NABP 2009 SYMPOSIUM

• Cannabis in the Treatment of Chronic Pain
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Lecture Outline

• Brief History
• Biology/Pharmacology of Marijuana (Cannabis)
• Clinical Trials
• Using Cannabinoids in this Setting
Historical Aspects

• Has been used medicinally, spiritually, and recreationally for thousands of years
• Was legal in USA until 1937 and was on the US Pharmacopoeia until 1942: this was done AGAINST the advice of the AMA (then known as the American Medical Society)
• Harry Anslinger – responsible for “Reefer Madness”: thus opiates became the pathway for pain management
Biology of Cannabis

- Very complex: see papers
- Over 100 different cannabinoids
- Lipid soluble
- 21 carbon “terpenes”
- Cannabinoids very similar to flavinoids found in chocolate
Biology of Cannabinoids

• Endogenous System
• Receptor Based Mechanisms
• THC is most common AND most psychoactive (Marinol)
• Cannabidiol and Cannabinol are also very prevalent
Cannabinoid Receptors

- G-protein-coupled receptors
- $\text{CB}_1$ receptors highly expressed in the brain
  - $\text{CB}_1$ receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- $\text{CB}_2$ receptors are expressed primarily in immune cells
  - $\text{CB}_2$ receptor expression in neurons is being studied

Key ECS Elements

Cannabinoid receptors are G-protein-coupled receptors

Endocannabinoids

- Anandamide
- 2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors

CB₁ receptor

CB₂ receptor

- Central nervous system
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α-cells)

Immune cells and tissues
- T cells, B cells
- Macrophages
- Dendritic cells
- Spleen, tonsils
- Adipose tissue

The CB₁ Receptor

The CB₁ receptor consists of 7 transmembrane helices

Courtesy of Patricia Reggio, PhD
Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

Presynaptic

Postsynaptic

Retrograde neurotransmitter

Presynaptic

Postsynaptic

Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis.

- Endocannabinoids affect a large number of physiologic processes including:
  - Feeding behavior
  - Energy balance, metabolism, and GI function
  - Pain perception
  - Motor control and posture
  - Learning, memory, and emotions
  - Immune and inflammatory responses
  - Cardiovascular function
  - Reproduction
  - Bone formation

~15,000 articles on chemistry and pharmacology of cannabis and cannabinoids
2,000+ articles on endocannabinoids
10 + RCTs with cannabis published in the US in the last 7.5 yrs
American Cannabinoid Medicines in Perfectly Legal Use:  
Chemicals, Extracts, Botanicals

Dronabinol (Marinol™)  
Nabilone (Cesamet™)  
Cannabis Sativa L. Extracts (Sativex™)  
Cannabis Sativa L. Cigarettes

Since 1985  
Since 1985  
Since 2006  
Since 1976
Biology of Cannabis

• Percent of different cannabinoids depends on plant strain and how it is grown
• THC effects are modulated by other cannabinoids
• Endogenous cannabinoids: Anandamide
• May be responsible for “runner’s high”
Clinical Pharmacology

- Receptors mainly in hippocampus, cerebellum, and peripheral nerves
- Brainstem receptors inhibit nausea, NOT respiration
- Pharmacology greatly affected by bioavailability
- Smoking/Vaporization versus ingestion
Clinical Pharmacology

• Analgesia: different mechanism than opiates, some synergy though.
• Spasticity: likely GABA mediated
• Appetite enhancement: hippocampal?
• Anti-emetic: cerebellar?
Clinical Pharmacology

• Adverse effects: mainly seen in new users
• Euphoria versus paranoia
• Short term memory impairment
• Balance, incoordination
• These are reversible, short lived effects (3-4 hours max)
• Serious adverse effects NOT seen in chronic users
Metabolism

- Hepatic Cytochrome P450 system
- Quickly deactivated but slowly metabolized and cleared
- Excreted in urine and feces
- In high doses may compete with P450 system with other drugs
Clinical Trials

- Hampered by government regulations
- Must use federally produced cannabis
- Mixed Results
- Methodological problems
Clinical Trials

- Works for neuropathic pain (Abrams, et al)
- Mixed results for spasticity (Wade, Zajicek, et al)
- Appetite improved by THC
- Generally very well-tolerated; minimal drug-drug interactions; minimal adverse effects (Ware, et al)
Using Cannabis

- Chronic Pain
- Palliative care
- Complementing other drugs or therapies
- Unique delivery may be an advantage: inhalation
Central and Peripheral Mechanisms of Cannabis

What symptoms may respond in this setting?

