Objectives

• Describe the basic pharmacology of cannabinoids
• Consider the evidence for cannabinoids in pain management
• Identify patient risk factors or potential contraindications to cannabinoid use
Patient Case S.P.

- 60 year old male with chronic low back pain & L leg radicular symptoms stemming from a fall at work 19 years ago
  - L2-3 laminectomy in 1996
  - Multiple lumbar epidural steroid injections
  - Select nerve root blocks
  - Lidocaine infusions
  - Spinal cord stimulator trial
  - Gabapentin, duloxetine, and nortriptyline have helped but he is still debilitated
Patient Case S.P.

• On long-term opioids with contract with PCP with no aberrancies noted
• Recent MRI showing posterior disk bulges at L2-3 (largest bulge), L3-4, L4-5, L5-S1
• PMH: Hyperlipidemia, prediabetes, basal cell carcinoma, anxiety
• Current medications: duloxetine 60 mg QD, simvastatin 20 mg QD, oxycodone 30 mg Q4H PRN pain
• Inquires about medical marijuana
Pharmacology of Cannabinoids
Types of Cannabinoids

- Endocannabinoids
- Phytocannabinoids
  - $\Delta-9$ tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
- Synthetic

JAMA. 2015 Jun 23-30;313(24):2474-83
# Pharmacokinetics

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Smoked/Vaporized</th>
<th>Oral Ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Seconds – minutes</td>
<td>30 – 120 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>6 – 10 minutes</td>
<td>4 – 6 hours</td>
</tr>
<tr>
<td>Distribution</td>
<td>Highly lipophilic, accumulates in fatty tissues and reaches peak concentrations in 4-5 days. Tissue $t_{1/2} = \sim 7$ days with complete elimination taking up to 30 days</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Phase 1 &amp; 2 in liver</td>
<td></td>
</tr>
<tr>
<td>11-OH-THC metabolite (active)</td>
<td>Lower concentrations</td>
<td>Higher concentrations</td>
</tr>
</tbody>
</table>
| Elimination $t_{1/2}$ (chronic use) | THC = 4.1 days
11-OH-THC = 12.6 days |                         |

Adapted from Chemistry & biodiversity. 2007;4(8):1770-1804
Drug/Drug Interactions

• Metabolism
  – THC and CBN
    • CYP 3A4 & 2C9
  – CBD
    • CYP 3A4 & 2C19
• Synergy with CNS depressants
• Opioids: Cross tolerance and mutual potentiation
Pharmaceutical Cannabinoids

• Dronabinol and nabilone
  – Synthetic Δ-9-THC
  – Oral ingestion

• Nabiximols
  – Synthetic Δ-9-THC / CBD
  – Oromucosal spray
  – **Not currently available in the U.S.**
    • Phase IIIB/III trials underway for cancer pain
Brief Evidence Review – Focus on Pain
Qualifying Medical Conditions in OH

- AIDS
- Amyotrophic lateral sclerosis (ALS)
- Alzheimer’s disease
- Cancer
- Chronic traumatic encephalopathy (CTE)
- Crohn’s disease
- Epilepsy or another seizure disorder
- Fibromyalgia
- Glaucoma
- Hepatitis C
- Inflammatory bowel disease (IBD)

- Multiple sclerosis (MS)
- Pain that is either chronic and severe or intractable
- Parkinson’s disease
- Positive status for HIV
- Post-traumatic stress disorder (PTSD)
- Sickle cell anemia
- Spinal cord disease or injury
- Tourette’s syndrome
- Traumatic brain injury (TBI)
- Ulcerative colitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Condition</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skrabek et al, 2008</td>
<td>Nabilone</td>
<td>Fibromyalgia</td>
<td>Placebo</td>
</tr>
<tr>
<td>Narang et al, 2008</td>
<td>Dronabinol</td>
<td>Chronic noncancer pain</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pinsinger et al, 2006</td>
<td>Nabilone</td>
<td>Chronic therapy-resistant pain</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wissel et al, 2006</td>
<td>Nabilone</td>
<td>Spasticity-related pain</td>
<td>Placebo</td>
</tr>
<tr>
<td>Blake et al, 2006</td>
<td>Nabiximols</td>
<td>Chronic rheumatoid arthritis pain</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Condition</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al, 2009</td>
<td>Cannabis</td>
<td>Refractory polyneuropathy</td>
<td>Placebo</td>
</tr>
<tr>
<td>Abrams et al, 2007</td>
<td>Cannabis</td>
<td>HIV sensory neuropathy</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wilsey et al, 2008</td>
<td>Cannabis</td>
<td>CRPS, spinal cord injury, PN, nerve injury</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nurmikko et al, 2007</td>
<td>Nabiximols</td>
<td>PN and allodynia</td>
<td>Placebo</td>
</tr>
<tr>
<td>Berman et al, 2004</td>
<td>Nabiximols</td>
<td>Brachial plexus root avulsion</td>
<td>Placebo</td>
</tr>
<tr>
<td>Frank et al, 2008</td>
<td>Nabilone</td>
<td>Chronic neuropathic pain</td>
<td>Opioid</td>
</tr>
</tbody>
</table>

*HIV- human immunodeficiency virus, CRPS- complex regional pain syndrome, PN- peripheral neuropathy, VAS- visual analog scale, NRS- numeric rating scale.

