11th Canadian Conference on Dementia
Toronto, Ontario | November 2-4, 2023
Sheraton Centre Toronto Hotel

Update on cannabis as a novel therapeutic for agitation in Alzheimer's disease: rationale, research and results

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HURVITZ BRAIN SCIENCES PROGRAM

Faculty/Presenter Disclosure

- **Faculty:** Krista L. Lanctôt, PhD
- **Relationships with commercial interests:**
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Mitigating Potential Bias

- Research presented funded by peer-reviewed grants
- No funding from makers of nabilone or proprietary CBD oil (Avidekel)

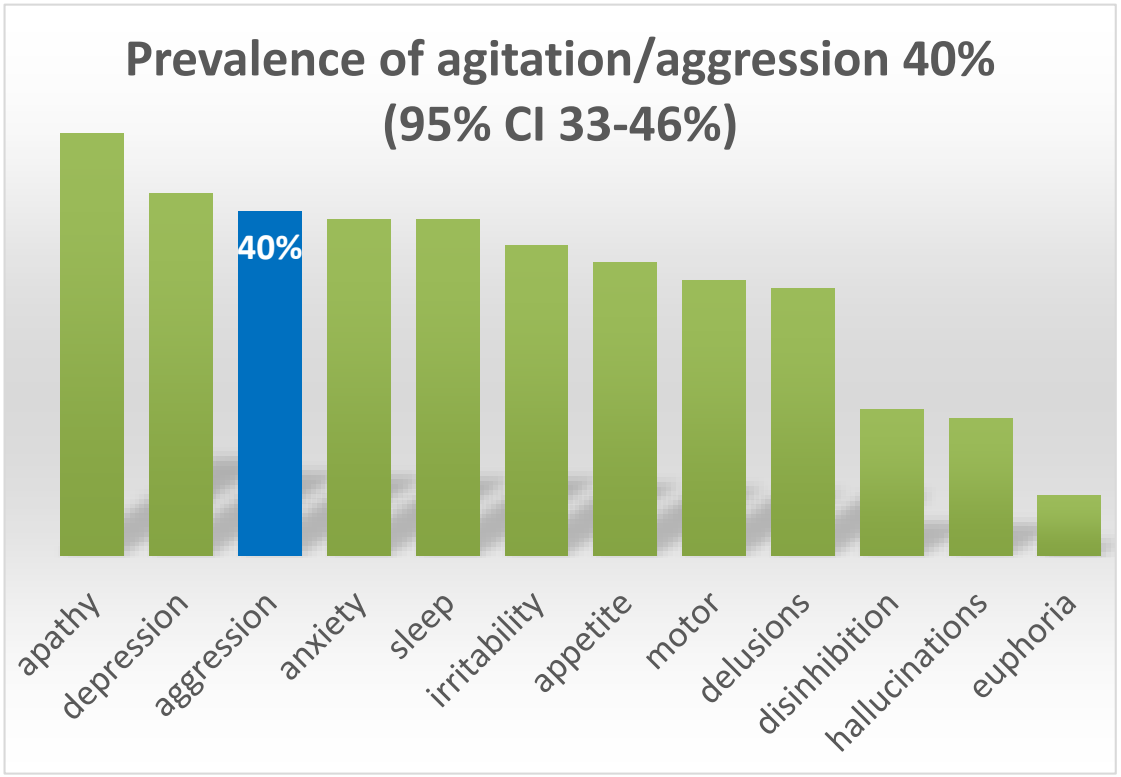
Learning Objectives

At the end of the session participants will be able to:

- Describe the rationale for use of cannabinoids for agitation in Alzheimer's disease
- Discuss the evidence to date in this area
- Determine the current place of cannabinoids in clinical management of agitation

