Seddon Savage, MD, MS, is a clinician, educator and advocate in the fields of addiction medicine and pain medicine. She is Medical Director of the Chronic Pain and Recovery Center at Silver Hill Hospital in Connecticut (www.silverhillhospital.org) and serves as an advisor to the Dartmouth-Hitchcock Health System on substance and pain-related education and practice improvement. She serves on New Hampshire Governor’s Commission on Alcohol and other Drugs and as Co-Chair of the Commission’s Task Force on Opioids and Healthcare Task Force of the Commission. She is co-chair of the Chronic Pain Work Group of the Federal Pain Research Strategy (FPRS), an initiative lead by the National Institutes of Health aimed at developing priorities for federal funding of pain research. Dr. Savage served as President of the American Pain Society (www.ampainsoc.org) from May, 2010-May, 2012 and as President of the New Hampshire Medical Society in 2007. She is an Associate Professor of Anesthesiology on the adjunct faculty of the Geisel School of Medicine at Dartmouth.

She has served as a consultant on addiction and pain issues to numerous national organizations, including the American Medical Association (AMA), the National Center on Addiction and Substance Abuse of Columbia University (CASA), the National Institutes on Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA) and the US Centers for Substance Abuse Treatment (CSAT), among others. She chaired the Committee on Pain of the American Society of Addiction Medicine and the Liaison Committee on Pain and Addiction (between ASAM, APS and the American Academy of Pain Medicine) each for over ten years. She is a frequent lecturer on issues at the interface of pain and addiction, including prescription opioid use, misuse and addiction, and has authored numerous papers and chapters on related topics.

She earned a BA in Art History from Barnard College; an MS in Human Nutrition from the Columbia University College of Physicians and Surgeons; and her MD from Dartmouth Medical School. She earned a certificate of added qualifications in Pain Management from the American Board of Anesthesiology in 1984 and is certified in Pain Medicine by the American Board of Pain Medicine. Dr. Savage is certified in Addiction Medicine by the American Board of Addiction Medicine (ABAM) and is an elected fellow of American Society of Addiction Medicine (ASAM).

OBJECTIVES:
Participants should be better able to:

1. Describe reasonable indications for the use of opioids and/or cannabis in clinical care;
2. Describe potential risks and adverse consequences of clinical use of opioids &/or cannabis in clinical care;
3. Explain current Federal policies and/or guidelines related to the use of opioids and/or cannabis in clinical care.
Cannabis & Opioids
Clinical and Policy Considerations

NAMDRD Annual Education Conference
Seddon R. Savage MD, MS
Silver Hill Hospital Chronic Pain & Recovery Center
Geisel School of Medicine at Dartmouth

Disclosures

No commercial conflicts
Employment/major contracts
• Silver Hill Hospital Chronic Pain Recovery Program
• Dartmouth-Hitchcock Health System
Objectives

• Attendees will be able to describe:
  • Clinical considerations in the use of opioids and/or cannabis
  • Potential risks and adverse consequences of clinical use of opioids &/or cannabis
  • Current Federal policies and/or guidelines related to the use of opioids and cannabis

• Opioids: history, policy, clinical issues
• Cannabis: history, policy, clinical issues
• Opioid & cannabis: considerations in co-use
Opium & Cannabis

• Ancient herbal remedies
• Diverse historical uses in healing
  • Opioids: analgesia, sleep-inducing, anxiolysis, antitussive, anti-diarrheal, others
  • Cannabis: analgesia, sleep-inducing, anxiolysis, anti-spasticity, others
• Produce reward & euphoria
  • Beneficial in some circumstances
  • Risk of misuse, diversion, addiction & harm in others

• Opioids: history, policy, clinical issues
• Cannabis: history, policy, clinical issues
• Opioid & cannabis: considerations in co-use
Opioid Question

- Which of the following is strongly supported by scientific evidence
  a. No patients experience improved pain and function when using opioids for pain long-term
  b. Patients may develop increased pain sensitivity due to long term opioid use
  c. Tolerance to opioids is predictable and makes long-term use of opioid essentially futile
  d. Opioid reward can be mitigated and risk of addiction reduced with use of intermittent dosing

