Medicinal Marijuana: A Critical Review of Selected Literature

THERESA MALLICK-SEARLE
Senior Nurse Practitioner
Stanford Pain Management
Tmallick@stanfordmed.org

No Disclosures

Any views or opinions in this presentation are solely those of the author/presenter and do not necessarily represent the views or opinions of the American Society for Pain Management Nursing®.

Learning Objectives

• Explore history of cannabis use & current science.
• Objectively evaluate clinical applications of cannabinoids, supported by the research.
• Verbalize the limitations of scientific research on cannabis.
History

- 2737 B.C. Early writings in China note the use of marijuana for medicinal purposes.
- In 1545 the Spanish brought marijuana to the New World.
- The late 1800's William Brooke O'Shaughnessy, an Irish physician was the first to introduce the use of medicinal marijuana into Western Medicine.
- Marijuana was listed in the United States Pharmacopoeia from 1850 until 1942.
National

A campaign conducted in the 1930s by the U.S. Federal Bureau of Narcotics (now the Bureau of Narcotics and Dangerous Drugs) sought to portray marijuana as a powerful, addicting substance that would lead users into narcotics addiction.

1937 Marijuana Tax Act

The Controlled Substances Act of 1970

National

The Compassionate Investigational New Drug Program (1978), is a government-sponsored program allowing a limited number of patients to use medical marijuana grown at the University of Mississippi. Closed to new entrants (1990), there are only seven surviving patients who were grandfathered into the program.

Under the Bush administration, federal agents have raided medical marijuana farms and cannabis clubs in several states.

Obama Administration in 2009, Stop Raids on Medical Marijuana Dispensaries. 2011/2012: era of decreased tolerance and increased scrutiny states MM laws.

2009 Attorney General Eric Holder said that the Justice Department will no longer raid medical marijuana clinics that are established legally under state law. Marking a major shift from the previous administration.

2011 U.S. Attorney General Eric Holder promised to clarify the Justice Department’s position on state medical marijuana laws after federal prosecutors warned they might prosecute everyone from licensed growers to regulators.

Several U.S. states have started reassessing their medical marijuana laws after U.S. attorneys recently sent stern warnings that anyone from licensed medical marijuana growers to regulators could be subjected to prosecution. The agencies were told to jettison in California, Colorado, Montana and Rhode Island.
Veterans Administration Marijuana Policy

... pursuant of Federal Law, VA physicians, nurse practitioners, or other licensed clinicians are not authorized or permitted to participate in the recommendation for treatment of or prescribing medical marijuana to a VA patient.

... it is acknowledged that testing positive for marijuana in a patient, based upon random drug screening, will not serve as a breach of the current pain management agreement if the patient submits documentation in support of the marijuana being prescribed and dispensed in conformity with state law.

States

Alaska (1998)
Arizona (2012)
California (1996)
Colorado (2000)
Connecticut (2012)
Delaware (2011)
DC (2010)
Hawaii (2000)
Maine (1999)
Michigan (2008)
Montana (2004)
Nevada (2000)
New Jersey (2010)
New Mexico (2007)
Oregon (1998)
Rhode Island (2006)
Vermont (2004)
Washington (1998)

6 states with pending legislation or ballot measures to legalize medical marijuana:

Illinois
Massachusetts
Missouri
New York
Ohio
Pennsylvania
Chemistry of Marijuana

- Marijuana contains more than 400 chemicals. Approximately 60 are called cannabinoids.
- Marijuana is a cannabinoid drug.

1964. Rafael Mechoulam discovered the chemical structure of the THC molecule.

THC = delta-9-tetrahydrocannabinol
CBD = cannabidiol
Mechanism of Action

- 1988 discovery of the cannabinoid (THC) receptor site in the brain @ St. Louis University Medical School.

- Cannabinoids (THC) produce euphoria, enhancement of sensory perception, tachycardia, antinociception, difficulties in concentration and impairment of memory.

