Beyond Medical Marijuana: Toward Cannabinoid-Based Medicines

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Marijuana is a green, brown, or gray mixture of dried, shredded leaves, stems, seeds, and flowers of the hemp plant.

**Sinsemilla:** A form of marijuana obtained from the un-pollinated or seedless portion of the cannabis plant, it has a higher THC concentration than regular marijuana, as high as 6%.

**Hashish:** A drug containing the resin of cannabis flowers, the THC concentration ranges from approximately 8 to 14%.

**Hashish Oil:** A drug produced by boiling hashish, leaving the potent psychoactive residue, the THC concentration ranges from 15 - 60%.

**Hashish oil crystals:** Solid form of hashish oil.

**Bhang:** A liquid form of marijuana, popular in India.
Cannabinoids are the chemical constituents of the cannabis plant and include over 60 different compounds. THC is the most psychoactive cannabinoid.

The level of THC contained within the plant’s flowers determines the potency of the drug.

THC content of a Cannabis Sativa plant ranges from .01 to 10 percent, with the later being 1,000 times more potent.
Varying Dose-Response

- Cannabinoids can produce sympathomimetic effects but they are not generally regarded as stimulants.

- Cannabinoids can produce sedative effects, but a person faces no risk of slipping into a coma or dying.

- Cannabinoids can produce mild analgesic effects, but they are not related pharmacologically to opioids.

- Cannabinoids can produce hallucinations at high doses, but their structure does not resemble LSD or any other drug formally categorized as hallucinogen.
DESIRED EFFECTS

- Sense of well being
- Relaxation
- Euphoria
- Modified level of consciousness
- Altered perceptions
- Intensified sensory experiences
UNDESIRED EFFECTS

- Panic and anxiety
- Delusions
- Hallucinations
- Acute mania
- Acute paranoia
- Depression
- Cognitive deficits
ER VISITS VS. POTENCY CAUSE AND EFFECT?

[Graph showing the correlation between ER visits and potency of tested seized cannabis from 1988 to 2003.]
### Acute and Long terms Effects of Cannabis Use on Executive Cognitive Functions

<table>
<thead>
<tr>
<th>Executive Function Measured</th>
<th>Acute Effects</th>
<th>Residual Effects</th>
<th>Long-term Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/concentration</td>
<td><strong>Impaired</strong> (light users)</td>
<td>Mixed findings</td>
<td>Largely normal</td>
</tr>
<tr>
<td>Decision-making and risk taking</td>
<td>Mixed findings</td>
<td><strong>Impaired</strong></td>
<td><strong>Impaired</strong></td>
</tr>
<tr>
<td>Inhibition/impulsivity</td>
<td><strong>Impaired</strong></td>
<td>Mixed findings</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Working memory</td>
<td><strong>Impaired</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Normal</td>
<td>Mixed findings</td>
<td>Mixed findings</td>
</tr>
</tbody>
</table>

Acute effects denote 0-6 hours after last cannabis use; residual effects 7 hours to 20 days after last use; and long-term effects denote 3 weeks or longer after last cannabis use.

DSM-5  Cannabis Withdrawal

Clinical Note: Withdrawal symptoms adversely impact attempts to quit and motivate use of marijuana and other drugs for relief.

A. Cessation of cannabis use that has been heavy and prolonged (i.e. usually daily, or almost daily use over a period of at least a few months).
Cannabis Withdrawal

B. Three or more of the following signs and symptoms develop approximately 1 week after cessation:

- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g., insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood

At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremor, sweating, fever, chills or headache.
**Cannabis Withdrawal**

C. The signs or symptoms in Criterion B causes clinically significant distress or impairment in school, occupational, or other important areas of functioning.

D. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorders, including intoxication or withdrawal from another substance.
Is Marijuana “Addictive”?

Abuse potential = Dopamine agonist within brain’s reward circuitry (mesocorticolimbic pathway)

The Gold Standard for whether a drug is addictive or not:
1. It is self-reinforcing (activates brain reward circuitry)
2. Lab animals will self-administer the drug repeatedly and show preference for the drug over other stimuli
Is Marijuana Addictive?

For scientists, the “cannabinoid story” has shifted radically from marijuana the plant, to the cannabinoids and the brain.

It’s no longer a question of why marijuana makes people high but more about what role and function does the “natural” (endogenous) cannabinoid system have for human behavior.
There are four lines of evidence of physical addiction and withdrawal caused by THC.

First, administering THC for seven days, followed by SR141716A (a cannabinoid antagonist that leads to sudden displacement of THC from cannabinoid receptors), produces similar symptoms across several animal species—snout rubbing, difficulty sleeping with characteristic EEG disturbances, “wet-dog shakes,” and so on.

