved over placebo (p&lt;0.001) especially in MS (p&lt;0.0042) [Notcutt et al. 2004]</td>
</tr>
<tr>
<td>48</td>
<td>Brachial Plexus Avulsion</td>
<td>6 weeks in 3 two-week crossover blocks</td>
<td>Benefits noted in Box Scale-11 pain scores with high-THC extract (p=0.002) and nabiximols (p=0.005) over placebo [Berman et al. 2004]</td>
</tr>
<tr>
<td>66</td>
<td>Central Neuropathic Pain in MS</td>
<td>5 weeks</td>
<td>Numerical Rating Scale (NRS) analgesia improved over placebo (p=0.009) [Rog et al. 2005]</td>
</tr>
<tr>
<td>125</td>
<td>Peripheral Neuropathic Pain</td>
<td>5 weeks</td>
<td>Improvements in NRS pain levels (p=0.004), dynamic allodynia (p=0.042), and punctuate allodynia (p=0.021) vs. placebo [Nurmikko et al. 2007]</td>
</tr>
<tr>
<td>56</td>
<td>Rheumatoid Arthritis</td>
<td>Nocturnal dosing for 5 weeks</td>
<td>Improvements over placebo morning pain on movement (p=0.044), morning pain at rest (p=0.018), DAS-28 (p=0.002), and SF-MPQ pain at present (p=0.016) [Blake et al. 2006]</td>
</tr>
<tr>
<td>117</td>
<td>Pain after spinal injury</td>
<td>10 days</td>
<td>NSD in NRS pain scores, but improved Brief Pain Inventory (p=0.032), and Patients Global Impression of Change (p=0.001) (unpublished)</td>
</tr>
<tr>
<td>177</td>
<td>Intractable cancer pain</td>
<td>2 weeks</td>
<td>Improvements in NRS analgesia vs placebo (p=0.0142), THC extract NSD [Johnson, 2010 #6899]</td>
</tr>
<tr>
<td>135</td>
<td>Intractable lower urinary tract symptoms in MS</td>
<td>8 weeks</td>
<td>Improved bladder severity symptoms including pain over placebo (p=0.001) (unpublished)</td>
</tr>
<tr>
<td>360</td>
<td>Intractable cancer pain</td>
<td>5 weeks/DB</td>
<td>CRA of lower and middle dose cohorts improved over placebo (p=0.006)/GWCA0701 [Johnson 2010]</td>
</tr>
</tbody>
</table>

Sativex/nabiximols is approved in 27 Countries
USA: A Patchwork of Cannabis Laws (from mpp.org)
USA: A Patchwork of Cannabis Laws (from mpp.org)

Map after January 2017
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
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 CB$_1$ 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.