Agitation in Alzheimer's Disease

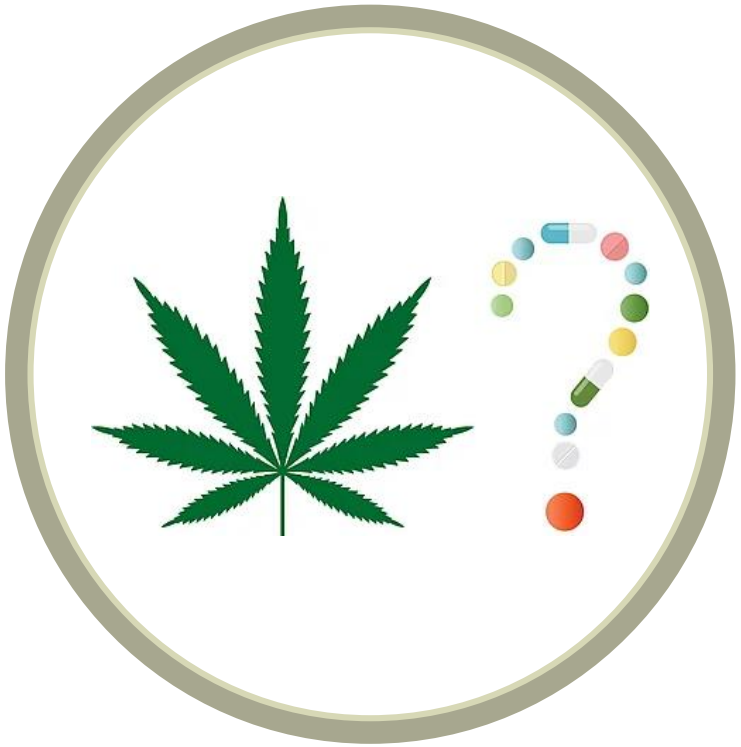
- Meta-analysis of 48 studies in AD



Zhao et al., 2016

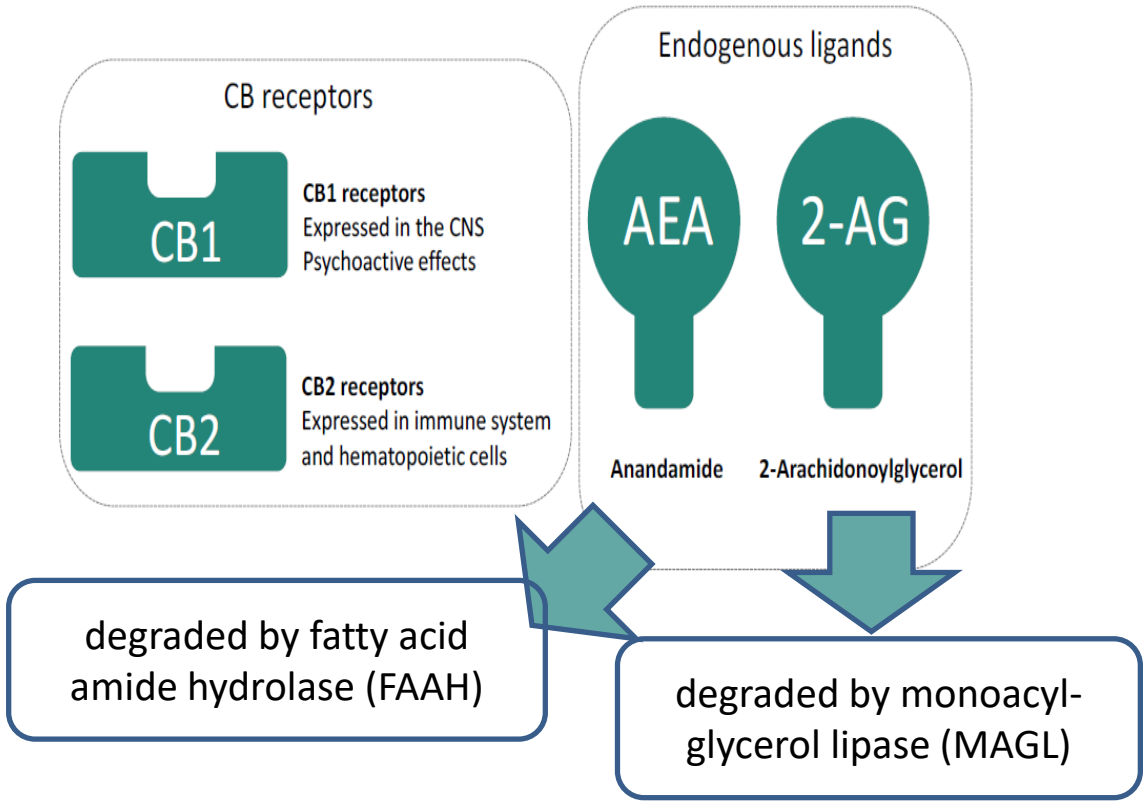
- Common
  - 5-year prevalence estimate of 42% (Cache County Study) [Steinberg et al 2008]
  - Nursing home up to 71% [Hendriks et al 2015]
- Caregiver Impact
  - caregiver burden [Rabins et al 1982, Nygaard 1988, Keene 1999], institutionalization [Steele et al 1990, Cohen 1993, Okura 2011], principal management problem in nursing homes [Cohen-Mansfield 1986]
- Patient Impact
  - physical restraints [Evans 1988], health problems (falls & weight loss) [Merriam et al 1988, Marx 1990], functional decline [Lopez et al 1999], risk of death [Walsh et al 1990, Allen et al 2005]
- Current treatments have efficacy and/or safety concerns

RATIONALE



Endocannabinoid system (ECS)

- 2 endocannabinoids: anandamide (AEA) and 2-arachidonoyl glycerol (2-AG)
- 2 receptors: CB1 (CNS) and CB2 (immune)



- Cerebral cortex
  - Altered consciousness, perceptual distortions, memory impairment, delusions & hallucinations
- Hypothalamus
  - ⇑ appetite
- Brain stem
  - Antinausea, ⇑ HR, ⇓ BP, drowsiness, ⇓ pain
- Hippocampus
  - Memory impairment
- Cerebellum
  - ⇓ spasticity, impaired coordination
- Amygdala
  - Anxiety +/-, ⇓ hostility

Cannabis

- 2 major neuroactive components in cannabis
  - psychoactive Δ9-tetrahydro-cannabinol (THC)
  - non-psychoactive cannabidiol (CBD)
    - non-psychoactive indicates lack of psychotropic effects that produce a ‘high’
- THC activates the endocannabinoid system
- CBD enhances endocannabinoid signaling

Devinsky et al 2014

CBD and THC

- CBD may potentiate some of THC's beneficial effects
  - reduces THC's psychoactivity to enhance its tolerability and widen its therapeutic window
  - counteract some functional consequences of CB1 activation in the brain
  - preparations with high CBD:THC ratios are less associated with psychotic symptoms

Devinsky et al 2014

CBD and THC: recent evidence

- N=46 healthy, infrequent cannabis users in double-blind, within-subject, randomized trial of 10 mg THC with varying in CBD content
- CBD:THC ratios most common in medicinal cannabis products
  - 0 mg (0:1 CBD: 10 mg THC)
  - 10 mg (1:1),
  - 20 mg (2:1)
  - 30 mg (3:1)
- associated with impaired delayed verbal recall and positive psychotic symptoms (PANSS)
  - effects not significantly modulated by any dose of CBD
- no evidence that CBD protects against the acute adverse effects of cannabis

Englund et al 2023

Variability in medical cannabis

- Plant variability
  - Commercial cultivars contain various amounts of THC/CBD
  - Effects of “minor” cannabinoids and terpenes
  - Influence of harvesting variations
- Processing variations
- Difficult to know contents

- 75 samples of edible medical cannabis analyzed with HPLC and results compared with label
- Only 17% accurately labeled
  - 60% over-labeled wrt THC content
  - 23% under-labeled wrt THC content
  - 0nly 59% had detectable levels of CBD and only 13 products had CBD content labeled

Vandrey et al, JAMA 2015

Available cannabinoids

Cannabinoid	MOA	Indication
dronabinol (Marinol®)	• synthetic THC • CB1/CB2 agonist	Antiemetic Appetite and weight loss (AIDS)
nabilone (Cesamet®)	• THC derivative • CB1/CB2 partial agonist	Antiemetic
nabiximols THC and cannabidiol (Sativex®)	• Cannabis extract • CB1/CB2 agonist + CB1 antagonist	Neuropathic pain in multiple sclerosis
THC (Namisol®)	• pure natural THC (>98%)	n/a
Purified cannabidiol (Epidiolex®)	• CB modulator	Anticonvulsant

Possible benefits of CB1 and CB2 activation

CNS Drugs (2015) 29:615–623
DOI 10.1007/s40263-015-0270-y

LEADING ARTICLE

Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease

Celina S. Liu[1,2] · Sarah A. Chau[1,2] · Myuri Ruthirakuhan[2] · Krista L. Lanctôt[1,2,3] · Nathan Herrmann[2,3]

CURRENT OPINION

Cannabinoids for the treatment of neuropsychiatric symptoms, pain and weight loss in dementia

Chelsea Sherman[a,b], Myuri Ruthirakuhan[a,b], Danielle Vieira[b], Krista L. Lanctôt[a,b,c], and Nathan Herrmann[b,c]

Can we <u>safely</u> treat agitation with cannabinoid agonists?

