Medical Marijuana and Cannabinoids Usefulness? For Elderly?

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Objectives

- 1. Recall the history of therapeutic cannabis use.
- 2. Outline the function of the endocannabinoid system.
- 3. Analyze the pharmacology of exogenous cannabinoids in clinical or experimental use.
- 4. Discuss potential side effects and areas of safety concern when medicinal cannabis and other cannabinoids are used.
- 5. Describe the potential therapeutic benefit and appropriate indications for the medical use of marijuana and other cannabinoids.
- 6. Identify primary indications, side effects, chronic effects, and contraindications to therapeutic cannabinoid use.
- 7. Discuss pros and cons of medical marijuana
- *** Remember botanical cannabis versus pharmaceutical (dronabinol) are NOT medicinally equivalent

THE COMPLETE GUIDE TO MEDICAL MARIJUANA FOR SENIORS (Aging.com)

- CANCER - primarily nausea / vomiting BUT Studies are ongoing in both animals and humans to see how medical marijuana can help treat tumors as well as the symptoms and illness that come with cancer
- ALZHEIMERS DISEASE - Journal of Alzheimer's Disease that analyzed the "potential therapeutic effects of THC" on the disease."
- Effect of THC on beta-amyloids / proteins in brain AD
- Helped slow the advancement of these beta-amyloids, and the results from the study "strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease."

THE COMPLETE GUIDE TO MEDICAL MARIJUANA FOR SENIORS (Aging.com)

- GENERALIZED PAIN - CHRONIC PAIN

  National Institute for Drug Abuse show that the presence of legal marijuana laws and marijuana dispensaries show a link between:
- Fewer deaths caused by prescription opioids
- Less treatment for opioid addiction
- General prescribing of opioids
- A reduced number of people self-reporting opioid misuse

- PSYCHIATRIC DISORDERS (CBD component) – including - Obsessive compulsive disorder (OCD) Post-traumatic stress disorder (PTSD), Panic attacks, Moderate depression, General anxiety, eating disorders
- GLAUCOMA

Medicinal marijuana in elderly (all age groups)

- Because of the lack of research and funding, reputable literature on the impact of marijuana on older adults is scarce.
- (Consult Pharm Jun 1 2017)

Short history

- 36 million years ago -Cannabis sativa in Central Asia
- 2737 BC – Shen Nung used cannabis for malaria, constipation, surgical anesthetic
- 1000 BC – Hindu religion
- Middle east, Africa, Arabian peninsula – used by Arabic physicians
- 1839 - England used for analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant
- 1900 – over 100 scientific articles on efficacy

Short history continued

- Early 1900s research on therapeutic use, limitations including poor water solubility, delayed onset if oral, potency and individualizing dose.
- Early 20th century – US drug companies (Merck, Bristol Meyers etc) marketed extracts of cannabis.
- 1900-1930 – less prescribed – hard standardize preparations, not isolated active component and new effective meds (ie: opioids) came out.
- 1924 – prominent US journals listed indications for use including:

  sedative/ hypnotic, analgesic, appetite/digestion
- 1937 – Marihuana Tax Act
- 1942- removed from US pharmacia
- Prohibition- sanctioned medical and recreational use – AMA fought against

Short history continues

- 1964 isolated chemical THC
- 1970 Controlled Substance Act – classified as C 1
- 1980's – AIDS epidemic – refractory nausea and wasting syndrome use
- 1993 – US surgeon general Jocelyn Elders book entitled
- "Marihuana: The Forbidden Medicine" – advocating legalizing.
- 1996 - legalized medical use in California
- 2000 – RCTs for indications and contraindications
- 2017 – 28 states and District of Columbia
- - 8 include legal recreational use

Results of RCT studies – general indications for medical marijuana use

NOT a first line treatment – "when standard therapies have been ineffective or intolerable"

Adults over 18 yo

Strong support in literature for use:

- Disorders of pain / spasticity = spinal cord injury, MS
- Chronic neuropathic pain = phantom limb pain, facial neuralgia, postherpetic neuralgia, HIV related
- Pain related to cancer and HIV disease
- Nausea/ vomiting related to chemo/xrt, hiv and hep c
- Neuropsychiatric disorders – PTSD
- Autoimmune disorders – crohns, lupus, RA
- Appetite stimulant – wasting syndrome
- Treatment resistant glaucoma

Results of RCT studies – general indications for medical marijuana use

- Strong support in literature for use:
- **Analgesic enhancement in long term opioid analgesic use and potential opioid dose reduction**