WHERE MARIJUANA ACTS

HYPOTHALAMUS
- Coordinates appetite, stress levels and metabolism

NEOCortex
- Responsible for higher cognitive functions such as thinking, attention, and decision-making

BASAL GANGLIA
- Involved in motor control and planning, plays a role in the initiation and termination of action

HIPPOCAMPS
- Important for memory and the formation of long-term memories

ANTERIOR CINGULATE CORTEX
- Responsible for empathy, emotion and social function

BRAIN STEM AND SPINAL CORD
- Important for breathing, heart rate, and the sensation of pain

Mechanism of Action

- CB1 receptors: expressed by central & peripheral neurons.

- CB2 receptors: expressed mostly by cells of the immune system.
An excerpt from the BBC series Horizon

http://www.youtube.com/watch?v=QGKpbyqXwqg84

YouTube - Cannabinoid Receptors - Horizon: Cannabis - The Evil Weed
The Endocannabinoid System (ECS)

- The endocannabinoid system is endogenous, previously unknown neurotransmitter system that "mimics" many of the same responses seen using exogenous cannabinoids.
- Cannabinoid receptors, CB1 and CB2.
- In 1992 Raphael Mechoulam discovered the existence in our brain of a natural occurring cannabinoid, which he called anandamide (2-AG).
- Memory
- Appetite
- Stress response
- Exploration, social behavior, & anxiety
- Immune function
- Autonomic nervous system
- Analgesia

The Endocannabinoid System (ECS)

- Our endocannabinoid system works to modulate the sensitivity of our brain to many of the other neurotransmitters that are present, such as dopamine and serotonin.
- Our experience of pain, especially from inflammation (the endocannabinoid system interacts with our endorphin system to reduce pain).
- Our response to stress (the entire stress response, from brain (hypothalamus) to endocrine glands (adrenal cortisol secretion) is regulated by the endocannabinoid system).
- THC affects the brain by mimicking our natural cannabinoid transmitters!
- Ethan Russo’s paper on “clinical endocannabinoid deficiency syndrome”

Forms & Preparations

- Herb 3-22% THC
- Hashish/Hash Oil 40-90% THC
- Synthetic:
  - Dronabinol (Marinol) CII
  - Nabilone (Cesamet) CII
  - Nabiximols (Sativex)
**Modes of Administration**

- Smoke
- Inhale Vaporizer
- Lingual/sublingual
- Baked Goods/Teas
- Pill/Capsules

**Medicinal Uses/Safety of Marijuana**

- **US**
  - Center for Medicinal Cannabis Research
  - National Center for Natural Products Research (NCNPR) at the University of Mississippi
  - National Institute on Drug Abuse (NIDA)
  - National Institutes of Health (NIH)
- **Canada**
  - Canadian Institutes of Health Research
- **Europe**
  - The Medicinal Cannabis Research Foundation (MCRF): a UK registered charity set up to promote and sponsor medicinal cannabis research and to raise public awareness
  - Spain, Germany, Italy
  - ICRS: http://www.cannabinoidsociety.org
  - 'Big Pharma': Sanofi-Aventis, GW Pharmaceuticals, Pfizer

**Center for Medicinal Cannabis Research**

www.cmcr.ucsd.edu/research/research.htm

**CMCR Research Statement**

The center will be seen as a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities.

To conduct randomized trials to compare the efficacy and safety of various methods of cannabis administration, in patients diagnosed with HIV/AIDS, cancer, seizures or muscle spasms associated with a chronic debilitating condition, or any other serious condition providing sufficient theoretical justification.
**Medicinal Uses/Safety of Marijuana**

• 3 minute search of PubMed (research, THC, marijuana, cannabis, medicine, addiction, safety) = Results: 1 to 20 of 3333959.

• Largest body of literature
  – Neurological & movement disorders: antispasmodic
  – Wasting syndromes (AIDS): appetite stimulation
  – Cancer: chemotherapy induced nausea/vomiting
  – Addiction & abuse potential, safety
  – Pain


http://norml.org/component/zoo/category/recent-research-on-medical-marijuana

---

**Clinical and Psychological Effects of Marijuana in Man**

ANDREW T. WEIL, M.D., NORMAN E. ZINBERG, M.D., & JUDITH M. NELSEN, M.A.