What is the benefit of central effects?
Pain-Sensing System Malfunction in Chronic Pain

Pain Sensing

In chronic pain, pain signals are generated without physiologic significance

Normal pain:
Pain-sensing signals are initiated in response to a stimulus
- They elicit a pain-relieving response

Chronic pain:
Pain signals are generated for no reason and may be intensified
- Pain-relieving mechanisms may be defective or deactivated

Pathogenesis of Chronic Pain

1. Injury
2. Pain and inflammation
3. Injury heals but pain signals continue
4. Structural CNS changes alter neural transmission
   - Chronic pain
   - Allodynia
   - Hyperalgesia
   - Spread of pain

(Adapted from Marcus, 2000)
Components of Pain That May Respond to Cannabis

- Neuropathic – burning, lancinating
- Mechanical: dull, aching
- Inflammatory: acute, sharp
- Our data show that patients use cannabis to treat multiple pain syndromes
Pros/Cons/Risks/Benefits

- Good analgesia
- High dosing ceiling vs toxicity
- Risk for psychological addiction
- Minimal physical dependence
- Little drug-drug interactions
Pros/Cons/Risks/Benefits

- Tolerance may develop
- Long term users may need higher doses
- Patient/family will have to buy it
- Marinol NOT as effective – only has THC
- Has street value but NOT as much as opioids!
Other Uses of Cannabis in This Setting

• Spasticity
• Appetite (may offset narcotic or chemotherapy induced anorexia or nausea)
• Mood enhancement
• Animal studies show cannabinoids have a neuroprotective and anti-tumor effect
• No respiratory suppression!
Cannabis Helps Patients with Many Forms of Chronic Pain

- Myofascial Pain Syndrome (MPS)
- Diabetic Neuropathy (DN)
- Neuropathic Pain Syndrome (NPS)
- Central Pain Syndrome (CPS)
- Phantom Pain (PP)
- Spinal Cord Injury (SCI)
- Fibromyalgia Syndrome (FMS)
- Osteoarthritis (OA)
- Rheumatoid Arthritis (RA)
- Discogenic Back Pain (DP)
- HIV Neuropathy (HIV)
- Malignant Pain (MP)
Patient Snapshots

- **Patient #101**: “He has been using marijuana on his own, as he feels [it] gives him the best pain relief of anything that he has used.” 2-3 inhalations on a MJ cigarette 2-3[x]/day, & this improves his pain levels drastically w/o incapacitating him.

- **Patient #7**: “using MJ successfully on a daily basis; pain from 8-9/10—>2-3/10; needs only ~2-3 inhalations from a MJ cigarette to get pain relief”
Patient Snapshots

- **Patient #38**: “marijuana daily with no SE; only thing she is now currently using for pain”;

- **Patient #67**: “She has been using cannabis in the past and has had excellent results with respect to her migraine headaches.” Using <1/4 oz/week
Patient Snapshots

• **Patient #126**: “states openly that he has used marijuana in the past and it has helped his pain substantially. Tolerates it much better than opiates and his use of marijuana has substantially decreased his dependence on opiates”

• **Patient #133**: “he is using MC to control his pain with good luck with that. He also uses oxycodone and oxyContin, but he tries to limit this.”
Our Data

- Stereotypes and myths about MC must be dispelled
- Our data should help deconstruct myths about the kinds of patients accessing MC treatment:
  - Our randomly picked study patients were 1) not young males; 2) not malingers; 3) not feigning disease to access cannabis
  - Our data, both subjective and objective diagnostic data, shows that MC patients are middle aged women and men, with complex medical problems
The Role of the Pharmacist in Medicinal Cannabis...

- Pharmacists NEED to be involved: Help educate patients in proper use - counsel the patient and family
- Pharmacists could be involved in the compounding of cannabis tinctures, ointments, salves, inhalers, and capsules
- Pharmacists can help regulate the dosing and help ensure that patients are using high quality medicinal cannabis to improve efficacy
- Pharmacists can help in formulating delivery routes that maximizes benefits and minimizes side effects
How Do We Move Forward?

EDUCATION and COLLABORATION

• Need physicians and pharmacists to be knowledgeable and organized
• Pharmacies should be the source of medical cannabis: NO “street deals”
• Growing and cultivation are other areas for opportunity
• Efforts to influence public opinion about MC are made by federal law enforcement spokespersons, as seen in the following two illustrations

• “Dr. Pot” and “Dr. Pat” appear on a Drug Enforcement Administration (DEA) prevention Web site targeted toward adolescent education entitled “Rx pot: a prescription for disaster.”
Finally…

• Cannabis is effective and safe but IS a medication: Pharmacists MUST be involved
• Physicians need to remember the four “A’s”: Analgesia (symptom relief); ADLs; Adverse Effects; Aberrant Usage
• Follow the law and use proper documentation
• Use science and logic to guide the way medicinal cannabis is regulated, not propaganda and politics
Thanks for attending

• For questions we can be contacted by e-mail:
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