Results of RCT studies – general indications for medical marijuana use

- POSSIBLE efficacy – fibromyalgia, IBS, seizures

- CONTRAINDICATION –
- less than 18 yo
  - Personal / family hx of psychosis
  - Pregnant / breast feeding

PHARMACOKINETIC PROPERTIES OF INHALED VS. DIGESTED CANNABINOIDS

	INHALED	ORALLY DIGESTED
PEAK BLOOD LEVELS (MIN)	3 -10	60 - 120
BIOAVAILABILITY (%)	10 -40	< 15
TIME TO PEAK PSYCHOACTIVE ACTIVITY (MIN)	20	120 - 240
MAXIMUM DURATION (MIN)	DOSE DEPENDENT	240 -360

Mechanism of action

- ECS = endogenous cannabinoid system
- Regulates neural transmissions / excitatory and inhibitory and inflammation
- Cannabinoid receptors
- CB1 = cns – psychotropic and behaviorial
- CB2 = immune cells ……..others

Effect of activating CB receptors

- "stress" – increased calcium release ---→ releases 2 –AG ---→ binds and activates CB receptors ---→ increases CB receptor expression --→
- "protective role" to decrease certain symptoms (Normal individual)
- CB1 receptors in CNS – inhibit release of serotonin, glutamate, acetylcholine, GABA, noradrenaline, dopamine, etc.
- CB2 receptors on immune cells in gut – inhibit cytokine production and block neutrophil and macrophage migration AND on dorsal root ganglion and spinal cord
- ***** CBD RECEPTORS LACK PSYCHOACTIVE EFFECT OF THC
- (COMPONENT CAN HELP MAXIMIZE ANALGESIA AND MINIMIZE HIGHS)

Pain and ECS

- **** Different mechanisms to psychoactive and analgesic effect
- THC – synergistic with kappa opioid receptor agonist
- Interact with opioid, serotonin, and NMDA receptors
- Interacts with COX-2 inhibitors – synergistic inhibit PG and increase endocannabinoid activity -→ used together increased analgesic effect

THC component of cannabinoids

- Many formulations –THC and CBD
- THC – greatest psychoactive and analgesic effect
- Analgesia – 4 mechanisms
- 1) inhibits 5 HT release from platelet and increases cerebral production
- of 5HT ----→ treat migraine headaches
- 2) dopaminergic inhibition
- 3) effects glutamatergic system and reduces NMDA response
- 4) stimulates beta-endorphin production ---→ opioid sparing effect
- 5) inhibits PGE2 synthesis (produces 20 times anti-inflammatory potency
- of aspirin and twice the potency of HCT)

Pharmacokinetics

- Metabolism – cytochrome P450
- Elimination – 20-35 % urine and rest GI
- Side effects – use generally well tolerated with other drugs
- dose response relationship and duration of use
- Serious adverse effects – respiratory, GI, and cns
- (RCT THC vs placebo and no SS difference incidence of side effects
- Nonserious side effects – dizziness, dry mouth, blurry vision, sedation, altered mood, low bp, confusion
- Increased side effects – younger, concurrent etoh other drug use, neuropsychiatric illnesses

Safety concern

- Contaminants related to plant
- Fungus, bacteria, heavy metals, organophosphate pesticides
- Immunosuppressed

Toxicity / Overdose

- "virtually impossible to induce fatal toxicity" with THC
- Rare acute complications
- - greatest risk in children
- - neuropsychiatric, cns even respiratory depression or coma

- Adults - mild

Medical treatment of side effects

Palpitations / tachycardia - propranolol

Arrhythmia – afib – flecainide, propafenone, digoxin

Acute psychotic state – olanzapine, haloperidol

Acute panic / anxiety / manic – benzodiazepines, antipsychotics

ARGUMENTS AGAINST

- **ADDICTION**
- - not an issue for palliative care
- - compare to opioid and benzodiazepines, alcohol, tobacco that are legal???
- "KIN" of legal drugs – Heroin similar to morphine
  - Ecstasy similar to drugs used for ADHD
  - PCP similar to ketamine

ARGUMENTS AGAINST

- **CARCINOGENIC**
- Head and neck cancer – squamous cell

  - no direct evidence THC or other cannabinoids cause cancer

BUT "smoke" –

1) Contains some of same carcinogens as tobacco – often up to 50% more.
2) Three times tar.
3) Causes precancerous changes to bronchial cells with chronic use.