---

**Clinical and Psychological Effects of Marijuana in Man**

• Early attempts to investigate marijuana in a formal double-blinded study model.

• Few early studies involving human subjects in US/Internationally.

• It is also the first attempt to collect basic clinical and psychological information on the drug by observing its effects on marijuana-naive human subjects in a neutral laboratory setting.
Clinical and Psychological Effects of Marijuana in Man

Weil, A., Zinberg, N., & Nelson, J. – Boston University School of Medicine, Boston, MA. Science. 1968,162(12),1234-1242.

Design: Single center, randomized, double-blind, placebo controlled.

N = 9 healthy male volunteers, 21-26 y/o, Daily tobacco smokers, marijuana naïve.
N = 8 healthy male volunteers, 21-26 y/o, chronic marijuana smokers.

All subjects smoked 2 standardized cigarettes per session.

Naïve = placebo, low dose (4.5mg THC), high dose (18mg THC)
Experienced = placebo, high dose (18mg THC)

Randomized subjects 1 of 3 groups, all completing a series of 3 sessions (Naïve subjects required a 4th "practice session")

I High Placebo Low
II Low High Placebo
III Placebo Low High

Physiological Parameters Measured: heart rate, respiratory rate, pupil size, blood glucose level.

The Psychological Tests: Continuous Performance Test (CPT)-5 minutes, The Digit Symbol Substitution Test (DSST)-90 seconds, CPT with strobe light distraction-5 minutes, Self-rating bipolar mood scale-3 minutes, Pursuit rotor-10 minutes.

Findings:

It is feasible and safe to study the effects of marijuana on human volunteers who smoke it in a laboratory.
Marijuana increases heart rate moderately.
No change in respiratory rate follows administration of marijuana by inhalation.
No change in pupil size occurs in short term exposure to marijuana.
Marijuana treatment produces no change in blood sugar levels.
Regular users of marijuana do not show the same degree of impairment of performance on the tests as do naïve subjects in some cases, their performance even appears to improve slightly after smoking marijuana.
Regular users often report that the body feels lighter after smoking marijuana which may lead to higher nicotine intake within 30 minutes of inhalation, to be abated after 1 hour, and to be completely dissipated by 3 hours.

"I think it's really dumb to grow cotton in Arizona, when growing hemp makes much more sense."
**Neurochemical Basis of Cannabis Addiction**


**Design:** Systematic Review (Standard medical/scientific literature databases 1977-2011).

Review body of literature that explored the specific involvement of CB1 cannabinoid receptor in the addictive properties of cannabinoids, along with advancing the knowledge based related to the specific contributions of different neurochemical systems in cannabis addiction.

**Findings:**
1) CB1 cannabinoid receptors are responsible for all the addictive properties of cannabinoids.
2) Involvement of the CB2 receptors undetermined.
3) Dopaminergic, Opioid, & Cannabinoid systems are involved in the NC substrate of addiction.
4) NA, 5HT, GABA, GLU, Ach, Hormones = addiction

---

**Schematic summary of the main neurochemical mechanisms involved in cannabis addiction.**

---

**Study**

Ferdinand et al. (2005)
Friedman et al. (2001)
Hull & Degenhardt (2009)
Henquet et al. (2005)
Copeland & Swift (2009)
Lynskey et al. (2003)
Hall (2006)
Ware & St. Arnaud-Trempe (2010)
Wade et al. (2010)
Karschner (2011)

**Results**

Marijuana use has been associated with low academic achievement, legal problems, unemployment, and risk for development of psychotic disorders.

Early cannabis consumption is often associated with an elevated risk of later problematic use of cannabis, poor academic performance, mental health problems, and enhanced prenatal behavior.