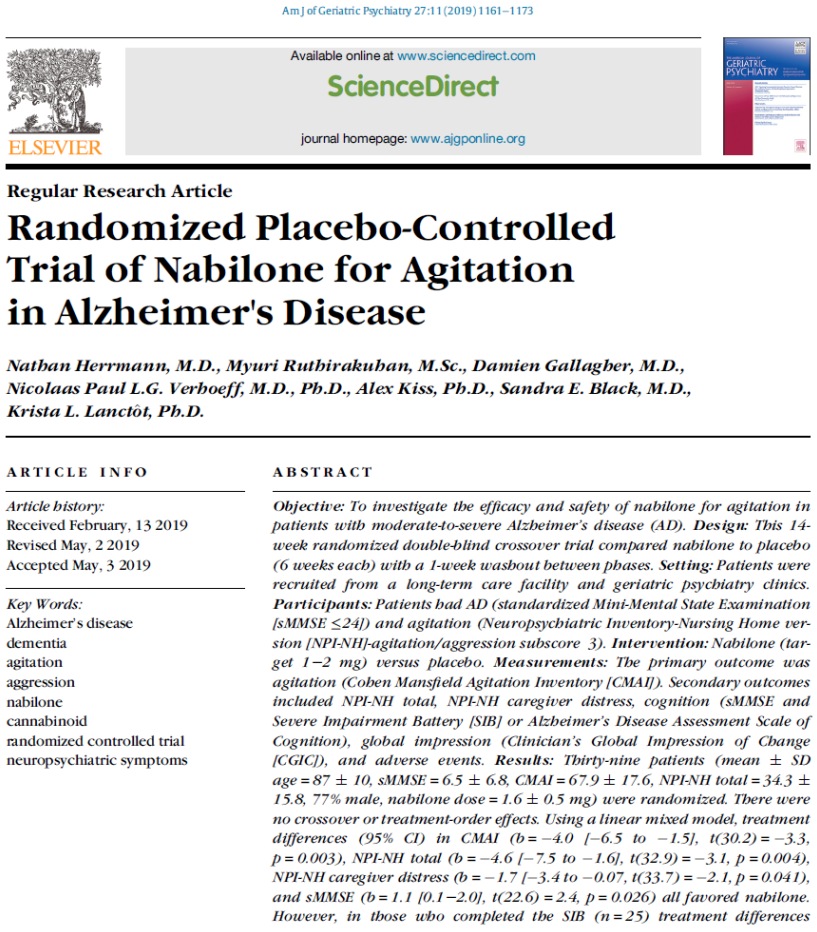
- Possible benefits of CB1 and CB2 activation Clinically
  - Mild sedation, anti-anxiety, increase appetite, decrease pain
- Endocannabinoid signaling modulates numerous pathological processes [Aso & Ferrer 2014]
  - neuroinflammation
  - excitotoxicity
  - mitochondrial dysfunction
  - oxidative stress
  - Loss of endogenous cannabinoids in AD leads to loss of protection from excitotoxicity
- CB1/CB2 agonists
  - prevented microglial activation, improved memory performance in rat models of AD [Marchalant 2008] and normal aging

Reviewed by Liu et al, 2016, Sherman et al 2018

Cannabinoids for agitation in Alzheimer’s disease

EVIDENCE TO DATE

Nabilone for the treatment of agitation in ADD



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Regular Research Article

Randomized Placebo-Controlled Trial of Nabilone for Agitation in Alzheimer's Disease

Nathan Herrmann, M.D., Myuri Rutbirakuban, M.Sc., Damien Gallagher, M.D., Nicolaas Paul L.G. Verhoeff, M.D., Ph.D., Alex Kiss, Ph.D., Sandra E. Black, M.D., Krista L. Lanctôt, Ph.D.

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ABSTRACT

Objective: *To investigate the efficacy and safety of nabilone for agitation in patients with moderate-to-severe Alzheimer's disease (AD).* ***Design:*** *This 14-week randomized double-blind crossover trial compared nabilone to placebo (6 weeks each) with a 1-week washout between phases.* ***Setting:*** *Patients were recruited from a long-term care facility and geriatric psychiatry clinics.* ***Participants:*** *Patients had AD (standardized Mini-Mental State Examination [sMMSE ≤24]) and agitation (Neuropsychiatric Inventory-Nursing Home version [NPI-NH]-agitation/aggression subscore ≥3).* ***Intervention:*** *Nabilone (target 1–2 mg) versus placebo.* ***Measurements:*** *The primary outcome was agitation (Cohen Mansfield Agitation Inventory [CMAI]). Secondary outcomes included NPI-NH total, NPI-NH caregiver distress, cognition (sMMSE and Severe Impairment Battery [SIB] or Alzheimer's Disease Assessment Scale of Cognition), global impression (Clinician's Global Impression of Change [CGIC]), and adverse events.* ***Results:*** *Thirty-nine patients (mean ± SD age = 87 ± 10, sMMSE = 6.5 ± 6.8, CMAI = 67.9 ± 17.6, NPI-NH total = 34.3 ± 15.8, 77% male, nabilone dose = 1.6 ± 0.5 mg) were randomized. There were no crossover or treatment-order effects. Using a linear mixed model, treatment differences (95% CI) in CMAI (b = −4.0 [−6.5 to −1.5], t(30.2) = −3.3, p = 0.003), NPI-NH total (b = −4.6 [−7.5 to −1.6], t(32.9) = −3.1, p = 0.004), NPI-NH caregiver distress (b = −1.7 [−3.4 to −0.07, t(33.7) = −2.1, p = 0.041), and sMMSE (b = 1.1 [0.1–2.0], t(22.6) = 2.4, p = 0.026) all favored nabilone. However, in those who completed the SIB (n = 25) treatment differences*

