COMPLEMENTARY AND ALTERNATIVE MEDICINE

Allen C. Bowling, MD PhD
Colorado Neurological Institute (CNI)

Conflict/Disclosure Information

- Research, consulting, advising, speaking services
  - Acorda, American Academy of Neurology, Bayer, Biogen-Idec, Center for Disability Services, Consortium of MS Centers, EMD-Serono, Evergreen Health, Genzyme, Mandell Center for Multiple Sclerosis, National MS Society, Novartis, Pfizer, ProCE, Questcor, Teva Neuroscience
Off-Label Information

◆ This presentation will include off-label discussion of:
  – Marijuana (cannabis)
  – Cannador, nabiximols (Sativex), and other marijuana extracts
  – Tetrahydrocannabinol (THC, dronabinol, Marinol)
  – Nabilone (Cesamet)

COMPLEMENTARY AND ALTERNATIVE MEDICINE
Summary

- Biologically Based Therapies
  - Marijuana
  - Vitamin D
  - Lower salt diet
  - Paleolithic diets

Marijuana and MS

- Increasing legalization
- MS-relevant pharmacology/clinical trials
- BUT potential challenges for health professionals
  - Emotional response
  - Politics
  - Lack of familiarity with trial data
  - Novel features: herbal medicine, inhaled, cannabinoid pharmacology
Medical Marijuana:
“Approved Conditions”

- Pain and spasticity AND/OR multiple sclerosis
- Typical text
  - “...severe pain;...persistent muscle spasms, including those that are characteristic of MS...”
“Cannabinoids”

- Many different potentially active molecules:
  - THC: delta-9-tetrahydrocannabinol
  - CBD: cannabidiol
  - About 60 others

Variability of Marijuana Plants and Products

- Two major “subspecies”
  - Cannabis sativa: mainly THC
  - Cannabis indica: THC and CBD

- Many different hybrids

- Other variables
  - Growing and storage
  - State of maturity
  - Processing/formulation
Marijuana

**Actions**
- CB1 receptors
  - Neurons
  - “DSI” and “DSE”
- CB2 receptors
  - Lymphocytes
- Other effects
  - Antioxidant, excitotoxicity, calcium flux
  - May be independent of receptor effects

Cannabinoid Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Opioid</th>
<th>Cannabinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td>µ, κ, δ, ORL-1</td>
<td>CB1, CB2</td>
</tr>
<tr>
<td>Endogenous ligands</td>
<td>Endorphins, enkephalins, dynorphins, endomorphins</td>
<td>Anandamide, 2-AG (2-arachidonoyl glycerol)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Brain stem, cortex, amygdala, hypothalamus, hippocampus, spinal cord, intestinal tract, peripheral tissues</td>
<td>Basal ganglia, hippocampus, hypothalamus, cerebellum, cerebral cortex, immune system, peripheral tissues</td>
</tr>
<tr>
<td>Physiological role</td>
<td>Thermoregulation, endocrine, pain, tolerance</td>
<td>Inflammation, pain, movement, memory, reward, mood, appetite</td>
</tr>
<tr>
<td>Indications</td>
<td>Analgesia</td>
<td>Anorexia, nausea, analgesic</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>
Possible Cannabinoid Effects in MS

Forms of Marijuana

- **Leaf**
  - Smoked, eaten ("edibles"), vaporized
- **Plant resin: "hashish"**
  - Smoked, eaten
- **Oil extracts**
  - Nabiximols (Sativa), Cannador, many others that are unregulated and non-standardized
- **Single molecule preparations**
  - THC: Marinol, dronabinol
  - Synthetic THC: Cesamet, nabilone
Prescription/Research-Grade Cannabinoids

*Marinol (Δ-9 tetrahydrocannabinol – THC) (2.5 - 10mg)*
- Oral capsule
- Approved for chemotherapy-induced nausea and vomiting and anorexia associated with HIV/AIDS