# JAMA 2015 Meta-analysis Summary of Chronic Pain Parallel-Group Studies

<table>
<thead>
<tr>
<th>No. of studies (n)</th>
<th>Cannabinoid (No. studies)</th>
<th>Outcome</th>
<th>GRADE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (1370)</td>
<td>Smoked THC (1), Nabiximols (7)</td>
<td>Pain reduction $\geq 30%$ NRS or VAS</td>
<td>Moderate</td>
</tr>
<tr>
<td>6 (948)</td>
<td>Nabiximols (6)</td>
<td>Pain NRS scores</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 (613)</td>
<td>Nabiximols (3)</td>
<td>Pain Brief Pain Inventory</td>
<td>Moderate</td>
</tr>
<tr>
<td>6 (267)</td>
<td>Nabiximols (5), Nabilone (1)</td>
<td>Patient global impression of change</td>
<td>Low</td>
</tr>
<tr>
<td>5 (764)</td>
<td>Nabiximols (5)</td>
<td>Neuropathic Pain Scale</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 (573)</td>
<td>Nabiximols (3)</td>
<td>Quality of life</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*NRS- numeric rating scale; VAS- visual analog scale

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zajicek et al, 2003, &amp; Freeman et al, 2006</td>
<td>Oral cannabis extract</td>
<td>Spasticity; incontinence episodes</td>
<td>Placebo</td>
</tr>
<tr>
<td>Aragona et al, 2009</td>
<td>Nabiximols</td>
<td>Psychopathology, cognition</td>
<td>Placebo</td>
</tr>
<tr>
<td>Kavia et al, 2010</td>
<td>Nabiximols</td>
<td>Incontinence episodes</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vaney et al, 2004</td>
<td>Oral cannabis extract</td>
<td>Change in spasticity</td>
<td>Placebo</td>
</tr>
<tr>
<td>Fox et al, 2004</td>
<td>Oral cannabis extract</td>
<td>Change in tremor index</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wade et al, 2004</td>
<td>Nabiximols</td>
<td>VAS, most troublesome symptom</td>
<td>Placebo</td>
</tr>
<tr>
<td>Killestein et al, 2002</td>
<td>Dronabinol; Oral cannabis extract</td>
<td>Spasticity</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

*VAS- visual analog scale  
<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zajicek et al, 2012</td>
<td>Oral Cannabis Extract</td>
<td>Muscle stiffness</td>
<td>Placebo</td>
</tr>
<tr>
<td>Collin et al, 2007</td>
<td>Nabiximols</td>
<td>Spasticity</td>
<td>Placebo</td>
</tr>
<tr>
<td>Underleiger et al, 1987</td>
<td>Oral THC</td>
<td>Spasticity</td>
<td>Placebo</td>
</tr>
<tr>
<td>Svendsen et al, 2004</td>
<td>Dronabinol</td>
<td>Median spontaneous pain intensity</td>
<td>Placebo</td>
</tr>
<tr>
<td>Rog et al, 2005</td>
<td>Nabiximols</td>
<td>Pain, sleep disturbance</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of studies (n)</th>
<th>Cannabinoid (No. studies)</th>
<th>Outcome</th>
<th>GRADE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (519)</td>
<td>Nabiximols (2)</td>
<td>50% reduction spasticity symptoms</td>
<td>Low</td>
</tr>
<tr>
<td>2 (519)</td>
<td>Nabiximols (6)</td>
<td>30% reduction spasticity symptoms</td>
<td>Low</td>
</tr>
<tr>
<td>5 (1244)</td>
<td>Nabiximols (4), THC/CBD (1), Dronabinol (1)</td>
<td>Spasticity, Ashworth Spasticity Scale</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 (698)</td>
<td>Nabiximols (2), Nabilone (1)</td>
<td>Spasticity, NRS or VAS scores</td>
<td>Low</td>
</tr>
<tr>
<td>4 (1433)</td>
<td>Nabilone (2), Dronabinol (1), THC/CBD (1)</td>
<td>ADLs, Barthel Index of ADL</td>
<td>Moderate</td>
</tr>
<tr>
<td>2 (497)</td>
<td>Nabiximols (2)</td>
<td>Walking speed as assessed by timing</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 (461)</td>
<td>Nabiximols</td>
<td>Patient Global Impression of Change</td>
<td>Low</td>
</tr>
</tbody>
</table>