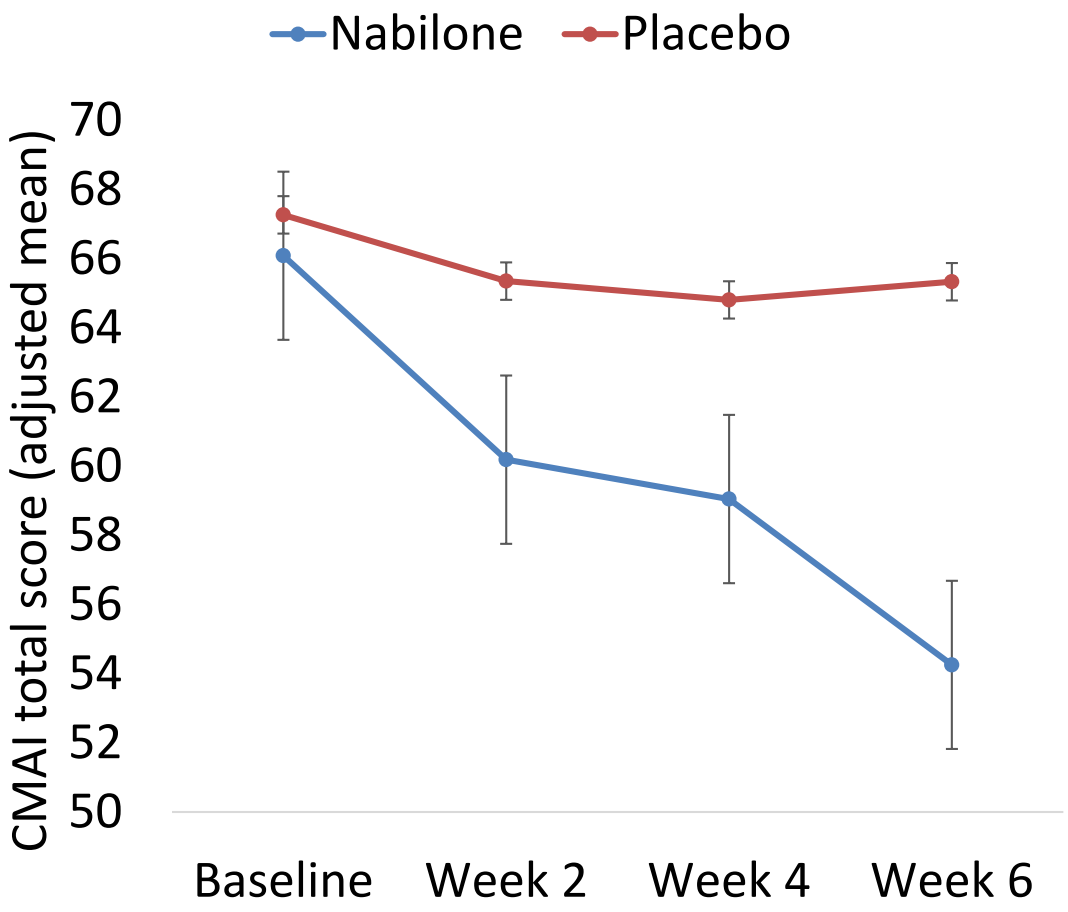
- Nabilone--synthetic derivative of THC
  - CB1/CB2 partial agonist
  - marketed in Canada for nausea and vomiting associated with cancer chemotherapy
  - high oral bioavailability
  - duration of action 8-12 hours
- Double blind, placebo-controlled, cross-over trial in 38 patients with agitation and ADD
- Efficacy and safety of nabilone (1-2 mg/d) versus placebo (6 weeks each)