Second, clinical reports by humans seeking treatment for marijuana dependence include similar symptoms of irritability, anxiety, insomnia with characteristic EEG disturbances, restlessness, etc.
Is Marijuana Addictive?

Third, epidemiologic studies reveal that approximately 9% of people who begin smoking marijuana at twenty-one years or older eventually satisfy the criteria for cannabis dependence.

The fourth line of evidence is the *sine qua non* for any addictive substance: THC causes a rise in dopamine levels in the nucleus accumbens (a major area of the MCLP)).
Treatment options

- Self-help
- Brief intervention
- Motivational Interviewing
- Contingency Management
- Pharmacotherapy:
  - Diazepam 5 mg tds x 3-5 days) for cannabis withdrawal sx
  - Neurontin 1200 mg/day (off label)
Goals of behavioral treatment

- Reviewing benefits of cutting down/stopping
- Reviewing harms of continued use
- Identifying likely risk times for using
- Discussing means of avoiding risk situations
- Setting realistic goals
Synthetic Cannabinoids (SCs)

- Spice/K2 brands marketed as natural herbal incense
- “Not for human consumption”
- Available convenience stores, gas stations, Internet
- Cannabis substitute

Pharmacology

- delta-9 tetrahydrocannabinol ($\Delta^9$-THC) agonism of cannabinoid receptor type 1 (CB1)
- SCs are more potent
- Typical doses are often less than 1mg
- Not readily detectable
Psychoactive Effects

Marketed as similar to cannabis:

- Euphoria
- Sociability
- Anxiolytic
- Relaxation
- Stimulant

Cross tolerance with THC?
Side Effects of SC Products

- Anxiety
- Paranoia
- Headache
- Vomiting
- Psychosis
- Diaphoresis – dehydration – UTI – acute renal failure
- HR/BP increase
- Seizures
Is a Medical Marijuana Realistic?

Toward Cannabinoid-Based Medicines
Some whole plants can be medicinal:

- **Artichoke** may reduce LDL cholesterol levels
- **Cranberry** may be effective in treating recurring urinary tract infections
- **Garlic** may lower total cholesterol levels
- **St. John's wort**, for the treatment of mild to moderate depression
- **Valerian root** for insomnia
- **Feverfew** for migraines
Some plants have constituents that can be medicinal:

- **Nicotine** from the tobacco plant
- **Taxol** from Yew Tree bark (cancer fighting drug)
- **Digoxin** from Foxglove or Digitalis (cardiac drug)
- **Morphine** from the opium poppy
- Certain **cannabinoids** from the Cannabis plant
The inhalation of smoke from burning vegetation is inherently unhealthy.
Why?

Burning Cannabis plant releases over 200 other compounds in the smoke including:

- Polycyclic hydrocarbons
- Ammonia
- Benzene
- Carbon monoxide (in a 1:5 ratio compared to tobacco)
- Toluene
- Hydrogen cyanide
Is there any basis for a “medical marijuana”?
Yes

but the more accurate question is . . .

is there a basis for cannabinoid-based medicines that embraces a standard of care?
Cannabis contains *phytocannabinoids*, some of which are bioactive - defined by their ability to target and activate specific cannabinoid receptors in the brain. Research is investigating several cannabinoids for potential use as medicines.

1. Extracting them from their botanical base and testing them as individual substances
2. Observing any polypharmacy including effects from combined cannabinoids and drug-drug interactions
3. Developing improved and more efficient drug delivery systems
4. Standardized purity levels and dose-response parameters
5. Identifying contraindications in certain populations with certain medical conditions
New Drug Research

The basic research blueprint – extract the psychoactive substance from a plant’s oily residue, label it, discover and map receptor sites within the brain, and then find the endogenous ligand for those receptors—replicates the path earlier paved by opiate researchers.

Except the endocannabinoid system is at least tenfold the size of the endorphin system. In fact, endocannabinoids are found in higher concentrations than any other receptor in the brain . . . and the endocannabinoid system acts essentially in just about every physiological system that people have looked into.
The Discovery of the Endocannabinoid System

The endocannabinoid system is a physiological system consisting of cannabinoid receptors and corresponding chemical messengers believed to play an important role in regulating body weight, glucose and lipid metabolism, pain, movement, cognitive functioning and even addiction.

The word, endocannabinoid, is a word condensed from two other words; endogenous: (from within), and cannabinoid: (substances resembling the components within the Cannabis plant)
Cannabinoid Receptors

Two cannabinoid receptors, CB1 and CB2, have been distinguished and are expressed both in the nervous system and peripheral tissues and organs.