*NRS- numeric rating scale; VAS- visual analog scale; ADL- Activities of Daily Living

### JAMA 2015 Meta-analysis Summary of Parallel-Group Studies

<table>
<thead>
<tr>
<th>Indication</th>
<th># of Studies (# patients)</th>
<th>Cannabinoid (# studies)</th>
<th>Comparator</th>
<th>Outcome Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic and cancer pain</td>
<td>31 (4535)</td>
<td>Smoked THC (1), Nabiximols (29), Nabilone (1)</td>
<td>Placebo</td>
<td>Majority cannabinoid</td>
</tr>
<tr>
<td>Spasticity</td>
<td>21 (5371)</td>
<td>Nabiximols (13), THC/CBD (2), Dronabinol (2), Nabilone (3)</td>
<td>Placebo</td>
<td>Majority cannabinoid</td>
</tr>
<tr>
<td>Depression</td>
<td>3 (408)</td>
<td>Nabiximols</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>1 (24)</td>
<td>Cannabidiol</td>
<td>Placebo</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1 primary (22); 11 in other indications (2167)</td>
<td>Nabilone (1), Nabiximols (10), THC/CBD (1)</td>
<td>Placebo</td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2 (70)</td>
<td>Cannabidiol</td>
<td>Amisulpride</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; study: CBD; 2&lt;sup&gt;nd&lt;/sup&gt; study: Amisulpride</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>4 (69)</td>
<td>THC capsules</td>
<td>Placebo</td>
<td>THC</td>
</tr>
<tr>
<td>CINV</td>
<td>3 (102)</td>
<td>Dronabinol (2), Nabiximols (1)</td>
<td>Placebo</td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 (88)</td>
<td>Dronabinol</td>
<td>Placebo</td>
<td>Dronabinol</td>
</tr>
</tbody>
</table>
Adverse Effects and Precautions
# Medical Marijuana Adverse Effects

<table>
<thead>
<tr>
<th>System Affected</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Dizziness, numbness, nightmares, visual disturbances, headache, feeling intoxicated, drowsiness, anxiety, cognitive impairment, emotional changes, mental slowness, impaired reaction time, dysphoria</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, orthostatic hypotension, hypertension, palpitations, paroxysmal atrial fibrillation, peripheral vasodilation</td>
</tr>
<tr>
<td>Other</td>
<td>Dry mouth, nausea, syncope, hyperemesis, exacerbation of immunosuppression, fertility</td>
</tr>
</tbody>
</table>

Driving Impairment

• Independent risk factor for motor vehicle accidents (MVA)
• Associated with increased fatality in MVA
• Avoid driving
  – Inhalation – 4 hours
  – Oral ingestion – 6 hours
  – Euphoria experienced – 8 hours

Controversial Adverse Effects

- Cognitive impairment
  - Importance of age 25
- Mental Illness
  - Role of pre-existing/family history
- Gateway Hypothesis
  - Direct cause vs association

2) Substance Abuse and Rehabilitation. 2016;7:41-53  
Cannabis Use Disorder

• 10 – 30 % of users will develop
  – Most common age and timeframe

• DSM-5 Diagnostic Criteria (at least two within previous 12 months):
  – Tolerance
  – Withdrawal
  – Increasing amounts of use over time
  – Inability to control consumption
  – Craving
  – Recurrent use causing negative impacts on social, professional, and educational life
Cannabis Withdrawal Syndrome

• Symptoms
  – Nightmares and strange dreams
  – Trouble sleeping
  – Anxiety
  – Irritability
  – Physical tension
  – Low mood and depression
  – Reduced appetite

• Symptom appearance and duration
Your patient asks for medical marijuana for pain, what do you do?
Place in Therapy

• Refractory neuropathic or chronic pain
• Consider first
  – Other evidence based pharmacologic and non-pharmacologic therapies
  – Adequate trial of pharmaceutical cannabinoids
• Consider a treatment agreement
• Re-evaluate at each visit
  – Consider periodic urine drug screens

“Authorizing Dried Cannabis for Chronic Pain or Anxiety”. The College of Family Physicians of Canada Website.
Importance of Constituents

- THC trends over time
  - 1980s ~4%
  - 2012 average concentration from police confiscation ~15%
  - 2015 ~20% with potencies up to 30%

- Percentage of constituents play a role in therapeutic applications, adverse effects, etc.

1) “Marijuana far more potent than it used to be, tests find” article. CBS News Web site. Published 3/23/2015.  
Discontinuation of Authorization

• Runs out early or obtaining from unauthorized source
• Concomitant alcohol or drug use that becomes problematic
• Signs of cannabis use disorder
• Therapy not effective or is causing harm
Helpful Resources

- **State Regulatory Status/Updates**
  - [http://medicalmarijuana.ohio.gov/](http://medicalmarijuana.ohio.gov/)

- **Overview and counseling points**

- **JAMA Reviews:**
References


References


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References