Société Alzheimer Society CANADA

Alzheimer's Drug Discovery Foundation

Herrmann et al 2019

Agitation improved significantly during nabilone compared to the placebo phase

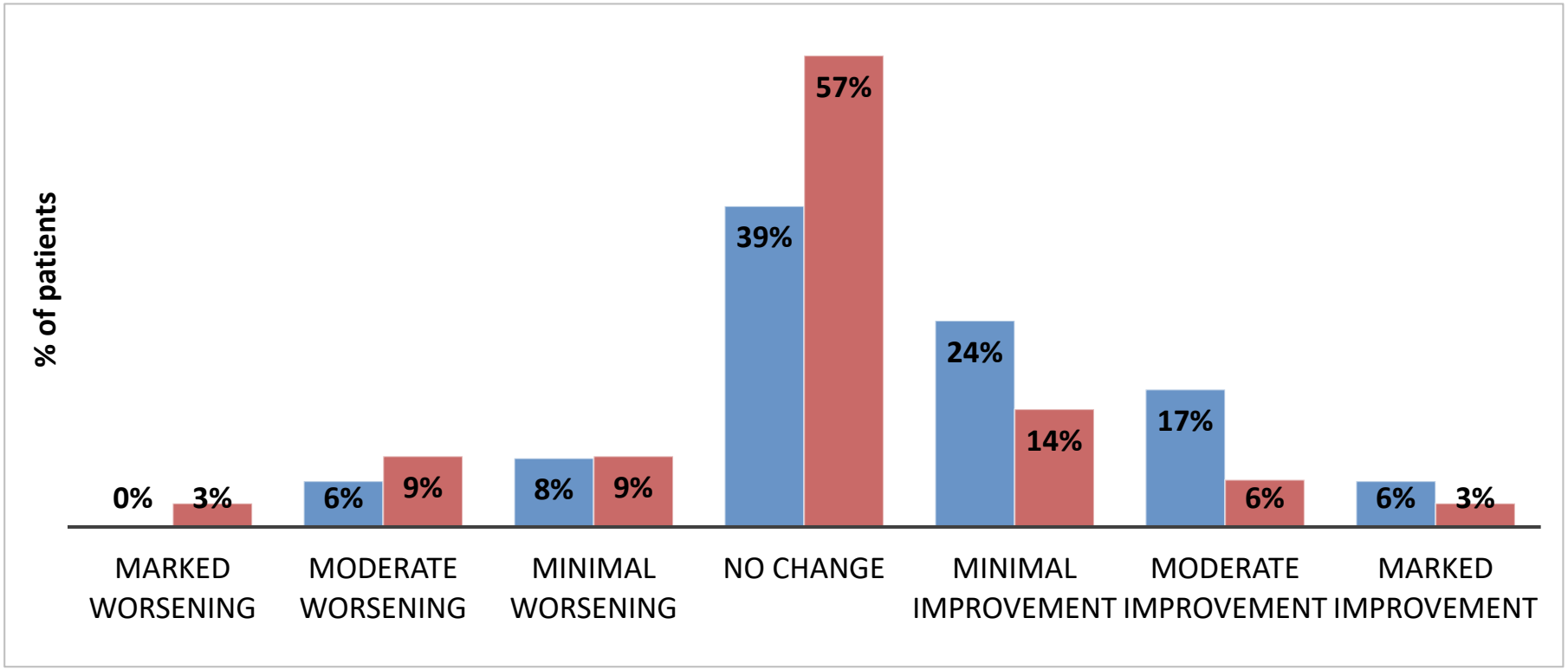


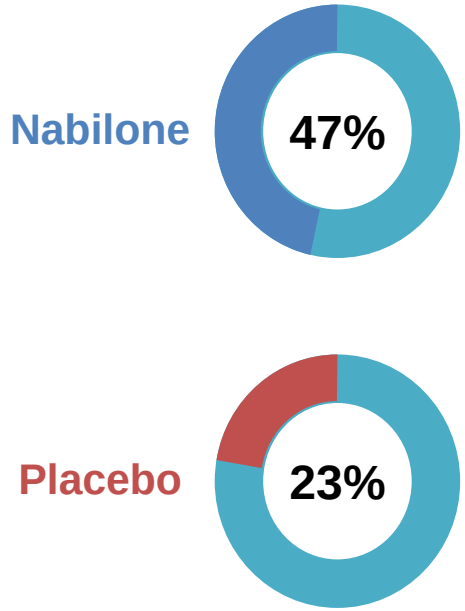
- estimated treatment difference [95% CIs] on CMAI was b= -4.0 [-6.5 to -1.5], p=.003 favouring nabilone
  - no carry-over (t(32)=1.6, p=.11), no treatment order effect (t(31)=0.2, p=.85)
- *significant differences
  - Week 2--nabilone: 62.5±19.2 versus placebo 68.3±16.3, (t(32)= -2.39, p=.03);
  - Week 6/endpoint-- nabilone: 55.8±15.9 versus placebo: 65.9±13.7, (t(32)=-3.77, p=.001).

Herrmann et al 2019

CGIC during nabilone versus placebo phases

- CGIC “minimal” to “marked” improvement (McNemar’s test, p=.09)





Herrmann et al 2019

Secondary outcomes and tolerability

Secondary outcomes favoured nabilone

- **overall behaviours** (NPI-NH) significantly lower (*b*= -4.6 [-7.5 to -1.6], p=.004) during nabilone
- **agitation/aggression** (NPI) was significantly lower (*b*=-1.5 [-2.3 to -0.62], p=.001) during nabilone
- **total caregiver distress** was significantly lower (b= -1.7 [-3.4 to =0.7], p=.041) during nabilone
- significant difference in **cognition** (MMSE) (*b*= 1.1 [0.1 to 2.0], p=.026) that favoured nabilone
  - ❖ MMSE ≤15 (n=25), there was a significant difference in SIB score (b= -4.6 [-7.3 to -1.8], p=.003), that favoured placebo

Tolerability

- mean nabilone dose 1.6±0.5mg/day
  - 53% 2 mg/day, 13% 1.5 mg/day, and 34% 1 mg/day
- more **sedation** during nabilone (17 vs. 6 McNemar's test, p=.02)
  - no differences in treatment-limiting sedation (5 vs. 1 McNemar's test, p=.22)
  - did not contribute significantly to response
- no difference in
  - falls (8 vs. 7 McNemar's test, p=1.0)
  - SAEs (5 vs. 4 McNemar's test, p=.69)
  - study discontinuations (3 vs. 2 McNemar's test, p=.08)
  - deaths (1 vs. 1)

Herrmann et al 2019

Exploratory: Appetite and pain

Nutrition and weight

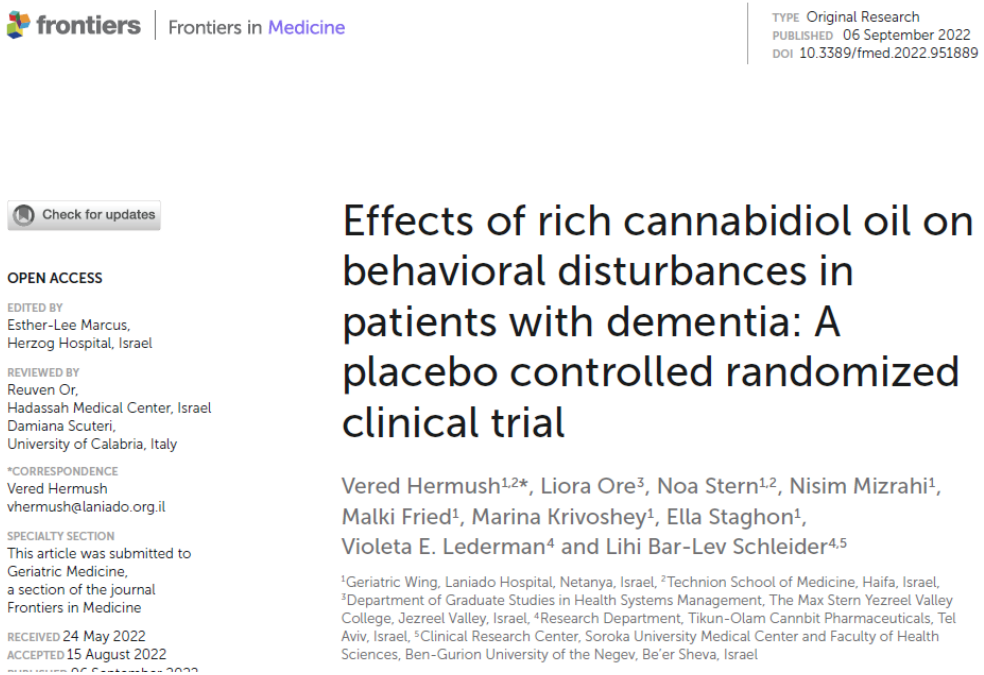
- significant differences on nutrition (MNA-SF)
  - (b= 0.2 [0.02 to 0.4], p=.03), favouring nabilone
  - Baseline average 8.7±2.9 (at risk of malnutrition)
- No significant difference in weight change (kg)
  - (b=0.01 [-0.69 to 0.71], p=.97)
  - Average baseline weight: 67.9±14.1 kg