ARGUMENTS AGAINST

- **CARCINOGENIC**
- Head and neck cancer – squamous cell

- BUT no in vitro or in vivo evidence increased risk of cancer with cannabinoids
- 3 studies – increased risk with use – up to 2.6 fold increase
- *****Nasopharyngeal cancer / related to HPV – increased risk likely due to immunosuppression related to CBD component.

ARGUMENTS AGAINST

- **CARCINOGENIC**
- Head and neck cancer
- Several studies with no association with HNSCC cancer
- (one from NZ)

- **INHANCE Consortium** -
- 4000 patients with HNSCC cancer and 5000 controls
- Controlled for ETOH and tobacco use
- NO link between marijuana use and cancer

ARGUMENTS AGAINST

- **CARCINOGENIC**

- **BOSTON** study over 400 HNSCC cancer patients
- ****** 10 – 20 years of use associated with decreased risk of cancer

ARGUMENTS AGAINST

- **CARCINOGENIC**
- **LUNG CANCER**
- 19 studies from 1996 – 2006 --- NO significant association with
- marijuana use and lung cancer (despite changes to bronchial
- mucosa.)

- **INHANCE** Consortium – 1200 lung cancer patients –
- no correlation with use and cancer risk

ARGUMENTS AGAINST

- **CARCINOGENIC**
- **LUNG CANCER**
- **BUT** NZ study found age 55 or less an increased risk of lung cancer by 8% versus nonsmokers of marijuana / increased yearly.
- **OTHER CANCERS**
- No increased risk for colorectal, melanoma, or breast cancer.
- Trend for increased risk of prostate and cervical (HPV) cancers
- U.S. study increased risk of malignant gliomas.

??? Marijuana – carcinogenic???

- **CONFOUNDING EVIDENCE**
- truly documenting use
- dose / composition are not controlled / not controlled drug
- not clear “true receptors” on tumour cells that are effected.

ARGUMENTS FOR

- Early 1970s – adenocarcinoma of lung –
  found cannabinoids inhibited tumour growth in vitro and in vivo
  in GBM, breast, prostate, thyroid, colon, skin, pancreatic,
  leukemia and lymphomas

Colon cancer – cannabinoids caused TNF and ceramide apoptosis in vitro and in vivo.

ARGUMENTS FOR

- ANTICANCER
- "Suppression" of tumour growth via anti-angiogenesis, stimulating apoptosis and autophagy.
- CB1 greater affect than CB2 – inhibiting cell growth

  - prostate cancer

  - HER 2 receptor positive breast cancer- decreased tumour growth and lung metastases

ARGUMENTS FOR (ONLY FOR CERTAIN CANCERS?)

CANNABINOID RECEPTORS – matter!!

1) AMOUNT OF RECEPTORS

- **Breast cancer** – with "low" receptors – cannabinoids INCREASE tumour growth!
- **Bladder cancer** – responds to cannabinoids / decrease tumour
- growth REGARDLESS of receptors.

2) AFFECT / RESPONSE OF RECEPTORS

- **Hepatocellular carcinoma** – increased expression of CB1 and 2 receptors = BETTER prognosis.
- **Gliomas** - increased expression of CB2 = WORSE prognosis.

ARGUMENTS FOR

- ONE clinical trial – refractory GBM
- 9 patients with debulking surgery then infused THC DIRECTLY into brain –
- 10-64 days – one patient has psychotropic effect and stopped.
- Rest – **THC decreased tumour growth both by MRI and labs.**

Debunk specific contraindications

- **Pulmonary** – JAMA – 20 yr longitudinal study cannabis only smokers – no change in PFT
- VS. Tobacco concomitant use
- Vaporized use creates less byproducts – CO, hydrocarbons.

- **Immunosuppression** - HIV patients no effect on viral load with use of smoked cannabis or dronabinol BUT
- Cannabinoid groups – increased T cell counts and weight gain
- NB - increased CB2 activity may inc risk of legionella

Debunk specific contraindications

- **Neurocognitive impairment** - acute effects based on amount, ratio of THC to CBD, genetic susceptibility
- Longterm effects – heavy chronic adolescent use / developing brains
- ? Amotivational syndrome

- **Schizophrenia and psychoses** -
- Acute anaphylactic reaction – young, risk of psych

Debunk specific contraindications

- **Gateway drug** - no evidence of causality of marijuana use with progression to "hard" drugs – vs. etoh and nicotine cited
- **Cannabis addiction** – estimated **9%** of recreational users – vs. **32%** nicotine,**23%** heroin, **17%** cocaine, and **15%** etoh users

