Marijuana: Drug of Abuse or Therapeutic Option?
Learning Objectives

• Explain how cannabinoids affect the body and the brain

• Educate patients about:
  – Evidence of efficacy for mental health and other conditions
  – Potential risks of cannabis use
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>~2000 BC</td>
<td>Chinese emperors recommend marijuana as medicine</td>
</tr>
<tr>
<td>1851</td>
<td>Marijuana listed as a medication in US Pharmacopeia</td>
</tr>
<tr>
<td>1851</td>
<td>Marijuana is labeled Schedule I by the US Substance Abuse Act; this restricts both personal use and access for research purposes</td>
</tr>
<tr>
<td>1943</td>
<td>Marijuana removed from listing as a medication in US Pharmacopeia</td>
</tr>
<tr>
<td>1961</td>
<td>United Nations Single Convention on Narcotic Drugs: marijuana said to be dangerous with no medical value</td>
</tr>
<tr>
<td>1963</td>
<td>Cannabidiol isolated</td>
</tr>
<tr>
<td>1964</td>
<td>THC isolated</td>
</tr>
<tr>
<td>1989? 90?</td>
<td>Discovery of binding site for THC—CB1 receptor</td>
</tr>
<tr>
<td>1992</td>
<td>Endogenous cannabinoid anandamide discovered</td>
</tr>
<tr>
<td>1995</td>
<td>Endogenous cannabinoid 2-AG discovered</td>
</tr>
<tr>
<td>2015</td>
<td>Elimination of US Public Health Service oversight for obtaining marijuana for research purposes</td>
</tr>
<tr>
<td>Aug 11 2016</td>
<td>DEA declines to reschedule marijuana</td>
</tr>
</tbody>
</table>
THE INTERSECTION OF THE HEALTHCARE AND CANNABIS INDUSTRIES
What is Cannabis?

500 chemicals
100 cannabinoids
Best understood:
THC and CBD
### Scheduling of Controlled Substances

<table>
<thead>
<tr>
<th>Schedule I</th>
<th>Schedule II</th>
<th>Schedule III</th>
<th>Schedule IV</th>
<th>Schedule V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>Cocaine</td>
<td>Tylenol w/</td>
<td>Tramadol</td>
<td>Robitussin AC</td>
</tr>
<tr>
<td>Heroin</td>
<td>Methamphetamine</td>
<td>codeine</td>
<td>Alprazolam</td>
<td>Lyrica</td>
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<tr>
<td>LSD</td>
<td>Dexedrine</td>
<td>Ketamine</td>
<td>Zolpidem</td>
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<tr>
<td>Ecstasy</td>
<td>Adderall</td>
<td>Anabolic steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methaqualone</td>
<td>Ritalin</td>
<td>Testosterone</td>
<td></td>
<td></td>
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<tr>
<td>(Quaalude)</td>
<td>Vicodin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peyote</td>
<td>Methadone</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Meperidine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **Schedule I**: No medicinal value, high potential for abuse
- **Schedule II**: High potential for abuse
- **Schedule III**: Moderate to low potential for abuse
- **Schedule IV**: Low potential for abuse
- **Schedule V**: Lower potential for abuse

Do you think the use of marijuana should be made legal?\(^1\)

% Yes

<table>
<thead>
<tr>
<th>Year</th>
<th>% Yes</th>
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<tr>
<td>1969</td>
<td>12</td>
</tr>
<tr>
<td>1973</td>
<td>16</td>
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<td>1981</td>
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<td>1985</td>
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<td>1997</td>
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<td>2001</td>
<td>34</td>
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<td>2005</td>
<td>34</td>
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<tr>
<td>2009</td>
<td>36</td>
</tr>
<tr>
<td>2013</td>
<td>58</td>
</tr>
<tr>
<td>2013</td>
<td>58</td>
</tr>
</tbody>
</table>

% who perceive great risk of harm from monthly use\(^2\):

\[ 28.5\% \]

Cannabis is marketed as a therapeutic, medicinal product—but not developed or dispensed by health professionals.