The CB1 receptor

The CB1 receptor is present in both the nervous system and other tissues and organs of the body. Researchers have determined that this receptor is responsible for the psychoactive actions of THC and other cannabinoids.
• CB1 is presumed to mediate the CNS effects of cannabinoids

• Very high levels of CB1 receptors found in brain hippocampal areas

• CB1 receptors localized in the ventral tegmental area (VTA) and their association with the dopamine reward system implicates the role of the cannabinoid system in addictive behaviors.

• CB1 receptors play a central role in the appetite control process
The CB2 receptor

• The CB2 receptor is not expressed in the brain. It is particularly abundant in immune tissues. Among the formed elements of blood, the largest concentrations have been detected in B-cells and natural killer cells.

• CB2 somehow plays a role in immuno-modulatory effects. That is, depending on activation level, some immune cells are suppressed while others are stimulated.

• CB2 also plays a role in analgesia (pain suppression).
Endogenous Cannabinoids: 
Cannabis naturally in the human body?

Sort of. In the way the body has its own natural morphine (endorphins) chemically similar to morphine from the opium plant; the body also has its own version of substances resembling those of the cannabis plant, called *endocannabinoids*.

Endogenous ligands for the cannabinoid receptors discovered to date are arachidonic acid derivatives termed *anandamide*, and arachidonyl glycerol (known as 2-AG).
Anandamide

is derived from the Sanskrit word for bliss (*ananda*) due to its cannabimimetic, psychotropic properties.

Although the structure of anandamide is different from THC, experiments have shown that it binds to cannabinoid receptors.

It has also been shown to share most of the pharmacological properties exerted both in the CNS and peripheral system.
Anandamide is a fatty acid derivative and acts as a partial agonist at CB receptor sites. Anandamide is found in:

- Basal ganglia & cerebellum (movement)
- Cells of the Dorsal Root Ganglia (analgesia)
- Frontal cortex (thought)
- Hippocampus (learning & memory)
- Immune system (lymphocytes & spleen)
Toward A Cannabinoid Pharmacotherapy

- Treat nausea & vomiting (antiemetic)
- Appetite stimulant in patients with wasting diseases
- Brain protection following head injury
- Spasticity secondary to neurological diseases
- Pain syndromes
- Addiction and compulsivity

(NOTE: we can separate therapeutic effects from psychedelic effects!)
Some phytocannabinoids of research interest 15 years ago

- **Cannabidiol**: May possess sedative properties. Potential use as an anxiolytic. Alternative to benzodiazepines?

- **Cannabinol**: May have anti-inflammatory effects through Prostaglandin-E inhibition. Alternative to NSAIDS and COX inhibitors?

- **Canaflavonoids**: May possess anti-inflammatory properties and analgesic effects. Alternative to traditional analgesics?
Toward cannabinoid-based medicines

The discovery of critical pieces to the biochemical puzzle can now allow for new developments of selective targeting of drug action

- Endocannabinoid system
- Endocannabinoids
- Cannabinoid receptors
- Testing and discovery of agonist/antagonist properties
- Contraindications
Beyond Phytocannabinoids
(research in the last several years)

AGONISTS & ANTAGONISTS

With the discovery of the endocannabinoid system, associated receptor sites, and at least 2 cannabimimetic ligands, research is now investigating targeted agonists/antagonist drugs to produce more specific and better controlled responses for identified treatments.
**Therapeutic possibilities**

The endocannabinoid system has been defined as a neuroendocrine system that controls appetite, fat distribution, energy balance, and multiple addictive/compulsive behaviors.

Therapies could be through agonist/antagonist properties acting at cannabinoid receptors, or by targeting the synthesizing, or degrading, enzymes responsible for making endocannabinoids.
Clinically, CB1-receptor activation has proved useful in addressing 2 common wasting syndromes. The CB1 agonist, *Marinol*, has been successfully used for years as an appetite stimulant in cancer cachexia and AIDS wasting syndrome.
As a result of new discoveries about the endocannabinoid system, there is a growing formulary of new drugs beyond what medical marijuana can provide and with more safe and efficient drug delivery systems.
CB1 Receptor Related Medical Conditions

• Regulation of food intake and body weight
• Glucose and lipid metabolism
## Impact of Overactive CB$_1$ Receptors