Debunk specific contraindications

- **Cannabis withdrawal syndrome** - chronic heavy use – resembles opioid withdrawal - irritability, restless, dysphoria – no diarrhea, sweats , piloerection.
- 2- 6 days up to 2 weeks
- **Cannabinoid Hyperemesis syndrome** – cyclical nausea / vomit with heavy use – rare - ? Due to decreased motility- resolves with stopping

Specific treatment efficacy Neuropathic

- Placebo double blind RCT
- Journal of Pain 2008 – 38 pts -CRPS, spinal cord injury, MS, diabetic neuropathy – "dose ceiling" and comparable to opioids / alleviate sensory and affective pain not result of tranquilizing/ relaxing effect.
- Neuropsychopharmacology 2009 – HIV polyneuropathy – used 7 weeks – greater than 30% reduction in pain for 46% on cannabis vs. 18% on placebo -mild side effects of sedation and concentration problems
- Dose ceiling / therapeutic window – optimal dose "medium" range and indication that biphasic dose-response - ? Higher doses enhance pain

Specific treatment efficacy Nausea

- 2007 and 2011 studies – chemo induced n/v – dronabinol comparable to 5HT3 drug ondansetron and better than placebo.
- BMJ 2001 -Vaporized vs dronabinol – 748 chemo pts – reduced n/v 70-100 % in smoked vs 76 -88% oral - ease to administer and titrate, more rapid relief, other therapeutic effects.

Specific treatment efficacy PTSD

- Refractory to other treatments
- Nabilone – oral 1-2 mg bd (FDA approved for refractory chemo n/v)
- 2009 study 47 patients – stopped or reduced nightmares, decreased flashbacks, night sweats, and improved sleep in near 72%.

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review.JAMA. 2015; 313(24):2474-83 (ISSN: 1538-3598)

- Use of marijuana for chronic pain, neuropathic pain, and spasticity due to **multiple sclerosis** is supported by high-quality evidence.
- Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis.
- Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

Specific treatment efficacy Seizures

- CBD rather than THC concentrations
- Children refractory seizures
- 2013 – 19 pts – refractory average of 12 drugs – 84% reduced seizures and 11% seizure free – per parent observation more alert, better sleep and mood – mild side effect of drowsiness / fatigue.
- **** no longterm safety evidence

Dose/ administration

- **PILLS**:
- Start low – go slow
- Refractory pain – 2.5 grams day
- Other indications – nausea, anorexia – no more than 5 grams day
- Netherlands and Israeli studies – average dose was 0.68 to 1.5 grams per day
- Nausea – dronabinol – start 2.5 mgs bedtime up to 20 mgs

  - nabilone – 1-2 mgs bd up to 6 mgs

Dose / administration

- **VAPORIZED**
- Vaporized – rapid relief, used 2-3 times same cannabis – recommended 1-2 times day with 5-15 min in between – takes up to 2 weeks for steady state / therapeutic effect.
- NABIXIMOL – vaporized form –

- **TEA**

limited water solubility / bioavailability -0.5 gms in boiled pint for 15 minutes

- better "tall white" tea – fat in milk helps absorption.

Contraindications / Precautions

- Current, past or family history of schizophrenia or other psychoses
- Hypersensitivity to cannabinoids or smoke
- Severe cardiopulmonary disease
- Severe liver or renal disease
- Pregnancy
- Breastfeeding

Cautions

- Smoked cannabis in copd / asthma
- History of substance abuse
- Nonpsychotic psychiatric diseases – anxiety, panic attacks
- Current CNS depressant therapy

Patient Education

- Monitor for possible side effects – memory, mental, behavioral changes

- Limit / abstain from etoh
- No vehicle/ heavy machinery
- CYP 450 interactions
- Stop vaporizing – dizzy, ataxia, agitation, anxiety, tachycardia, psychosis hallucinations/ disorientation, orthostatic hypotension
- Close followup ? Potential opioid / adjunct reduction.

Cannabis … to be continued

- Circumstantial now more evidence based indications / risk- benefit, proper dosing and side effect profile to cannabis
- THC most potent therapeutic component with most side effects
- CBD some therapeutic use ? Seizures in kids
- Understanding use outside nausea and anorexia/ wasting syndrome
  - Pain refractory, chronic, neuropathic and inflammatory as adjunct to opioids and other meds
  - Use neuropsych disorders – MS, PTSD
  - More research , more regulation of formulations

QUESTIONS

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