9 Major Health Benefits of Medical Marijuana

1. Treats Migraines
   Cannabis has been shown to help in the treatment of migraines.

2. Slows Down Tumor Growth
   Studies have shown that cannabis can slow the growth of tumors in cancer.

3. Relieves Symptoms of Chronic Diseases
   Marijuana is one of the best natural pain relievers that can help relieve chronic pain.

4. Prevents Alzheimer’s
   Cannabis can alleviate the symptoms of Alzheimers’ patients.

5. Treats Glaucoma
   Research has shown that cannabis can reduce the pressure in the eye.

6. Prevents Seizures
   Cannabis can help in the treatment of epilepsy.

7. For ADD and ADHD
   Many people with ADD/ADHD find that cannabis helps alleviate their symptoms.

8. Relieve PMS
   Cannabis can help alleviate the symptoms of PMS.

9. Calm those with Tourette’s and OCD
   Cannabis can help in the treatment of Tourette’s and Obsessive-Compulsive Disorder (OCD).
Remember when cigarettes, alcohol, and heroin were marketed as therapeutic products to treat specific conditions?
Concerns for Healthcare Professionals: Increasing Potency


DEA-seized materials.
WHAT DOES CANNABIS DO?

The Endocannabinoid System
The Endocannabinoid System Regulates:

- Neurodevelopment
- Memory
- Cognition
- Reward
- Coordination
- Emetic reflex
- Heart rate
- GI motility
- Stress
- Appetite
- Intraocular pressure
- Immune function
- Female reproductive function
- Neurodevelopment
- Coordination
- Memory
- Cognition
- Reward
- Stress
- Appetite
- Intraocular pressure
- Immune function
- Female reproductive function
The Endocannabinoid System: Retrograde Neurotransmission

1. EC precursors in lipid membranes

CB receptor
The Endocannabinoid System: Retrograde Neurotransmission

1. EC precursors in lipid membranes
2. NT binding (or depolarization) triggers enzymatic reaction to form and release EC
3. Released EC binds to presynaptic CB1 or CB2 receptors
4. Inhibits release of inhibitory and excitatory NTs
The Endocannabinoid System: Receptors and Ligands

central and peripheral neuron terminals

2-AG: high-efficacy agonist
anandamide: low-efficacy agonist

CB1

immune cells

2-AG: high-efficacy agonist
anandamide: very low-efficacy agonist

CB2
Pre- (and Post-)Natal Neurodevelopment: Role of Endocannabinoid System


Brain Changes During Adolescent Development

Competitive elimination of synapses (loss of dendritic arborization)

- Prefrontal excitatory synapses
- Prefrontal inhibitory synapses
- Prefrontal DA innervation
- Anandamide CB1 receptors

ECS regulates glutamate, GABA, synaptic pruning, and white matter development.

CB1: increase in striatum, PFC, and hippocampus. Abundant in white matter during neural development. Present in oligodendrocytes.

WHAT DOES CANNABIS DO?

Effects on Cognition, Motivation, Psychosis, and the Developing Brain
Potential Effects of Cannabis

- Memory
- Cognition
- Reward
- Emetic reflex
- Pain
- Heart rate
- GI motility
- Coordination
- Stress
- Appetite
- Intraocular pressure
- Immune function
- Female reproductive function
- Neurodevelopment
Potential Effects of Cannabis

Impaired short-term memory, concentration, alertness, judgment, time perception, reaction time, Amotivation

Risk of neuro-development d/o?

Tachycardia
CV risk

Treat chronic pain?

Anti-emetic?

Treat IBS?

Impaired coordination

Impaired fertility?

Treat wasting syndrome?

Treat glaucoma?

Treat cancer?
Treat autoimmune d/o?

Treat autoimmune d/o?

Treat chronic pain?
Effects of Chronic, Heavy Cannabis Use on Endocannabinoid System

• Reduced anandamide in cerebrospinal fluid\(^1\)
  – Correlated with persistent psychotic symptoms

• Reduced cannabinoid 1 receptor\(^2\)

• Abnormalities in brain regions high in CB1 receptors (hippocampus, PFC)\(^3\)
  – Associated with higher levels of cannabis use (dose, age of onset, duration)

Does Cannabis Use Affect Cognitive Capacity?