*Nabilone (0.25 - 1.0mg)*
- Oral capsule
- Approved for chemotherapy-induced nausea and vomiting

*Nabiximols (Sativex) (2.5mg THC + 2.7mg CBD)*
- Oromucosal spray
- Approved in Canada for multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain

*Cannador (2:1 of THC:CBD)*
- Oral
- Society for Clinical Research (Germany)

Review of CAM and MS

- Report of the Guideline Development Committee of the American Academy of Neurology
  - Yadav, Bever, Bowen, Bowling, Weinstock-Guttman, Cameron, Bourdette, Gronseth, Narayanaswami
- Medline search: 1970-Sept 2013
AAN Classification Scheme: Classes of Controlled Trials

♦ Class I
  – Randomized, controlled, objective outcome
  – Extra criteria: concealed allocation, primary outcome clearly defined, exclusion and inclusion criteria clearly defined, adequate accounting for dropouts and crossovers

♦ Class II: lacks one criterion

♦ Class III: all other controlled trials with independent outcome assessment

AAN Classification Scheme: Level of Recommendations

♦ Level A
  – High confidence in evidence (2 Class I)
  – Large value of benefit relative to risk

♦ Level B
  – Moderate confidence in evidence (1 Class I, 2 Class II)
  – Moderate value of benefit relative to risk

♦ Level C
  – Low confidence in evidence (1 Class II, 2 Class III)
  – Small value of benefit relative to risk

♦ Level U: “insufficient conclusion”
Review of CAM and MS: Marijuana

- 19 studies
  - 6 Class I
  - 4 Class II
  - 9 Class III

“EBM”

- Evidence-based medicine
“EBM”

- Evidence-based medicine
- “Emotion-based medicine”
  - Primary driver of opinion/recommendation is emotional response
  - Lack of awareness, disregard, or selective use of existing scientific and clinical evidence
- “PBM”
  - Politically based medicine

Review of CAM and MS: Marijuana

- 19 studies
  - 6 Class I
  - 4 Class II
  - 9 Class III
- Formulations
  - THC: 4
  - Oral cannabis extract (Cannador): 8
  - Nabiximols (Sativex): 8
  - Smoked: 2
Review of CAM and MS: Marijuana

Level A recommendation: “Clinicians might offer…”
- Cannador for subjective spasticity and pain

Level B: “Clinicians might offer…”
- THC for subjective spasticity and pain
- Sativex for subj. spasticity, pain, urinary frequency
- THC and Cannador: not objective spasticity, tremor
- Nabiximols: not obj. spasticity, urinary incontinence

Level C: “Clinicians should counsel…”
- Nabiximols: not tremor

Insufficient information: smoked

Review of CAM and MS: Marijuana Summary

Efficacy
- THC, Cannador, Nabiximols
  • Subj. spasticity, pain
- Nabiximols
  • Urin. frequency

Lack of efficacy
- THC, Cannador, Nabiximols
  • Obj. spasticity, tremor
- Nabiximols
  • Urin. incontinence
Review of Marijuana and Neurological Disorders


Report of the Guideline Development Committee of the American Academy of Neurology
- Koppel, Brust, Fife, Bronstein, Youssof, Gronseth, Gloss

Medline search: 1948-Jan 2013

Disorders
- MS: spasticity, pain, bladder dysfunction, tremor
- Dyskinesias: Huntington's disease, levodopa-induced in Parkinson's disease
- Cervical dystonia, tics of Tourette syndrome, epilepsy

MS spasticity
- Subjective: Cannador effective, nabiximols and THC probably effective
- Objective: generally ineffective except Cannador and THC possibly effective at one year
- Smoked: insufficient evidence

MS pain/painful spasms
- Cannador effective
- THC and nabiximols probably effective
- Smoked: insufficient evidence
Review of Marijuana and Neurological Disorders

♦ MS bladder dysfunction
  – Nabiximols probably effective for frequency and of unknown efficacy for overall bladder symptoms
  – THC and Cannador probably ineffective for bladder complaints