Synthetic cannabinoids (dronabinol, nabilone, nabazimols), are very rarely abused since they do not induce the same level of psychoactive effects as cannabis.
### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner &amp; Anthony (2002)</td>
<td>1:12 cannabis users will eventually become dependent on marijuana.</td>
</tr>
<tr>
<td>Maldonado (2002)</td>
<td>Evidence is indeterminate as to withdrawal syndrome associated with abrupt cessation of marijuana.</td>
</tr>
<tr>
<td>Young et al. (1983)</td>
<td></td>
</tr>
<tr>
<td>Abood et al. (2001)</td>
<td></td>
</tr>
<tr>
<td>Beardsley et al. (1986)</td>
<td></td>
</tr>
<tr>
<td>Budney &amp; Hughes (2006)</td>
<td></td>
</tr>
<tr>
<td>Stewart &amp; McMahon (2010)</td>
<td></td>
</tr>
<tr>
<td>R. Maldonado et al./Neuroscience 181 (2011) 1-17</td>
<td></td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Chiara et al. (2004)</td>
<td>Several heterologous systems different from the endocannabinoid system also participate in the addictive properties of cannabinoids.</td>
</tr>
<tr>
<td>Fattore et al. (2008)</td>
<td>Cannabinoids enhance the firing rate of dopaminergic neurons.</td>
</tr>
<tr>
<td>Gessa et al. (1998)</td>
<td>Dopaminergic neurons are under the control of excitatory &amp; inhibitory inputs that are modulated by CB1 receptor activation.</td>
</tr>
<tr>
<td>Maldonado et al. (2006)</td>
<td>Cocaine, amphetamines &amp; D2 receptor agonists enhanced the discriminative effects induced by low doses of THC, suggesting that activation of the D2 system positively modulates the cannabinoid response.</td>
</tr>
<tr>
<td>Fattore et al. (2008)</td>
<td>Opioid receptors and their endogenous ligands have been demonstrated to play an important role in brain reward processes, and to modulate the behavioral and neurochemical effects of multiple drugs of abuse including cannabinoids.</td>
</tr>
<tr>
<td>Solinas et al. (2010)</td>
<td>Cross-tolerance between cannabinoid and opiate agonists has been demonstrated in several studies.</td>
</tr>
<tr>
<td>R. Maldonado et al./Neuroscience 181 (2011) 1-17</td>
<td></td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigo et al. (2010)</td>
<td>Chronic contingent cannabinoid intake induces adaptive changes in the density and activity of mu-opioid receptors within brain reward circuits, which could contribute to the development of cannabinoid addiction.</td>
</tr>
<tr>
<td>Maldonado (2002)</td>
<td>Opioid receptors and their endogenous ligands have been demonstrated to play an important role in brain reward processes, and to modulate the behavioral and neurochemical effects of multiple drugs of abuse including cannabinoids.</td>
</tr>
<tr>
<td>Fattore et al. (2007a)</td>
<td>Cross-tolerance between cannabinoid and opiate agonists has been demonstrated in several studies.</td>
</tr>
</tbody>
</table>
Diagnostic and Statistical Manual of Mental Disorders (DSM-4) in May 2013 (DSM-5)

- Marijuana is an intoxicating substance, and it's chronic use can lead to abuse and dependence.
  - According to APA DSM IV, marijuana meets the criteria of a substance that can cause intoxication, abuse and dependence.
  - Since 1960's the psychoactive properties of cannabis r/t the THC content which has increased as much as 10-15%.
  - Alcohol & Opiates also meet criteria.

- Can cessation of chronic marijuana use result in a withdrawal syndrome?
  - the DSM-4 does not include marijuana withdrawal as a diagnostic category.

Adverse Effects of Medical Cannabinoids

Wang, T., Collet, JP., Shapiro, S., et al. - Department of Epidemiology & Biostatistics, Anesthesia & Family Medicine, McGill University, Montreal, Que., Canada.


Systematic review of safety studies of medical cannabinoids published over the past 40 years to create an evidenced base for cannabis-related adverse events and to facilitate future cannabis research initiatives.

Findings:
1) Short-term use of existing medical cannabinoids appeared to increase the risk of “non serious” adverse events.
2) Risks of long-term use poorly characterized by existing literature.
3) Additional "high-quality" trials on long-term effects were needed.