Millenia of Controversy

- “Joy plant” Sumeria 3000 BC
- “Among the remedies it has pleased almightly God to give man to relieve his suffering, none so beneficient nor efficacious as opium” Thomas Sydenham, 1600s
- “…save our people from the clutches of this hydra-headed monster which stalks the civilized world, wrecking lives and happy homes, filling our jails and lunatic asylums…” Witherspoon JA. A protest against some of the evils in the profession of medicine. JAMA. 1900;34 :1589–1592
- “The use of narcotics in the terminal cancer patient is to be condemned ... due to undesirable side effects ... dominant in the list of these ... is addiction” Lee LE Jr. Medication in the control of pain in terminal cancer. JAMA 1941;116:216-219
Opioid Use Trends

Late 1800s-early 1900s
- Post Civil War – opioids, willowbark, cannabis, cocaine
- Early 1900’s widespread prescribing & street opioid use
- Opioid maintenance of addiction common
- 1914 Harrison Act tracks & taxes opioids
- 1919 & 1920 Federal Decision–addiction outside realm of medical interest: opioids can not be used to treat
- Prescribing for pain legal, but use declined

Opioid Use Trends

1950s
- Opioid use discouraged
- Cancer feared, elective surgeries deferred, chronic pain tolerated

1960s
- Methadone treatment introduced, AMSA, Haight Ashbury Free Clinic
- St Christopher’s Hospice 1967

1970s
- IASP 1973, APS 1977, Pain Medicine
- Aggressive tx cancer pain & acute pain
- Interdisciplinary care of chronic pain (Bonica, Fordyce, others)
Opioid Use Trends

1980s
- Observation: cancer pts not inevitably addicted or tolerant
- Positive trials opioids for non-cancer pain reported
- Interdisciplinary care of chronic pain available

1990s
- JCAHO, VA-5th vital sign, other pain quality initiatives
- Opioid therapy of all pain increases
- Pain technologies evolve: pumps, stimulators, radiologically guided injections
  
  *Era of possibilities: pain can be vanquished!*
- Medicine as business: interdisciplinary pain care wanes

Opioid Use Trends 2000s

- Burgeoning concerns re: opioid misuse, abuse, addiction
- Research on misuse, risks, strategies for prevention
- Clinical & industry focus on risk reduction strategies
- Proliferation of opioid guidelines
- Efficacy, cost, duration of interventionalist tx debated
- DATA 2001 makes buprenorphine tx available
Opioid Use Trends

2010’s & beyond

- Renewed interest in interdisciplinary pain care
- Healthcare reform aims at EVB, cost-effective care
- Care of chronic illness a priority
- Heroin rises as prescription opioid misuse declines

U.S Opioid Prescribing Trends

Figure 1. Opioid Prescriptions Dispensed by US Retail Pharmacies. IMS Health, Vector One: National, Years 1991-1996, Data Extracted 201. IMS Health, National Prescription Audit, Years 1997-2013, Data Extracted 2014.

Volkow to Congress, NIDA, 2014
Drugs Involved in U.S. Overdose Deaths - Among the more than 64,000 drug overdose deaths estimated in 2016, the sharpest increase occurred among deaths related to fentanyl and fentanyl analogs (synthetic opioids) with over 20,000 overdose deaths. Source: CDC WONDER

Legal fields Tasmania
http://politonomicsandtravel.wordpress.com/2013/03/05/weekly-photo-challenge-lost-in-the-details-2-03-05-2013/

Deamuseum.org
Legal Opioids from Licensed Poppy Fields

- Leading growers
  - India
  - Turkey
  - Australia
    - Tasmania provides ~50% worlds supply
- Harvest methods
  - Poppy straw extraction
  - Opium gum

Business World, March 2013
Diacetyl Morphine (Heroin)

- Synthesized from opium in 1874
- “Non-addicting morphine”?  
- Relatively fast onset CNS action
- Rapidly metabolized to morphine  
  - UDT usually shows morphine only
  - 6-MAM is specific if found, but rare

Fentanyl & analogues

- Synthetic, not opium based
- Highly potent  
  - 50-100 X morphine
  - 30-50 X heroin  
  - Carfentanil 100x fentanyl potency
- Associated with major increase in overdoses  
- Manufactured in Colombia, Mexico, China
- Trafficker benefits  
  - $3300 per kg manufacture- no growers
  - $1M per kg sales
  - Easily transported