• Short-term: YES
• Long-term: mixed data
  – Meta-analysis: non-intoxicated users do worse than non-users, BUT
  – In studies with at least 1 month abstinence, difference not seen
• Neuroimaging data: inconsistent, don't seem to correlate with neuropsychological test performance
• Genetic factors that increase risk of impairment (COMT, AKT1)?
• Magnitude and persistence of impairment may depend on:
  – Frequency and duration of use
  – Age of onset of use
  – Length of abstinence

Does Cannabis Use Reduce Motivation?

Marijuana Use Blunts Nucleus Accumbens Response to Reward Anticipation

Left: Past marijuana use at age 20 (time 1) and NAcc activation during reward anticipation at age 22 (time 2). Right: Past marijuana use at age 22 (time 2) and NAcc activation during reward anticipation at age 24 (time 3).

Cannabis Users Show Reduced Striatal DA Synthesis Capacity

Does Cannabis Use Increase Risk of Acute Psychosis?

Healthy Human Participants: Transient Induction of Psychosis

Does Cannabis Use Increase Risk of a Psychotic Disorder?

Lifetime risk of schizophrenia in:

- **general population**: 1%
- **cannabis users**: 2%

Are there subgroups at higher risk?

13.7% of US population uses cannabis at least once per year

Risk of a Psychotic Disorder in Subgroups of Cannabis Patients

Lifetime risk of schizophrenia in:

- cannabis users¹
  - 2%
- frequent and/or high-potency users²
  - 6%
- users w/ first-degree relative¹,²
  - 20%

Does Cannabis Use Affect the Course of a Psychotic Disorder?


Greater risk of psychosis relapse in non-user
Greater risk of psychosis relapse in continued cannabis user
Does Cannabis Use Affect the Developing Brain?


Involved in neural stem cell survival

Stem cell

Immature neurons

Cannabis effects (animal data, acute pre/neonatal exposure)

Cortical cell death

Neurogenesis

Selection

Migration

Differentiation

Synaptogenesis

Position cortical interneurons

Direct axonal growth

Altered development of major NT systems

Promote neurite outgrowth

ECS effects

Involved in proliferation

Cannabinoids
Does Cannabis Use Affect the Developing Brain?

Cannabis use: downregulated CB1 receptors in white matter

Cannabis use: disrupted glutamate NT

Prefrontal excitatory synapses

Prefrontal inhibitory synapses

Prefrontal DA innervation

Anandamide CB1 receptors

ECS regulates glutamate, GABA, synaptic pruning, and white matter development

CB1: increase in striatum, PFC, and hippocampus. Abundant in white matter during neural development. Present in oligodendrocytes.

Heavy Cannabis Use Prior to Brain Maturation: Animal Studies

- Greater and more persistent cognitive deficits
  - Learning, working memory, object recognition
- Disruption in social behavior
- More depressive-like behaviors
  - Reduced consumption of palatable food, passive response to acute stress
- Impaired prepulse inhibition
- Increased locomotor activity

Does Cannabis Use Affect the Developing Brain?

Meier MH et al. PNAS 2012;109(40):E2657-64.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Change in Full-Scale IQ (in SD Units)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cannabis-dependent before age 18</td>
<td>n=17</td>
</tr>
<tr>
<td>2</td>
<td>Not cannabis-dependent before age 18</td>
<td>n=57</td>
</tr>
<tr>
<td>2</td>
<td>Cannabis-dependent before age 18</td>
<td>n=12</td>
</tr>
<tr>
<td>3+</td>
<td>Not cannabis-dependent before age 18</td>
<td>n=21</td>
</tr>
<tr>
<td>3+</td>
<td>Cannabis-dependent before age 18</td>
<td>n=23</td>
</tr>
<tr>
<td>3+</td>
<td>Not cannabis-dependent before age 18</td>
<td>n=14</td>
</tr>
</tbody>
</table>
• Adolescent Brain Cognitive Development Study
  – Funded by NIH
  – Prospectively following children for 10 years beginning at ages 9–10
  – Began recruiting September 2016
  – http://abcdstudy.org/
HOW MIGHT CANNABIDIOL ATTENUATE THE NEGATIVE EFFECTS OF CANNABIS?
Cannabidiol vs. psychoactive anxiogenic