♦ MS tremor
  – THC, Cannador, and Nabiximols are probably or possibly ineffective

Review of Marijuana and Neurological Disorders

♦ Involuntary movement disorders
  – Probably ineffective (PD) or underpowered (HD) or insufficient data (cervical dystonia, Tourette)

♦ Seizure frequency in epilepsy
  – Insufficient data
Two Independent Reviews: Summary

- Some level of effectiveness
  - THC, Cannador, Nabiximols
    - Subj. spasticity, pain
  - Nabiximols
    - Urin. frequency

- Probably ineffective
  - THC, Cannador, Nabiximols
    - Obj. spasticity, tremor

- Insufficient data: smoked

Conventional Medications for Spasticity

  - “The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing.”
Conventional Medications for Spasticity

- *Multiple Sclerosis and Related Disorders*, Rae-Grant et al, 2013
  - Bethoux and Willis
  - “Oral antispasticity agents are widely used, although clinical trial evidence to support the efficacy of these medications in MS is limited.”

Cannabis Side Effects

- Generally well tolerated in MS studies
- Dizziness, impaired balance, sedation, lightheadedness, memory difficulties
- Multiple gastrointestinal side effects
- Oral ulcers (nabiximols)
- Depression, psychosis, hallucinations, addiction, apathy
- Impaired driving, incoordination, visual difficulties, seizures, increased spasticity, leg weakness
- MI, cancer
Cannabis: Uncertain Potency and Purity

♦ Study of edibles in Colorado (2014)
  • N=13
  • No products contained the amount of THC on label
  • 1 product with 50% more
  • 3 products with 0.2-0.4%

♦ Colorado labelling
  • “Warning: There may be health risks associated with the consumption of this product... The product was produced without regulatory oversight for health, safety, or efficacy... The marijuana product contained within this package has not been tested for potency, consume with caution. The marijuana product contained within this package has not been tested for contaminants.”

Unanswered Questions, Unresolved Issues

♦ Majority of MS studies are with nabiximols and Cannador—but, these are not available in the US
♦ Products that are available
  – Most are non-standardized, non-regulated
♦ How to translate research studies with oral preparations to smoked products?
Unanswered Questions, Unresolved Issues

- Are some hybrids more effective and safer than others?
- What dose, frequency, and preparation?
- “Combination therapy” with meds (symptomatic/disease-modifying)?
- Relative safety and effectiveness of marijuana vs meds?

Future Directions: Studies of Specific Strains

- N=102, 23 with MS, VAS for subjective effects
- “Pharmaceutical grade”
  - Standardized for THC/CBD
  - “Low,” “medium,” and “high” THC
- Significant differences
  - Anxiety, “dejection,” appetite stimulation
Future Directions: More Targeted Pharmacology

Cannabinoid Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Opioid</th>
<th>Cannabinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td>µ, κ, δ, ORL-1</td>
<td>CB1, CB2</td>
</tr>
<tr>
<td>Endogenous ligands</td>
<td>Endorphins, enkephalins, dynorphins, endomorphins</td>
<td>Anandamide, 2-AG (2-arachidonoyl glycerol)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Brain stem, cortex, amygdala, hypothalamus, hippocampus, spinal cord, intestinal tract, peripheral tissues</td>
<td>Basal ganglia, hippocampus, hypothalamus, cerebellum, cerebral cortex, immune system, peripheral tissues</td>
</tr>
<tr>
<td>Physiological role</td>
<td>Thermoregulation, endocrine, pain, tolerance</td>
<td>Inflammation, pain, movement, memory, reward, mood, appetite</td>
</tr>
<tr>
<td>Indications</td>
<td>Analgesia</td>
<td>Anorexia, nausea, analgesic</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>
Future Directions: More Targeted Pharmacology

- Pryce et al, 2013 (*Mult Scler J*)
- FAAH inhibitors in EAE
- Multiple compounds decreased spasticity
  - No hypothermia (cannabinomimetic effect)
- No effect in FAAH-deficient mice