Prescription Surveillance system, Issue Brief, CDC, July 2017
Rx Opioid Use & Heroin

- 50-75% of injection heroin users report using prescription opioids prior to heroin  
  NIDA Research Report,  
  February, 2014; Pollini, R.A et al. Subst Abuse Rehabil 2(1):173

- Trajectory to addiction often initiated prior to opioid exposure  
  (OA following prescribed opioids 28x more likely with prior SUD)  
  Huffman KL et al. J Pain. 2015 Feb;16(2):126-34

- Most prescription opioid exposures do not lead to addiction  
  - Incidence clinically identified OUD in chronic pain treatment: 1/500 with no prior SUD. 3/100 general population  
    Fishbain et al, Pain Medicine, 2008  
    Edlund et al, J Drug and Alcohol Dependence, 2010

- How to target strategies to reduce opioid addiction & overdose  
  - Heroin/fentanyl is cheap, potent, available, snortable. Future initiation?

Non-Medical Prescription Opioid Use Sources  
NSDUH, 2006 (&2010)

<table>
<thead>
<tr>
<th>Source Where Respondent Obtained</th>
<th>Source Where Friend Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free from Friend/Relative</td>
<td>One Doctor 80.7%</td>
</tr>
<tr>
<td>Bought on Internet</td>
<td>More than One Doctor 3.3%</td>
</tr>
<tr>
<td>Drug Dealer/Stranger</td>
<td>Free from Friend/Relative</td>
</tr>
<tr>
<td>3.9%</td>
<td>7.3%</td>
</tr>
<tr>
<td>One Doctor</td>
<td>Bought/Took from Friend/Rel</td>
</tr>
<tr>
<td>15.1%</td>
<td>14.8%</td>
</tr>
<tr>
<td>More than One Doctor</td>
<td>Other 1</td>
</tr>
<tr>
<td>1.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Bought/Took from Friend/Relative</td>
<td>Drug Dealer/Stranger</td>
</tr>
<tr>
<td>21.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

1 The Other category includes the sources: "Wrote Fake Prescription," "Stole from Doctor’s Office/Clinic/Hospital/Pharmacy," and "Some Other Way."
Opioids for Pain

Positive

• Effective (at least initially)
• Simple to prescribe
• Relatively inexpensive
• Little organ toxicity

Negatives

• Palliative
  — may deter resolution cause of pain
  — May permit pain provoking activities
• Respiratory depression
• Physical dependence
• Tolerance
• Opioid induced hyperalgesia
• Reward & misuse
• Addiction

Opioid Indications

• The risk-benefit profile of opioids is more favorable than of other treatments

  or

• Other interventions are not effective in reducing pain and/or improving function
Guidelines

Opioids for Chronic Pain

- Federation of State Medical Boards, 2013
- American Pain Society, 2009
- ASIPP, 2012
- ACEOM, 2010
- State of Utah Dept. of Health, 2008
- Canadian National Pain Centre, 2010
  - EVB Guidelines “Low evidence, strong recommendations”
- Washington State Interagency, 2010
  - Prospectively consensus guidelines

CDC Guidelines

Focus: primary care, patients >18, exemption active cancer & palliative, non-binding but basis for some legislation

1. Non-pharm, non-opioids preferred for CP
2. Establish pain & function goals
3. Assess & discuss risks and benefits
4. Check PDMP prior to starting & q Rx to q 3 mo
5. UDT prior to start & at least annually
6. Start with immediate release medications
7. Use lowest effective dose (reassess at 50 MME and justify > 90 MME)
8. Short course usually sufficient for acute pain (3 d usual, >7 d rare)
9. Evaluate benefits & harms frequently
10. Mitigate risk (naloxone, small supplies, etc)
11. Avoid concurrent benzos
12. Refer for treatment of OUD
**CDC Guideline Challenges**

- Many states legislating guidelines into Board rules
- Insurers not reimbursing care outside guidelines
- Fear among clinicians regarding licensing sanctions if miss a requirement
- Guidelines (best practices) time consuming & balance difficult
  - Being used to justify not prescribing even when patients benefiting
  - Increasing reports of harm from reduced prescribing