RESULTS

Studies:

Initial search identified = 1720 articles.
Identified 321 studies met criteria
  - 290 (90.3%) = observational studies, case reports*
  - 31 (9.7%) = randomized control trials, case reports

Definitions: "serious adverse events & non serious adverse events" recommended by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (International Conference on Harmonisation, ICH).
- "serious adverse event" = hospitalization, persistent or prolonged disability, death.
- "non serious adverse event" = any untoward medical occurrence, need not have a causal relation to the treatment.
<table>
<thead>
<tr>
<th>Role of administration; study design</th>
<th>Reference</th>
<th>Conditions (characterizing study population)</th>
<th>Sample size</th>
<th>Age, mean (range) yr</th>
<th>Sex, % male</th>
<th>Duration of exposure</th>
<th>Nast, frequency reported adverse events (%)</th>
<th>Nast, frequencies reported adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical spray (8% tetrahydrocannabinol or 8% tetrahydrocannabinol cannabinoid)</strong></td>
<td>Cole et al.</td>
<td>Rhematoid arthritis</td>
<td>38</td>
<td>42.6</td>
<td>21</td>
<td>9 wk</td>
<td>Nervous system disorders: 13/22 (60)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Caliber et al.</td>
<td>Multiple sclerosis</td>
<td>189</td>
<td>46.9</td>
<td>46</td>
<td>6 wk</td>
<td>Nervous system disorders: 68/179 (38.7)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Hummels et al.</td>
<td>Neuropathy</td>
<td>120</td>
<td>53</td>
<td>41</td>
<td>5 wk</td>
<td>Gastrointestinal disorders: 40/105 (38.6)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Bag et al.</td>
<td>Multiple sclerosis</td>
<td>66</td>
<td>48.25</td>
<td>21</td>
<td>4 wk</td>
<td>Nervous system disorders: 23/76 (29.7)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Wade et al.</td>
<td>Multiple sclerosis</td>
<td>160</td>
<td>51.74</td>
<td>38</td>
<td>6 wk</td>
<td>Nervous system disorders: 32/180 (17.7)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td><strong>Cross-over randomized controlled trial</strong></td>
<td>Bernal et al.</td>
<td>Brachial plexus palsy</td>
<td>48</td>
<td>39</td>
<td>23.3</td>
<td>2 wk</td>
<td>Nervous system disorders: 30/48 (62.5)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Trenta et al.</td>
<td>Glaucoma</td>
<td>6</td>
<td>55</td>
<td>100</td>
<td>18 h</td>
<td>Gastrointestinal disorders: 7/19 (36.8)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Wade et al.</td>
<td>Neuropathy</td>
<td>21</td>
<td>48</td>
<td>50</td>
<td>2 wk</td>
<td>Nervous system disorders: 11/27 (40.7)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td><strong>Oral (8% tetrahydrocannabinol or 8% tetrahydrocannabinol cannabinoid)</strong></td>
<td>Buggy et al.</td>
<td>Postoperative pain</td>
<td>60</td>
<td>48.8</td>
<td>3</td>
<td>24 h</td>
<td>Nervous system disorders: 12/60 (20)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Fryk et al.</td>
<td>Chemotherapy-induced nausea</td>
<td>116</td>
<td>61</td>
<td>60</td>
<td>4 d</td>
<td>Nervous system disorders: 56/80 (70)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Strasser et al.</td>
<td>Cancer-related anorexia/cachexia</td>
<td>240</td>
<td>61</td>