Pain

- no treatment differences on PAINAD scale (b= 0.03 [-0.22 to 0.27], p=.82)
- PAINAD: The total score ranges from 0-10 points
  - 1-3=mild pain; 4-6=moderate pain; 7-10=severe pain.
  - Baseline average 2.6±1.4
- PAIN-AD
  - was higher in responders (3.3±1.3 vs. 2.2±1.4, t=-2.561, df=34, p=.015)

Herrmann et al 2019

Effects of rich cannabidiol oil on behavioral disturbances in patients with dementia



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Effects of rich cannabidiol oil on behavioral disturbances in patients with dementia: A placebo controlled randomized clinical trial

Vered Hermush[1,2]*, Liora Ore[3], Noa Stern[1,2], Nisim Mizrahi[1], Malki Fried[1], Marina Krivoshey[1], Ella Staghon[1], Violeta E. Lederman[4] and Lihi Bar-Lev Schleider[4,5]

[1]Geriatric Wing, Laniado Hospital, Netanya, Israel, [2]Technion School of Medicine, Haifa, Israel, [3]Department of Graduate Studies in Health Systems Management, The Max Stern Yezreel Valley College, Jezreel Valley, Israel, [4]Research Department, Tikun-Olam Cannbit Pharmaceuticals, Tel Aviv, Israel, [5]Clinical Research Center, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel

- Randomized controlled trial of CBD oil (Avidekel) x 16 weeks in patients with major NCD (all types), MMSE < 26, NPI agitation ≥3
  - 30:1 CBD/THC, 11.8 mg CBD and 0.5 mg THC per drop (0.04 ml)
  - **average dose 527.5 mg CBD and 22.3 mg THC per day**
- N=60 (40 drug:20 placebo), average age 79, 60% female
- Primary outcome: proportion with reduction of ≥4 on CMAI
- Study funded by drug company

Hermush et al 2022

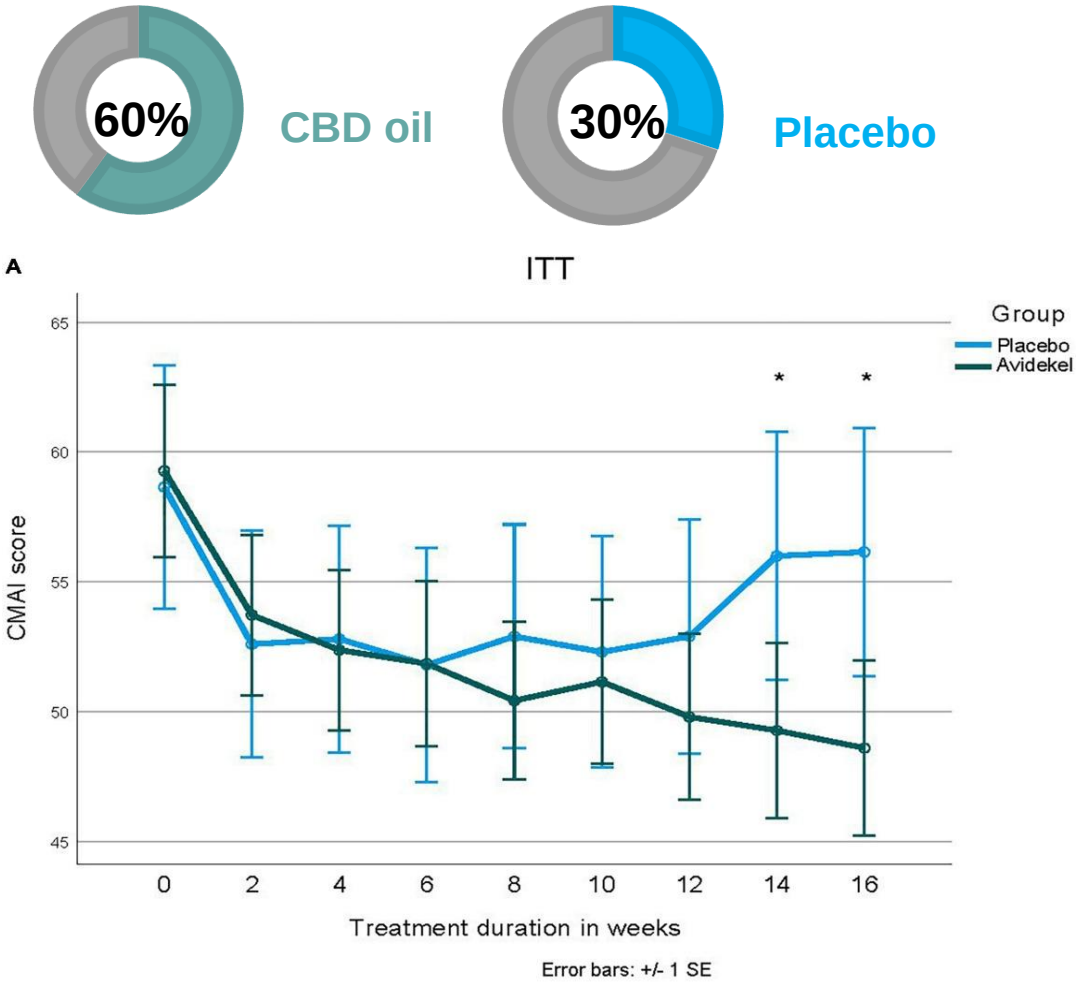
Results

Efficacy

- 60% drug vs. 30% placebo improved ≥4 points on CMAI (χ 2 = 4.80, p=.03/.06 Yates)
- decline in CMAI 10.7 points drug vs 2.5 placebo at wk 16 (F = 3.18, p=.02)
- No correlation between dose and outcome

Tolerability

- Drop outs: 8/40 CBD oil (including 2 deaths) vs 0 placebo, none reported as d/t AEs
- Sleepiness (48.6%), confusion and disorientation (45.9%), and decreased memory (32.4%) most frequent with CBD oil