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**Challenging Balance**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic pain as a disease</td>
<td>• Rising prescription drug abuse, associated harm &amp; deaths</td>
</tr>
<tr>
<td>• Affects &gt; 100 million American adults</td>
<td>• Chiefly related to opioids</td>
</tr>
<tr>
<td>• (37M high impact pain - PAINS initiative)</td>
<td></td>
</tr>
<tr>
<td>• Costs society $560–$635 billion/year</td>
<td></td>
</tr>
</tbody>
</table>

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*Controlling the Swing of the Opioid Pendulum*
George Comerci, Jr., M.D., Joanna Katzman, M.D., M.S.P.H., and Daniel DuHigg, D.D., M.B.A., *NEJM, February, 2018*
• Opioids: history, policy, clinical issues
• Cannabis: history, policy, clinical issues
• Opioid & cannabis: considerations in co-use

• Which of the following is true regarding Cannabis policies
  • Federal and State regulations are generally consistent with one another regarding therapeutic use of cannabis
  • Therapeutic cannabis (medical marijuana) laws are essentially identical from state to state
  • Federal policy allows use of cannabis on Federal land within the borders of a State if consistent with State law.
  • The current Federal administration’s policy related to medical and recreational cannabis has been inconsistent
Cannabis

- First mention 3-4000 BC, China
- Herb, tinctures & extracts used worldwide
- 1850 Added to U.S pharmacopeia (for neuralgia, convulsions, anti-emetic, alcoholism, opiate addiction, others)
- 1915-1927 10 states prohibit cannabis use, LoN limits use
- 1937 Taxation & licensing requirements pass, AMA opposed, prescribing declines
- 1942 Removed from U.S. pharmacopeia
- 1964 THC isolated, 1899 CBN, 1940 CBD
- 1970 CSA class I “no legitimate medical use”

Richard Glen Boire JD & Kevin Feeney JD Medical Marijuana Law, 2007
Rosalie Liccardo Pacula, State Medical Marijuana Laws: Understanding the Laws, Heath Policy, 2002

Herbal Cannabis is Here

MJ allowed for medical purposes-11
Eliminated jail time for possession (decriminalization)-4
Both medical & decriminalization-9
MJ legal for adult use, taxed & regulated-8

www.mpp.org
16 States Permit
High CBD-Low THC oils/extracts

- Alabama
- Delaware
- Florida
- Georgia
- Iowa
- Kentucky
- Mississippi
- Missouri
- North Carolina
- Oklahoma
- South Carolina
- Tennessee
- Texas
- Utah
- Virginia
- Wisconsin

October 3-6, 2013
Based on 1028 telephone interviews of persons age 18+ in random samples in 50 states weighted by age, gender, race, Hispanic ethnicity, region, pop density, cell vs landline status, adults in household.
Federal Law

- Cannabis is in CSA Schedule I: “illegal, without recognized medical use”
- State & Federal laws conflict
- August 2013 U.S. AG Eric Holder announced
  - Will not challenge use according to state marijuana laws
    (Upheld by Rohrabacher-Farr amendment through 2016)
  - Unless conflict with key enforcement priorities
    - Public health issues including use by minors, drugged driving
    - Diversion to states where not legal
    - Use or growing on federal lands
    - Associated criminality, violence, firearms, other drug sales
- Current Administration
  - Initial support for State determination
  - January, 2018 U.S. AG Sessions rescinded no interference policy