<td>54</td>
<td>6 wk</td>
<td>Gastrointestinal disorders: 70/467 (15.3)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Trinquart et al.</td>
<td>Multi work/stress syndrome</td>
<td>50</td>
<td>40</td>
<td>40</td>
<td>12 wk</td>
<td>Nervous system disorders: 13/50 (26)</td>
<td>0/5 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Role of administration; study design</th>
<th>Reference</th>
<th>Conditions (characterizing study population)</th>
<th>Sample size</th>
<th>Age, mean (range) yr</th>
<th>Sex, % male</th>
<th>Duration of exposure</th>
<th>Nast, frequency reported adverse events (%)</th>
<th>Nast, frequencies reported adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cross-over randomized controlled trial</strong></td>
<td>Zaglouk et al.</td>
<td>Multiple sclerosis</td>
<td>630</td>
<td>50 (18-64)</td>
<td>54</td>
<td>15 wk</td>
<td>Nervous system disorders: 75/255 (29.5)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Zaglouk et al.</td>
<td>Multiple sclerosis</td>
<td>631</td>
<td>50 (18-64)</td>
<td>54</td>
<td>37 wk</td>
<td>Nervous system disorders: 63/256 (24.6)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td><strong>Cross-over randomized controlled trial</strong></td>
<td>Corral et al.</td>
<td>Idiopathic Fracture disease</td>
<td>19</td>
<td>47 (7.7)</td>
<td>63</td>
<td>4 wk</td>
<td>Nervous system disorders: 19/37 (51.4)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Kilatan et al.</td>
<td>Multiple sclerosis</td>
<td>15</td>
<td>46</td>
<td>NR</td>
<td>4 wk</td>
<td>Nervous system disorders: 15/39 (38.5)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Naveh et al.</td>
<td>Healthy, cannabis-naive volunteers</td>
<td>12</td>
<td>Female: 25 Male: 27</td>
<td>56</td>
<td>8 h</td>
<td>Psychiatric disorders: 2/12 (16.6)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Mehlum et al.</td>
<td>Chemotherapy-induced nausea</td>
<td>73</td>
<td>43</td>
<td>58</td>
<td>2 d</td>
<td>Nervous system disorders: 61/79 (77.2)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Weng et al.</td>
<td>Pain associated with cause</td>
<td>10</td>
<td>51</td>
<td>28</td>
<td>3 d</td>
<td>Nervous system disorders: 10/32 (31.2)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Weng et al.</td>
<td>Pain associated with cause</td>
<td>36</td>
<td>51</td>
<td>28</td>
<td>1 d</td>
<td>Nervous system disorders: 36/160 (22.5)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Oh et al.</td>
<td>Chemotherapy-induced nausea</td>
<td>79</td>
<td>46 (22-71)</td>
<td>75</td>
<td>1 d</td>
<td>Psychiatric disorders: 49/79 (62)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Patel et al.</td>
<td>Multiple sclerosis</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>1 d</td>
<td>Psychiatric disorders: 3/9 (33.3)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Sampath et al.</td>
<td>Multiple sclerosis</td>
<td>54</td>
<td>50 (23)</td>
<td>42</td>
<td>3 wk</td>
<td>Nervous system disorders: 54/90 (60)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td></td>
<td>Vary et al.</td>
<td>Multiple sclerosis</td>
<td>57</td>
<td>54.4</td>
<td>45</td>
<td>2 wk</td>
<td>Psychiatric disorders: 21/45 (47)</td>
<td>0/5 (0)</td>
</tr>
</tbody>
</table>
Intermission