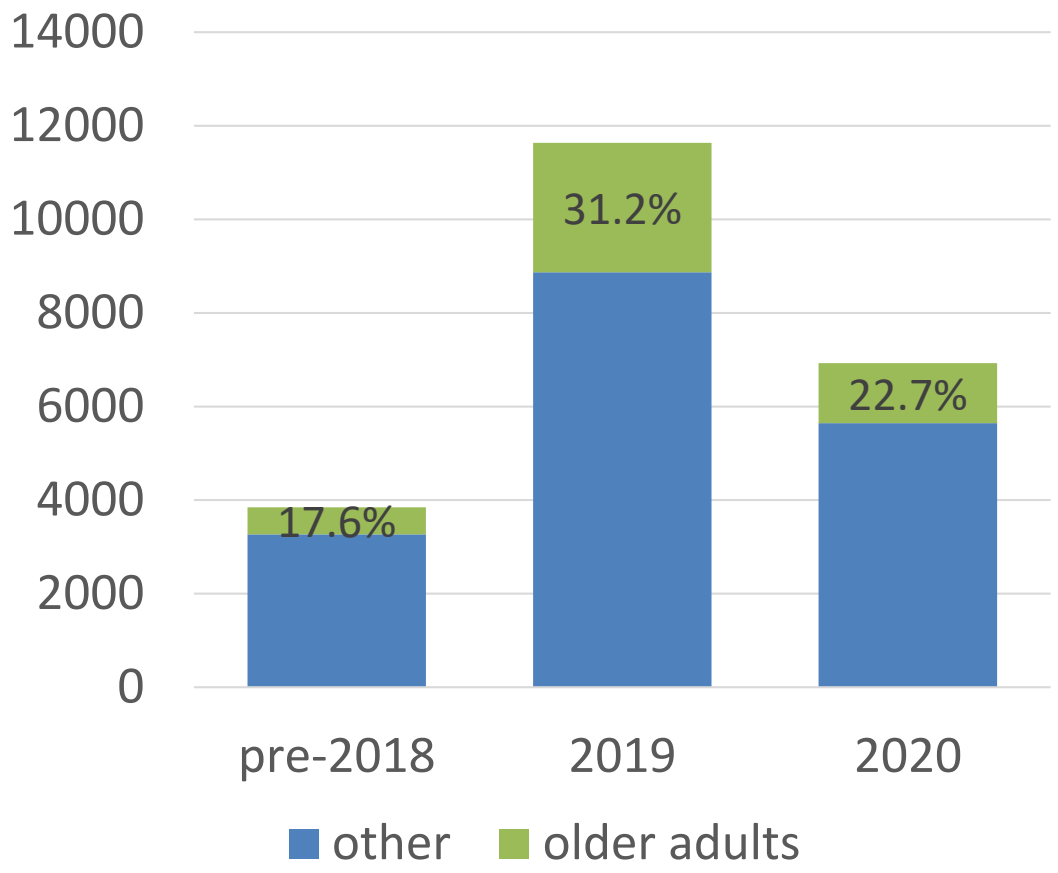


Hermush et al 2022

Does it have one?

PLACE IN THERAPY

Medical cannabis use is growing among older adults

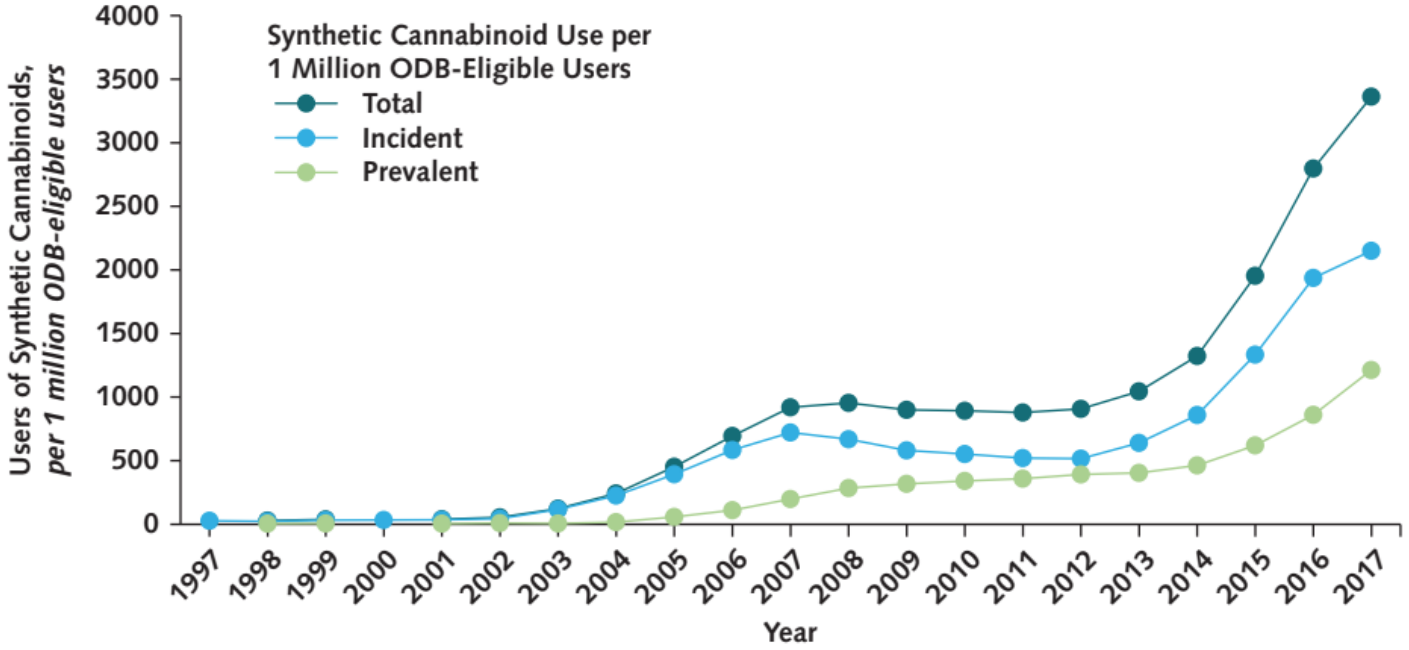


- October 2014 to October 2020 from medical cannabis provider
- n=9,766 older adults (≥65 years)(mean [SD] age=73.2 [6.8], females = 60.0%)
- proportion of older adults increased (odds ratio (OR)=1.20, p<0.001)
  - primary indication was pain (67.7%)
  - adverse effects dry mouth (12.8%), drowsiness (8.6%), and dizziness (4.0%)
  - improvements reported in pain (73%, compared to worsening or no change), sleep (65%), mood (53%)

Tumati et al 2022

Increasing use of synthetic cannabinoids

Figure. Trends in the medical use of synthetic cannabinoids among older adults in Ontario.