Isomer of THC

Psychoactive anxiogenic

NOT psychoactive anxiolytic anticonvulsant
under investigation by NIDA and NIH for therapeutic uses

Greydanus DE et al. Disease Month 2015;61:118-75;
THC vs. Cannabidiol: Different Binding Properties

central and peripheral neuron terminals

THC: partial agonist

CBD: does not bind CB receptors; may interact with 5HT receptors

immune cells

THC: partial agonist (low affinity?)

CB2

CB2
## THC vs. CBD: Psychiatric Effects

<table>
<thead>
<tr>
<th></th>
<th>Cannabis w/ Low CBD Content</th>
<th>Cannabis w/ High CBD Content</th>
<th>CBD alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis symptoms</td>
<td>Higher risk of hallucinations and delusions</td>
<td>Lower risk of hallucinations and delusions</td>
<td>Possible antipsychotic effects</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>Earlier age of onset</td>
<td>Later age of onset</td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Higher risk of acute memory impairment</td>
<td>Lower risk of acute memory impairment</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anxiogenic Increased amygdalar activity</td>
<td>Anxiolytic Reduced amygdalar activity</td>
<td></td>
</tr>
</tbody>
</table>

Shifting Ratio of THC: Cannabidiol

DEA-seized materials.

Cannabis vs. “The Synthetics”

THC: partial agonist

CBD

CB1

Synthetics: full agonist

800X greater affinity for CB1

No CBD

Cameron K et al. Psychopharmacology 2013;227(3):493-9;
CANNABIS AND CANNABINOIDS AS THERAPEUTIC TOOLS
The State of the Evidence
## Approved

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Formulation</th>
<th>Approval(s)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>Synthetic THC</td>
<td>Chemo-induced nausea and vomiting (US)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Oral capsule or solution</td>
<td>Appetite boost in AIDS wasting syndrome (US)</td>
<td></td>
</tr>
<tr>
<td>Nabilone</td>
<td>Synthetic THC analog</td>
<td>Chemo-induced nausea and vomiting (US)</td>
<td>II (due to its potency)</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>Purified ~1:1 THC and CBD</td>
<td>Spasticity caused by MS (UK, Canada, Europe, Australia, New Zealand, Israel)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>Pain in MS and in cancer (Canada, Israel)</td>
<td></td>
</tr>
</tbody>
</table>
# Cannabinoids for Medical Use: Meta-analysis

<table>
<thead>
<tr>
<th>MODERATE-QUALITY EVIDENCE</th>
<th>LOW-QUALITY EVIDENCE</th>
<th>VERY LOW-QUALITY EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spasticity in MS</strong></td>
<td><strong>Nausea/vomiting from chemo</strong></td>
<td><strong>Anxiety (public speaking)</strong></td>
</tr>
<tr>
<td>4 trials/2280 participants (nabiximols, nabilone, dronabinol, THC/CBD capsule)</td>
<td>28 trials/1772 participants (nabiximols, dronabinol)</td>
<td>1 trial/24 participants (cannabidiol)</td>
</tr>
<tr>
<td><strong>Chronic neuropathic or cancer pain</strong></td>
<td><strong>Weight gain in HIV</strong></td>
<td><strong>Depression</strong></td>
</tr>
<tr>
<td>28 trials/2454 participants (smoked THC, nabiximols)</td>
<td>4 trials/255 participants (dronabinol)</td>
<td>No direct study; documented as a result in 5 studies (nabiximols)</td>
</tr>
<tr>
<td>2 trials/36 participants (THC capsule)</td>
<td>2 trials/54 participants (nabilone)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 trials/71 participants (cannabidiol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Cannabinoids for Medical Use: American Academy of Neurology Review