Cannabidiol – Recent Advances

Mechoulam, R., Peters, M., Murillo-Rodriguez, E., et al. – Department of Medicinal Chemistry and Natural Products, Hebrew University Medical Faculty, Jerusalem, Israel. Chemistry & Biodiversity. 2007, 4:1678-1692

Design: Systematic Review of available scientific literature (human studies, animal models, in vitro models)

Review recent publications on cannabidiol (CBD2), a major non-psychoactive constituent of cannabis. Evaluate possible therapeutic/pharmacologic possibilities of the use of CBD2 on the endocannabinoid system.

Findings: Selected Therapeutic Applications – Neuroprotective, Cerebral Ischemia, Type-1 Diabetes, Anti-Emetic Effects, Anxiety, Rheumatoid Arthritis, Cancer.
Cannabinoid Analgesia as a Potential New Therapeutic Option in The Treatment of Chronic Pain

Burns, T., Ineck, J. – Dept of Pharmacy Practice, Creighton University Medical Center, Omaha, NE.


Review the literature concerning physiology of the endocanniboid system, current drug development of cannabinoid agonists, and current clinical research on the use of cannabinoid agonists for analgesia.

Findings:
1) Cannabinoids provide a potential approach to pain management.
2) Chronic pain often requires polypharmacy.
3) Cannabinoids are a potential addition to the arsenal of tx options.
4) Unfavorable adverse effects seen in most cannabinoid agonists trials.

Table 2. Clinical Trials with Cannabinoid Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC 26</td>
<td>high dose THC 20 mg or placebo 120 mg pain reduction = placebo (p &lt; 0.05) low dose THC 10 mg or placebo 65 mg significantly better than placebo no statistically significant differences in pain reduction between odinose and THC THC 20 mg highly satisfying, associated with dose-limiting effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC 12</td>
<td>THC 20 mg not significantly better that placebo in any test THC morphine suf fx better than placebo in TENS and cold wets morphine suf fx better than placebo in pressure, cold, and TENS tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC 40</td>
<td>no differences in mean EPO and 6 h to rescue analgesia between THC 5 mg and placebo groups postoperative pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBE 24</td>
<td>pain relief associated with both THC 2.5-120 mg/day and OBE superior to placebo THC and THC:CBD better than placebo for spasm on ALS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBE 34</td>
<td>THC and THC:CBD better than placebo for 2 main symptoms all OBE improved quality of sleep</td>
<td>moderate THC daily dose during treatment 18-20 mg</td>
<td></td>
</tr>
<tr>
<td>OBE 48</td>
<td>mean pain severity and sleep measures significantly improved with OBE NNT of 3 to reduce pain by 1 point NNT of 4 for 25% pain reduction with THC:CBD:OBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC 21</td>
<td>CT 0-40 and 60 mg/day significantly reduced VAS and VRS ratings vs placebo 60 mg did not increase analgesia or adverse effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Adverse Effects Occurring More Frequently with Cannabinoids than with Placebo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
<th>Frequency C vs Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>ataxia</td>
<td>29 and 44 vs 9</td>
</tr>
<tr>
<td></td>
<td>blurred vision</td>
<td>41 and 65 vs 9</td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
<td>59 and 97 vs 26</td>
</tr>
<tr>
<td></td>
<td>dry mouth</td>
<td>74 and 76 vs 36</td>
</tr>
<tr>
<td></td>
<td>increased appetite</td>
<td>26 and 21 vs 9</td>
</tr>
<tr>
<td></td>
<td>mental clouding</td>
<td>32 and 53 vs 18</td>
</tr>
<tr>
<td></td>
<td>sedation</td>
<td>71 and 94 vs 29</td>
</tr>
<tr>
<td>THC</td>
<td>anxiety</td>
<td>33 vs 0</td>
</tr>
<tr>
<td></td>
<td>euphoria</td>
<td>75 vs 6</td>
</tr>
<tr>
<td></td>
<td>hallucinations</td>
<td>50 vs 6</td>
</tr>
<tr>
<td></td>
<td>vertigo</td>
<td>93 vs 25</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>cough</td>
<td>5 vs 0</td>
</tr>
<tr>
<td></td>
<td>impaired balance</td>
<td>9 vs 0</td>
</tr>
<tr>
<td></td>
<td>sleepiness</td>
<td>10 vs 6</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>drowsiness</td>
<td>68 vs 33</td>
</tr>
<tr>
<td></td>
<td>dry mouth</td>
<td>63 vs 46</td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
<td>50 vs 6</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>dizziness</td>
<td>19 vs 6</td>
</tr>
<tr>
<td></td>
<td>dryness</td>
<td>21 vs 2</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>feeling drunk</td>
<td>6 vs 0</td>
</tr>
<tr>
<td></td>
<td>somnolence</td>
<td>19 vs 10</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>dizziness</td>
<td>NR</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>dry mouth</td>
<td>NR</td>
</tr>
<tr>
<td>THC:CBD CME</td>
<td>increased pain</td>
<td>NR</td>
</tr>
</tbody>
</table>
Cannabidiol in Medicine: A Review of its Therapeutic Potential in CNS Disorders

Scuderi, C., De Filippis, D., Iuvone, T., et al. - Department of Physiology and Pharmacology 'V. Erspamer', Sapienza University of Rome, Italy.