State Therapeutic Cannabis Laws

Variable

- Eligibility for use: criteria & process
- Source: dispensed, home-grown, both
- Possession amounts: dried herb, plant, edibles
- Clinician responsibilities & intervals
- Certify condition or symptom vs recommend
- No states collecting clinical level outcomes data
  - Canadian initiative
<table>
<thead>
<tr>
<th>State</th>
<th>Year</th>
<th>Act/Proposal/Section</th>
<th>Amount</th>
<th>Usable Plants</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska</td>
<td>1998</td>
<td>Ballot Measure 8</td>
<td>1 oz</td>
<td>6 plants (3 mature, 3 immature)</td>
<td>1.5</td>
</tr>
<tr>
<td>Arizona</td>
<td>2010</td>
<td>Prop 203</td>
<td>2.5 oz</td>
<td>12 plants</td>
<td>13.1</td>
</tr>
<tr>
<td>California</td>
<td>1996</td>
<td>Prop 215</td>
<td>8 oz</td>
<td>6 mature or 12 immature plants</td>
<td>19.4</td>
</tr>
<tr>
<td>Colorado</td>
<td>2000</td>
<td>Ballot Amendment 20</td>
<td>2 oz</td>
<td>6 plants (3 mature, 3 immature)</td>
<td>19.8</td>
</tr>
<tr>
<td>Connecticut</td>
<td>2012</td>
<td>House Bill 5386 (H. 21-13 S)</td>
<td>2.5 oz usable</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>2010</td>
<td>Amendment Act 8 (D.C. 2011)</td>
<td>2 oz</td>
<td>limits on other forms to be determined</td>
<td>5.1</td>
</tr>
<tr>
<td>Delaware</td>
<td>2011</td>
<td>Senate Bill 77 (14-14 S)</td>
<td>6 oz</td>
<td>usable</td>
<td>0.1</td>
</tr>
<tr>
<td>Hawaii</td>
<td>2000</td>
<td>Senate Bill 182 (20-18 H)</td>
<td>4 oz</td>
<td>7 plants</td>
<td>9.1</td>
</tr>
<tr>
<td>Illinois</td>
<td>2013</td>
<td>House Bill 1 (61-26 H)</td>
<td>2.5 oz</td>
<td>ounces of usable cannabis during a period of 14 days</td>
<td>0.3</td>
</tr>
<tr>
<td>Maine</td>
<td>1999</td>
<td>Ballot Question 2</td>
<td>2.5 oz</td>
<td>usable; 6 plants</td>
<td>18.3</td>
</tr>
<tr>
<td>Maryland</td>
<td>2014</td>
<td>House Bill 881 (H. 21-13 S)</td>
<td>30-day supply, amount to be determined</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Massachusetts</td>
<td>2012</td>
<td>Ballot Question 3</td>
<td>60-day supply for personal medical use (10 oz)</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Michigan</td>
<td>2008</td>
<td>Proposal 1 (D.C. 2011)</td>
<td>2.5 oz</td>
<td>usable; 12 plants</td>
<td>18.4</td>
</tr>
<tr>
<td>Minnesota</td>
<td>2014</td>
<td>Senate Bill 2470 (S. 69-40 H)</td>
<td>30-day supply of non-smokable marijuana</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Montana</td>
<td>2004</td>
<td>Initiative 141 (S.C. 69-40 H)</td>
<td>1 oz</td>
<td>usable; 4 plants (mature); 12 seedlings</td>
<td>13.2</td>
</tr>
<tr>
<td>Nevada</td>
<td>2000</td>
<td>Ballot Question 9</td>
<td>2.5 oz</td>
<td>usable; 12 plants</td>
<td>5.0</td>
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<tr>
<td>New Hampshire</td>
<td>2013</td>
<td>House Bill 573 (S.C. 69-40 H)</td>
<td>30-day supply of usable cannabis during a 10-day period</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>New Jersey</td>
<td>2010</td>
<td>Senate Bill 119 (S.C. 69-40 H)</td>
<td>2 oz</td>
<td>usable</td>
<td>0.4</td>
</tr>
<tr>
<td>New Mexico</td>
<td>2007</td>
<td>Senate Bill 623 (S.C. 69-40 H)</td>
<td>6 oz</td>
<td>usable; 16 plants (4 mature; 12 immature)</td>
<td>9.4</td>
</tr>
<tr>
<td>New York</td>
<td>2014</td>
<td>Assembly Bill 557 (H. 21-13 S)</td>
<td>30-day supply non-smokable marijuana</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>
The Perfect Wave

*We don’t generally recommend smoking opium, so why are patients vaping cannabis?*

- Policy history
- Legalization advocacy
- Money
- Research challenges
- Therapeutic reality

Legalization Advocacy

*eg Marijuana Policy Project*  www.mpp.org

“… envisions a nation where marijuana is legally regulated similarly to alcohol…”

“…MPP was the driving force behind the following ballot initiatives to legalize, regulate, and tax marijuana for adults 21 and older: Colorado in 2012; Alaska in 2014; and Maine, Massachusetts, and Nevada in 2016. Along with our allies, we aim to pass at least eight more laws to regulate marijuana like alcohol by 2019.”
Marijuana Policy Project
www.mpp.org