<table>
<thead>
<tr>
<th>&quot;A&quot; (strong)</th>
<th>&quot;B&quot; (moderate)</th>
<th>&quot;C&quot; (weak)</th>
<th>&quot;U&quot; (insufficient)</th>
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</thead>
<tbody>
<tr>
<td>Spasticity (MS) OCE</td>
<td>Spasticity (MS) THC, nabiximols</td>
<td>Tremor (MS) nabiximols</td>
<td>Spasticity (MS) smoked cannabis</td>
</tr>
<tr>
<td>Pain (MS) OCE</td>
<td>Pain (MS) THC, nabiximols</td>
<td></td>
<td>Pain (MS) smoked cannabis</td>
</tr>
<tr>
<td></td>
<td>Urinary dysfunction (MS) nabiximols</td>
<td></td>
<td>Huntingdon's disease</td>
</tr>
<tr>
<td></td>
<td>Urinary dysfunction (MS) OCE, THC</td>
<td></td>
<td>nabilone, CBD capsule</td>
</tr>
<tr>
<td></td>
<td>Tremor (MS) OCE THC, THC</td>
<td></td>
<td>Tourette syndrome THC</td>
</tr>
<tr>
<td></td>
<td>Levodopa-induced dyskinesia OCE</td>
<td></td>
<td>Cervical dystonia dronabinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epilepsy CBD</td>
</tr>
</tbody>
</table>

- **POSITIVE EFFECT**
- **NO EFFECT**

OCE: oral cannabis extract (THC or THC/CBD)

ECS-Based Medicines
No Longer Under Investigation

- Peripherally restricted CB1 agonists
  - Studied in pain; failed due to metabolic and cardiovascular effects
- Synthetic CB1 agonists
  - Damaged kidneys in young children; serious cardiovascular adverse effects
- Global CB1 antagonists
  - Efficacy in diabetes and obesity, but failed due to CNS side effects
  - Negative study for smoking cessation
- Fatty acid amide hydrolase (FAAH) inhibitors
  - Promote cardiovascular inflammation, metabolic side effects
  - Phase I study of French formulation in healthy volunteers halted due to death and serious brain injury
  - US FDA: "BIA 10-2474 exhibits a unique toxicity that does not extend to other drugs in the class"
## Under Investigation: Cannabidiol

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome (GW Pharma; epidiolex*)</td>
<td>Lennox-Gastaut syndrome (GW Pharma; epidiolex*)</td>
<td>tuberous sclerosis (GW Pharma; epidiolex)</td>
<td>severe pediatric epilepsies (INSYS)</td>
</tr>
<tr>
<td>glioma (GW Pharma; GWP42003*)</td>
<td>schizophrenia (GW Pharma; GWP42003)</td>
<td>neonatal hypoxic-ischemic encephalopathy (GW Pharma; GWP42003*)</td>
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</tr>
</tbody>
</table>

*Orphan drug designation*
### Under Investigation: Other

<table>
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<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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</thead>
<tbody>
<tr>
<td>cancer pain (GW Pharma; nabiximols spray)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS spasticity (GW Pharma; nabiximols spray)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 2 diabetes (GW Pharma; delta-9-tetrahydrocannabivarin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>epilepsy (GW Pharma; cannabidivarin)</td>
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</tbody>
</table>

*Orphan drug designation*
Why Is Medical Marijuana Not a Viable Prescription Option?

Drug approval standards

- Consistent, pure, well-defined chemical formulation
- Consistent, well-defined pharmacokinetic profile
- Safety data in healthy population and in specific medical disorder (double-blind, placebo-controlled RCT)
- Efficacy data in specific medical disorder (double-blind, placebo-controlled RCT)
- Warnings regarding all potential side effects

Medical marijuana status

- Unprocessed plant containing 500 chemicals with 100+ cannabinoids
- Compounds may vary from plant to plant
- Residual impurities (pesticides, fungal contaminants)
- Dosing is not well regulated
Cannabis Is Like a Box of Chocolates...

"...future medicinal uses will most likely lie in drugs based on cannabinoid chemicals or extracts with defined concentrations that can be reliably produced."

—Nora Volkow
Questions for Future Research

• What factors contribute to negative effects and risks of cannabis exposure?
  – Age at initiation?
  – Quantity used?
  – Frequency of use?
  – Potency?
  – Duration of use?