Design: Systematic Review of the available literature (Keywords: cannabidiol; Cannabis sativa; CNS disorder; phytocannabinoid).

The present review reports the pharmacological profile of CBD and summarizes results from preclinical and clinical studies utilizing CBD, alone or in combination with other phytocannabinoids, for the treatment of a number of CNS disorders.

Findings:
1) Cannabidiol exhibits an impressive plethora of actions, including anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties.
2) CBD is a compound well tolerated in humans, with a profile of very low toxicity, and devoid of psychoactive and cognitive effects.
3) Majority of studies have been carried out in the most part in animal or then cellular models. More clinical trials able to validate its beneficial properties in humans are warranted.

Do cannabis-based medicinal extracts have general or specific effects on symptoms of multiple sclerosis?

Multiple Sclerosis. 2004, 10, 434-441.

Nabiximols (THC 2.5mg/cannabidiol 120mg) v/s Placebo

Findings:
Participant reports indicated improvement in primary symptom scores
- Spasticity (P < 0.001)
- Spasms (P= 0.932)
- Sleep quality (P < 0.047)
- Pain (P > 0.241)
- Insomnia (P=0.816)
**Long-term efficacy and safety of dronabinol (Marinol) for AIDS-associated anorexia**

Beal, J.E., et. Al. – St John’s Hospital, Tulsa, Oklahoma

**Design:** multicenter, open-label, follow-up study involving 15 centers in the United States and Puerto Rico, conducted from July 1991 until January 1993. N=94.

All patients received dronabinol orally--2.5 mg twice daily (90%) or 2.5 mg once daily (10%). Appetite was measured using a visual analogue scale for hunger (VASH).

**Findings:**
Appetite – Mean appetite scores were greater than baseline for all study months.

Weight – Weight was maintained or slightly increased in pt’s previously tx with dronabinol (only reached P= 0.015 of significance during the first month). Weight was maintained or loss in pt’s previously tx with placebo.

Safety – 44% developed at least 1 tx related adverse effect, 2% developed sx considered severe, no evidence of drug:drug interactions were observed.

---

**Comparison of orally administered cannabis extract, THC & placebo on appetite and quality of life in patients with cancer-related anorexia**

Strasser, F, et. al. – Division of Oncology/Hematology, Department of Internal Medicine, Cantonal Hospital, St Gallen, Switz.

**Design:** Multicenter, phase III, randomized, double-blind, placebo-controlled. N=243.

Randomized to 1 or 3 groups:
THC 2.5mg & cannabidiol 1 mg THC 2.5mg placebo – bid for 6 weeks
VAS daily (appetite, mood, nausea), QOL, cannabinoid-related toxicity q2wks.

**Findings:**
No statistically differences were found between the study participants in relation to appetite, QOL, cannabinoid-related toxicity.

Cannabinoids were well tolerated at study dosing.

Future studies with higher dosing of cannabinoids.

---

**Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systemic review**


**Design:** Systematic Review (Medline, Embase, Cochrane library through 8/2000).

30 randomized comparisons of cannabis vs/plus or other antiemetic (oral nabilone, oral dronabinal, & IM levonantradol).

**Findings:**
Cannabinoids were more effective than antiemetics tested
Cannabinoids were not more effective in very low/very high emetogenic chemotherapy.
Where To Now??

Final Thoughts

- Endocannabinoid system vital regulation many body systems.
- Effects of exogenous cannabinoids.
- Cannabidiol vs THC safety, efficacy, addiction.
- Stigma, legality.
- Education/counseling.
- Drug to drug interactions.
- Keep abreast of the literature.
Selected References


Selected References


Selected References


References


Selected References


References & Resources

References & Resources