Future Directions

- Research
  - Rigorous studies designed to address the multiple unresolved issues
- Legalization/regulation/standardization
  - Quality standards and monitoring for purity and potency
Evidence-Based Opinions: Marijuana and MS

- Efficacy and safety information is still too limited, especially for available products
- Efficacy data are compelling but safety information is still too limited and unclear how to translate research into practice

Evidence-Based Opinions: Marijuana and MS

- Efficacy data are compelling, there is moderate safety information, and can try to translate research into practice
  - Thoughtful use in selected patients after considering risks/benefits/unknowns
- Similar to above but more widespread use
Information Resources

♦ Lay article

♦ Book

Summary

♦ Biologically Based Therapies
  – Marijuana
  – Vitamin D
  – Lower salt diet
  – Paleolithic diets
Vitamin D: Update

- NOT standard of care
- Intervention studies are limited
- Vitamin D is a hormone
  - Don’t be MS-centric!
  - Be thoughtful with dosing and levels
Dietary Salt

- One of single greatest dietary harms to health
- Average American: 4,000 mg/day
- Recommended amount: 1,500-2,300 mg/day
- High salt intake increases disease risk
  - High blood pressure, heart disease, stroke, congestive heart failure, kidney disease
- Effect of 1,200 mg decrease in salt intake in US
  - Dramatic decrease in death/disability
  - 150,000 lives and $10-24 billion saved annually

Dietary Salt

- Nature (April 2013, Vol 496)
  - 3 different articles
  - Increased salt conditions: increased production of pro-inflammatory TH17 cells and more severe EAE
  - Gut or other specific organs?
- Correale et al (ECTRIMS, 2013)
  - Medium salt intake: 2.75-fold increased attack risk
  - High salt intake: 3.95-fold increased attack risk, 3.4-fold increased risk of new MRI lesion, 8 more T2 lesions
Dietary Salt

- Salt shaker is minimal problem
- Main sources: processed food, restaurant food
- Wait for more data vs act now
  - Read labels: huge variations!
  - Substitute herbs and spices, use salt substitutes
  - Cook pasta and rice without salt
  - Rinse canned food
  - Make slow changes
  - Learn to enjoy taste of food, not taste of salt

Paleolithic Diets

- Hypothesis
  - Diseases of civilization, including autoimmune, are due to diet changes outpacing genetic changes
- Proponents
  - Primitive cultures have lower rates of obesity, heart disease, diabetes
- Critics
  - Region and era unclear, paleolithic diet unknown, human body can adapt within a lifetime and evolve over several thousand years
Paleolithic Diets

♦ MS
  – No well-designed studies
♦ Other diseases
  – Limited beneficial effects (over past 30 years)
♦ Drs. Konner and Boyd: 25 year followup
  – “much more research needs to be done”
  – “the ultimate validity” of the Paleolithic approach has not been proven

Paleolithic Diets

♦ “Best Diets”
  – 22 experts, 32 diets, 7 criteria
  – Paleolithic diet
    • All 7 criteria: #30-32
    • Overall score: tied for last place
  – Negatives
    • Hard to follow, may not obtain healthful effects of grains/dairy and other diets with better evidence of benefit
Acknowledgments

- Colorado Neurological Institute (CNI)
- Rocky Mtn. MS Center
- Thomas Stewart, JD, PA, MS
- Patricia Kennedy, RN, CNP
- Ronald Murray, MD
- Nathaniel Bowling
- Lee Shaughnessy
- Gina Ibrahim, PhD
- Julie Lawton
- National MS Society
- Consortium of MS Centers
- MS Foundation
- MS Association of America
- Teva Neuroscience, Biogen-Idec, EMD-Serono, Pfizer, Bayer
- HealthOne Foundation
- Denver Botanic Gardens
- Hudson Gardens
- Denver Medical Library