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<tr>
<th>Site of Action</th>
<th>Mechanism(s)</th>
<th>Enhance</th>
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<tbody>
<tr>
<td><strong>Hypothalamus</strong>&lt;br&gt;N. accumbens</td>
<td>↑ Food intake</td>
<td>Body weight&lt;br&gt;Waist circumference</td>
</tr>
<tr>
<td><strong>Adipose tissue</strong></td>
<td>↓ *Adiponectin&lt;br&gt;↑ Lipogenesis</td>
<td>Visceral fat&lt;br&gt;Dyslipidemia&lt;br&gt;Insulin resistance</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td>↓ Glucose uptake&lt;br&gt;↑ O$_2$ consumption</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>↑ Lipogenesis</td>
<td>Dyslipidemia&lt;br&gt;Insulin resistance</td>
</tr>
<tr>
<td><strong>GI tract</strong></td>
<td>↓ Satiety</td>
<td>Body weight&lt;br&gt;Waist circumference</td>
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* A protein hormone that regulates metabolism of glucose and influences the body’s response to insulin. Hi levels associated reduced risk of heart attack.
CB₁ receptor antagonists can modulate an overactive endocannabinoid system resulting in the restoration of balance.

Blocking the CB₁ receptor eliminates the part of obesity that is controlled by the endocannabinoid system such as increased appetite, excessive hunger and food intake.
CB1 receptors are associated with appetite, feeding behaviors as well as motivational and reward behaviors.

Overactivation of the endocannabinoid system (ECS) is associated with excessive food intake. ECS overactivation is also associated with nicotine addiction.

CB1 receptor blockade has the potential to treat craving behaviors in addiction.

CB1 inhibition may have a role in appetite suppression, reduced cravings associated with carbohydrate over consumption and drug addiction.
Cannabinoid Receptors in Alcohol Abuse

Measures of alcohol preference and intake in mice were obtained with different levels of CB1 receptors: wild type mice with normal levels of CB1; heterozygous mice with approximately 50% levels; and knockout (KO) mice that lack the gene for CB1 and therefore have no CB1 receptors.

Mice with the normal levels of CB1 receptors had a stronger preference for alcohol and drank more than the other two groups, with the CB1-deficient mice showing the lowest alcohol consumption!
Institute of Medicine (IOM)

1. Smoked crude marijuana has no medical value and is contraindicated in general

2. While early literature suggests some potential benefits if marijuana for the treatment of glaucoma, nausea, and muscle spasms, by today’s standards there are much better and safer drugs available.

3. Marijuana is not a benign substance as previously believed
1. There is no question that marijuana can be addictive; that argument is over.

2. The concept of a medical marijuana is flawed for several reasons:
   a. administering any medication via drawing hot smoke into the lungs is inherently unhealthy
   b. while use of vaporizers, sprays, and tinctures solve problems inherent in smoking, treatment of illness without standardization dose or content of the medication remain a safety issue
Clinical and Policy Considerations
The California Society of Addiction Medicine (CSAM) strongly urges all physicians who recommend the medical use of marijuana be held to all accepted medical standards of practice adopted by the California Medical Board in 2004 for recommending or approving any medication including:

- History and good faith examination of the patient
- Development of a treatment plan with objectives
- Provision of informed consent including a discussion of side effects
- Periodic review of treatment efficacy
- Consultation as necessary
- Proper record keeping that supports the decision to recommend the use of marijuana
And

- If a physician recommends or approves the medical use of marijuana for a minor, the parents or legal guardian must be fully informed of the risks and benefits of such use and must consent to that use.

- It is incumbent on the physician recommending marijuana to consult with the patient’s primary treating physician to obtain the appropriate patient records to confirm the patient’s underlying diagnosis and prior treatment history.

- The physician should determine that medical marijuana use is not masking an acute or treatable progressive condition, or that such use will lead to a worsening of the patient’s condition.
Failure to meet these standards of medical practice when recommending marijuana, an addictive psychoactive substance, should be treated by the California Medical Board with the same level of concern as failure to meet the medical standards of practice in prescribing other addictive substances.

What is a reasonable and founded policy for physician recommended marijuana use?
1. Founded on the IOM recommendations

2. Reinforced by CSAM Standards of Care

3. Sensitive to other clients in treatment – especially residential and sober living housing

4. Allows providers to case manage with client’s PCP or marijuana recommending physician
Challenges & Solutions

1. My client won’t sign a consent allowing me talk with her PCP or marijuana recommending physician

2. Clients in my group are upset because a medical marijuana client comes to group visibly stoned.

3. I have a consent to talk with my client’s physician about medical marijuana use but I don’t know how to talk with a physician.

4. How can I help my client achieve total abstinence when he is using medical marijuana approved by a physician?