Medical Marijuana > Decriminalization > Legalization

2017 Strategic Plan

• Medical marijuana
  • 28 states & DC now have due to MPP efforts
  • 2017: progress in Louisiana, Nebraska, South Carolina, Texas
• Decriminalization
  • 2017 targets: New Hampshire, Texas
• Legalization (state legislation & ballot initiatives)
  • 2016 successes: Arizona, Maine, Mass, Nevada
  • 2017: Vermont, Rhode Island
  • 2018: Michigan    2019: CT, DE, IL, MD, NH, TX

March 31, 2016. In Colorado 2,500 licensed businesses with revenue of $1 billion a year, paying $130 million in taxes. Cash.
Cannabis Research

Steps to Approval

- HHS determines researcher qualified & research has merit
- Obtain Schedule 1 research license/registration from DEA
- Interagency review & approval by PHS & DHHS
- IND number from FDA
- Review by NIDA & Federal DEA
- Local DEA Review & Site Inspection

Additional State restrictions may apply
(eg in CA all CS I & II drug studies must be approved by the Research Advisory Pain of the AG Office)

Requirement removed June 2015

Content from Mark Wallace, 2015
Cannabis Research

Other Limitations

• Historically single U.S. source of cannabis
  • NIDA contracts with U Miss for growth
  • THC concentrations low med high (1%-4%-7%)
  • 2015 NIDA announced higher CDB varieties & extracts
    8/12/16 DEA invites applicant to grow for research
• NIH funding has been limited: in 2015
  • $111M on cannabis & cannabinoids
  • Of this: $21M on therapeutics, $9M cannabidiol
• Regulatory, funding & source challenges result in
  high quality research being done elsewhere (Canada,
  Israel, Brazil & Netherlands)

Combined Consequences 2017

FDA Approved Medications

Opioids
• Morphine
• Codeine
• Oxycodone
• Hydrocodone
• Hydromorphone
• Oxymorphone
• Methadone
• Buprenorphine
• Tramadol
• Tapentadol
• Kappa agonists
• Myriad products using each molecule

Cannabinoids
• Dronabinol (THC)
• Nabilone (THC analogue)
• Cannabidiol? (Epidiolex)
• Nabiximols (Sativex) (50-50 THC/CBD)
Herbal Cannabis

- >100 cannabinoids and over 500 chemical constituents in herbal cannabis
  - THC – analgesic, euphorogenic
  - CBD – anxiolytic, anti-inflammatory, no euphoria
  - Many others, less studied, likely interactions
- Understanding of cannabinoid actions & interactions evolving
- Diverse strains bred with diverse effects
- Imprecise but potentially helpful in the absence of medications

Illustration from: Mehmedic et al, J Forensic Sci, September 2010, Vol. 55, No. 5

Endogenous Cannabinoid System

- CB1 receptors rich in CNS (densest in reward, nociception, appetite regulation), less in PNS
- CB2 primarily immune system, some CNS/PNS
- Endogenous cannabinoids
  - Anandimide (Sanskrit for bliss)
  - N-Arachidonyldopamine (NADA)
  - Many others, variable CB1/CB2 affinity
- Physiologic roles in neuromodulation
  - Nociception
  - Mood modulation including reward
  - Cognition, learning & memory
  - Energy balance, appetite

Clinical Actions Cannabis & Cannabinoids

National Academy of Science, Engineering & Medicine Report, 2017

- Substantial or conclusive evidence
  - Chronic pain in adults, particularly neuropathic pain (cannabis)
  - Chemotherapy-induced nausea & vomiting (oral cannabinoids)
  - Subjective MS spasticity (oral cannabinoids)
- Moderate
  - Short-term sleep (cannabinoids, primarily CBD)
- Limited
  - Appetite & weight loss in HIV/AIDS (cannabis & oral cannabinoids)
  - Objective MS spasticity (oral cannabinoids)
  - Tourettes symptoms (THC capsules)
  - Anxiety symptoms in social anxiety (cannabidiol)
  - PTSD symptoms (nabilone; single, small fair-quality trial)
  - Improved TBI or CVA outcomes—statistical association