• What are the long-term consequences of heavy cannabis use prior to brain maturation?
WHAT'S A HEALTHCARE PROFESSIONAL TO DO?
American Society of Addiction Medicine (ASAM) Recommendations

- Cannabis-related products **should not** be distributed unless/until they have FDA approval
- Smoking is not an appropriate drug delivery mechanism
- Need for federal regulatory standards for approval and distribution
- State should not enact regulatory standards more permissive than federal ones
- Clinicians who choose to discuss medical use of cannabis must:
  - Adhere to established professional tenets of proper patient care
  - Have a preexisting and ongoing relationship with the patient
  - Not recommend cannabis as a disproportionately large portion of practice
  - Not issue recommendation without adequate information regarding composition and dose
  - Have adequate training in identifying substance abuse and addiction

• Pain: only for patients with neuropathic pain that has failed to respond to standard treatment (including adequate trial of pharmaceutical cannabinoids)
• Anxiety: not appropriate therapy
• Insomnia: not appropriate therapy
• Not appropriate for:
  – <25 years of age
  – Personal/family history of psychosis
  – Current or past cannabis use disorder
  – Cardiovascular or respiratory disease
  – Pregnant, planning pregnancy, or breastfeeding
Screening for Cannabis Use Disorder

- NIDA Quick Screen—NIDA-modified ASSIST
- NM-ASSIST full
- CAGE-AID
- Risk factors
  - Current mood or anxiety disorder
  - History of substance use
Cautions About Cannabis Use: Time to Peak Concentration

**Inhalation**

- Fast brain uptake
- Higher risk of addiction
- Risk of impairment greatest immediately and within first 2 hours

**Oral**

- Delayed brain uptake
- Lower risk of addiction
- Risk of impairment delayed and may be greatest between 2–6 hours after consumption
Summary

• Wide-ranging role of endocannabinoid system suggests potential therapeutic uses of cannabis, but also potential adverse effects, especially during neurodevelopment
• Scant evidence beyond pain in cancer, nausea/vomiting, and spasticity in MS
• Hope for use in severe pediatric epilepsy (Phase III)
• Media hype but no actual evidence for use in psychiatric conditions (PTSD, anxiety, depression)
• Variations in potencies, cannabinoid constituents, dosing, and route of administration make medical marijuana difficult to recommend
• Potential for use in numerous therapeutic indications, but Schedule I status severely limits ability to research
Your patient, a 33-year-old woman whom you have been treating for 3 years for major depressive disorder, discloses to you that 6 weeks ago, she visited a cannabis clinic and was certified for the use of medical marijuana to treat chronic back pain resulting from a car accident and subsequent surgery 2 years ago. As part of your discussion regarding the risk/benefit assessment of cannabis use for chronic pain, you tell her that:

1. Randomized controlled trials provide moderate to strong evidence for efficacy in chronic back pain
2. Randomized controlled trials provide moderate to strong evidence for efficacy in some other types of chronic pain
3. Randomized controlled trials provide moderate to strong evidence for lack of efficacy in chronic pain
4. There are not enough data to help determine if there is efficacy for chronic pain
Your patient, a 26-year-old man whom you have been treating for 3 years for posttraumatic stress disorder (PTSD), discloses to you that 6 weeks ago, he visited a cannabis clinic and was certified for the use of medical marijuana to treat his PTSD symptoms. As part of your discussion regarding the risk/benefit assessment of cannabis use for PTSD, you tell him that:

1. Randomized controlled trials provide moderate to strong evidence for efficacy in multiple symptom domains of PTSD
2. Randomized controlled trials provide moderate to strong evidence for efficacy only in sleep/nightmares associated with PTSD
3. Randomized controlled trials provide moderate to strong evidence for lack of efficacy in PTSD
4. There are not enough data to help determine if there is efficacy for PTSD
Synthetic THC is approved for:

1. Nothing
2. Chemo-induced nausea
3. Appetite boost in AIDS wasting syndrome
4. Dravet syndrome (pediatric epilepsy)
5. 2 and 3
6. 2, 3, and 4