Clinical Herbal Cannabis

Side-Effects & Risk of Use

- Evidence mostly from studies of recreational use
- Risks therapeutic use may differ from recreational use
  - Could be lower be due to
    - Patterns and dosing of use
    - Later age of onset of use
    - Expectations
  - Could be higher due to
    - Drug interactions
    - Co-occurring morbidities
Herbal Cannabis

**Neurobehavioral Side-Effects & Risks**

- Cognitive & perceptual distortions, sedation, reward
  > Risk of MVAs, accidents and falls, particularly in elderly
- Impairment in work & social performance
- Physiologic dependence & withdrawal
- Cannabis use disorder mod-severe (9% recreational users)
- Low birth weight, pregnancy complications, NICU stays, neurodevelopmental changes
- Developmental changes in adolescents
  - Intellectual, motivational, maturational
- Increased risk of psychotic disorders, anxiety disorders
- Increased risk of SI, SA & completed suicide
- Increased BPD & mania/hypomania in BPD

Volkow et al, Adverse Health Effects of Marijuana, NEJM, 2014
National Academies of Science, Engineering & Medicine, 2017 Report

Herbal Cannabis

**Medical Side-Effects**

**Cardiopulmonary**

- Triggering myocardial infarction with acute use (NASEM limited)
- CVA: Ischemic or hemorrhage (Limited)
- Exacerbation COPD/asthma with smoking (Limited)

**Other**

- Non-seminoma testicular germ cell tumors (limited)
- Decrease some inflammatory cytokines (limited)
- Mixed effects on Type 2 diabetes (limited)

National Academies of Science, Engineering & Medicine, 2017 Report
Drug Treatment Demand – Age 12+
*Treatment Episode Data System (TEDS)  www.samhsa.gov*

Cannabis Treatment - Adolescents
*Treatment Episode Data System (TEDS) – www.samhsa.gov*
Clinical Herbal Cannabis

Public Health Considerations

- Framing as a medicine may reduce perceptions of drug-related risk, particularly among youth.
- Increased access for therapeutic use may increase access for non-medical use (as with opioids) with
  - Impaired driving & associated MVAs
  - Dependence & addiction
  - Other cannabis associated harm
- Edible forms attract use by babies & children
- May reduce opioid related harm (prescription & illicit users)

Clinical Herbal Cannabis

APS White Paper Clinical Recommendations
Journal of Pain, 2016

- Be aware of Federal laws & current enforcement
- Be aware of & work within State laws
- Be guided by evidence, not commercial messaging
- Advise patients on cannabis strains & extracts versus cannabinoid medications as possible
- Advise patients on routes of administration as possible

Clinical Herbal Cannabis

APS White Paper Clinical Recommendations
Journal of Pain, 2016

Manage with paradigm similar to universal precautions paradigm of opioids
- Establish clear goals of treatment
- Screen for risk of misuse, addiction & diversion
- Counsel on individualized risks & benefits
- Consider written understanding & agreement
- Consider urine drug screens
- Monitor: symptoms, function, substance use
- Continue or discontinue based on outcomes
- Intervene in harmful use with appropriate referrals
Clinical Herbal Cannabis

APS White Paper Research Recommendations
Journal of Pain, 2016

• Increase Federal funding for cannabis research
• Dual focus: herbal cannabis & cannabinoids
• Ease regulatory restrictions impeding research
  • Consider rescheduling from CS schedule I
• Improve access to high quality cannabis of diverse strains, derivatives & ratios
• Encourage states to collect individual & population level data

What’s the Rush?

Let Colorado & Washington do the Experiment.
• Opioids: history, policy, clinical issues
• Cannabis: history, policy, clinical issues
• Opioid & cannabis: considerations in co-use

• Which of the following statements is true of opioids and herbal cannabis
  a. Both are Schedule 2 drugs under the U.S. Controlled Substances Act and can be prescribed by physicians in States with medical marijuana laws
  b. Both act on endogenous systems that have naturally occurring ligands of their class (opioid & cannabinoid)
  c. They appear to act on entirely different physiologic systems that have no apparent interaction.
  d. Both are associated with roughly equivalent risk for addiction and respiratory suppression
Opioid & Cannabinoid Systems

**Complex Interactions**

- Neuroanatomic co-locations
- Rich neurochemical crosstalk, eg:
  - Naloxone and selective opioid antagonists variably reverse cannabinoid-induced analgesia and reward effects
  - Cannabinoid antagonists variably reverse opioid-induced analgesia and reward
  - Mice without CB1 receptors do not demonstrate CPP or SA with opioids
  - Mice without mu (but with K or d) opioid receptors do not demonstrate CPP or SA with THC.
- Exponential complexity given numerous cannabinoids, opioids, receptors & sub-receptors. Understanding evolving.


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Opioids & Cannabis

**Comparison Prominent Opioid Concerns**

- Overdose deaths
  - Opioids - single drug overdose deaths common with overuse
  - Cannabis — single drug overdose deaths not reported
- Addiction
  - ~9% recreational cannabis users develop addiction
  - 25-40%+ of recreational heroin users develop addiction
  - ~3% of therapeutic opioid users develop abuse/addiction (?)
  - No statistics available for therapeutic cannabis addiction
- Physiologic dependence
  - Opioids – dramatic & uncomfortable withdrawal
  - Cannabis – more subtle, though well-defined withdrawal
Possible Opioid Sparing Effects

Nielson et al, Neuropsychopharmacology 2017 - Opioid-Sparing Effects of Cannabinoids: Systematic Review & Meta-Analysis

- Animal studies (19)
  - Support opioid-sparing effects of cannabinoids
  - Synergistic analgesic effects of opioid & cannabinoid use
- Clinical studies reviewed (9)
  - Suggest improved pain control combining cannabinoid & opioid
  - Do not provide compelling evidence of less opioid use
- Author’s clinical observation of humans
  - Support opioid sparing effects of cannabinoids
  - Improved pain control with combo
- Suggest further studies with attention to
  - Opioid & cannabinoid types & dosing
  - Effects & side effects
  - Need for high quality study design

Possible Opioid Sparing Effects

Other studies

- Retrospective online survey of 118 cannabis clinic patients: reported 64% reduction in opioid doses
  
  *Boehnke et al, J Pain, 2016*

- Prospective open-label study, 176 patients beginning medical cannabis, reported 44% decrease opioid use at 1 yr
  
  *Haroutounian et al, Clin J Pain, 2016*

- Patients with opioid IDU & cannabis use report 25-50% reduction in opioid use
  
  *Kral et al, J Drug&AlcDep, 2015*

- 25% fewer opioid overdose deaths in states with medical marijuana access, with increased effect over time
  
  *Bachuber et al, JAMA Internal Med, 2014*
Summary

- Opioids and cannabis individually have risks & benefits
- Combined opioid & cannabis use may have
  - Therapeutic synergy with reduction in opioid doses
  - Combined or synergistic side effects & risks
- Cannabis may represent a harm reduction intervention for some patients
- Special care in considering prescribed opioids & authorized cannabis
- Universal precautions for both may limit harm
  - Clear goals
  - Tighten supervision
- Unauthorized cannabis indicates contact with illicit sources – caution

Considerations in Clinical Care

Risks
- Individual patients
- Public health

Benefits
- Individual patients
- Public health
Question 1
Which of the following is strongly supported by scientific evidence related to opioids:

A. No patients experience improved pain and function when using opioid for pain long-term.
B. Some patients may develop increased pain sensitivity due to long-term opioid use.
C. Tolerance to opioids is predictable and makes long-term use of opioid essentially futile.
D. Opioid reward can be mitigated and risk of addiction reduced with use of intermittent dosing.
Question 2
Which of the following is true regarding Cannabis policies:

A. Federal and State regulations are generally consistent with one another in regulation of the use of cannabis for medical purposes

B. Therapeutic cannabis (medical marijuana) laws are essentially identical similar from state to state

C. Recent Federal policy supports use of cannabis on Federal lands within the borders of a State so long as it is consistent with State law.

D. The current Federal administration policy related to medical and recreational cannabis has been inconsistent
Question 3
Which of the following statements is true of opioids and herbal cannabis

A. Both are Schedule 2 drugs under the U.S. Controlled Substances Act and can be prescribed by physicians in States with medical marijuana laws.
B. Both act on endogenous systems that have naturally occurring ligands of their class (opioid & cannabinoid) in the human body.
C. They appear to act on entirely different physiologic systems that have no apparent interaction.
D. Both are associated with roughly equivalent risk for addiction and respiratory suppression.