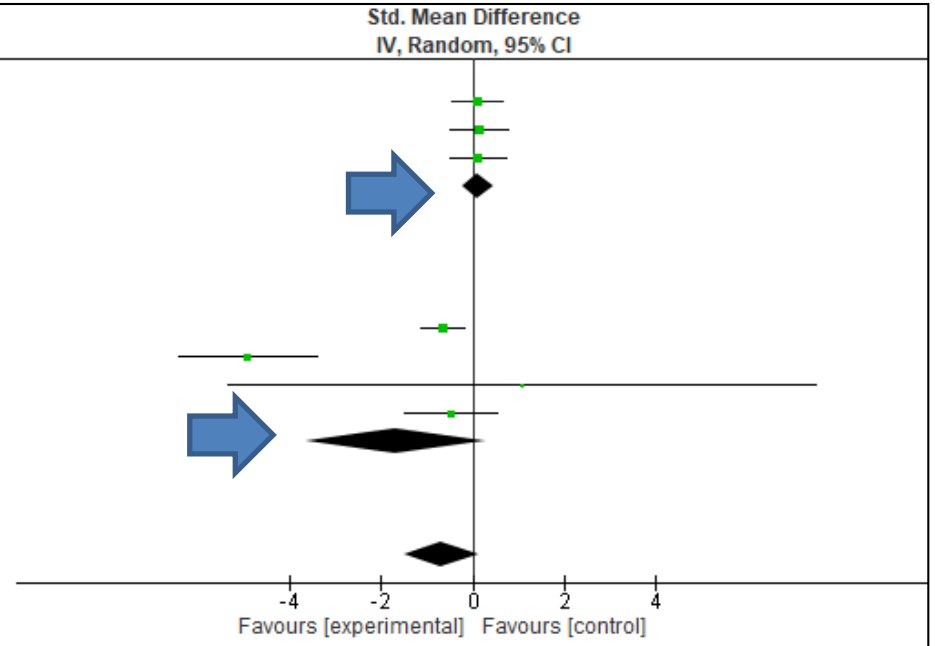
The number of ODB-eligible users per calendar year was calculated by determining the number of older adults in Ontario who filled at least 1 prescription using the ODB program during that calendar year. ODB = Ontario Drug Benefit.

Sommer et al. 2020

Meta-Analysis of Cannabinoids for Agitation

- double-blind placebo controlled RCTS of CBs for agitation in AD patients
  - 6 studies included, n=251

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 THC								
Van den Elsen et al [30]	-1.2	5.6	24	-1.8	6.1	26	18.0%	0.10 [-0.45, 0.66]
Van den Elsen et al [31] - 1st phase data	-4.45	3.21	20	-5.02	4.65	20	17.7%	0.14 [-0.48, 0.76]
Van den Elsen et al [31] - 2nd phase data	-3.43	4.91	20	-4.02	6.21	20	17.7%	0.10 [-0.52, 0.72]
Subtotal (95% CI)			**64**			**66**	**53.4%**	**0.11 [-0.23, 0.46]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.65 (P = 0.52)								
1.1.2 Synthetic Cannabinoid								
Lanctot et al [36]	-11.86	15.13	36	-2.46	13.72	35	18.4%	-0.64 [-1.12, -0.17]
Volicer et al [35]	-32.5	7.5	15	3	6.5	15	11.7%	-4.92 [-6.44, -3.41]
Walther et al [34]	-4	2.78	6	-2	4.54	10	15.0%	-0.47 [-1.50, 0.56]
Walther et al [32]	0.5	0.5	2	-1	1	2	1.5%	1.08 [-5.36, 7.52]
Subtotal (95% CI)			**59**			**62**	**46.6%**	**-1.67 [-3.65, 0.30]**
Heterogeneity: Tau² = 2.99; Chi² = 29.16, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 1.66 (P = 0.10)								
Total (95% CI)			**123**			**128**	**100.0%**	**-0.69 [-1.50, 0.13]**
Heterogeneity: Tau² = 0.88; Chi² = 43.53, df = 6 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.66 (P = 0.10)								
Test for subgroup differences: Chi² = 3.05, df = 1 (P = 0.08), I² = 67.3%								



- no effect on agitation (SMD: -0.69, P = .10), significant heterogeneity ($\chi^2_6 = 43.5$, $P < .00001$, $I^2 = 86\%$)
  - trend for greater difference in agitation with synthetic over THC ($\chi^2_1 = 3.05$, $P = .08$)
  - larger effect on agitation with greater cognitive impairment ($B = 0.27$, $t_6 = 2.93$, $P = .03$)
- sedation more likely in patients treated with CBs (risk ratio: 1.73; P=.04)

Ruthirakuhan et al 2019

Trends in emergency department visits associated with cannabis use

- Time-trend analysis of cannabis-related ED visits from all acute care hospitals in California from 2005-2019 for adults over 65 years
  - Legalized medical and recreational use in 2016
- Overall rate increased from 20.7 to 395.0 per 100,000 ED visits
  - 1804% relative increase
- Older adults with higher medical comorbidity had highest rate in 2019 and largest absolute increase
- Cannabis-related ED visits increasing among older adults
  - an adverse effect of cannabis use
  - increase was likely NOT accounted for by recreational use

Han et al 2022

Current studies: **N**abilone for **A**gitation **B**linded **I**ntervention **T**rial

- Larger and longer trial
  - Multi-centre, randomized, placebo-controlled
  - n=112 clinical diagnosis of Alzheimer's disease dementia [NIA-AA 2011]
  - meet criteria for agitation
  - 1-2mg of nabilone or placebo over 9 weeks
  - biomarkers potentially related to agitation and response
- 5 sites: Toronto (3), Whitby, Calgary
- recruitment ongoing

- study investigators
  - Sunnybrook: Drs. Krista Lanctôt, John Marotta, Helen Lee and Nathan Herrmann
  - Calgary: Dr. Zahinoor Ismail
  - Ontario Shores: Dr. Amer Burhan
  - CAMH: Drs. Tarek Rajji, Sanjeev Kumar
  - St. Mike's: Dr. Corinne Fischer

Current studies: **Ca**nnabinoid **L**iquid for **A**gitation **M**edication **I**ntervention **T**rial

- Treating agitation in patients with Alzheimer's disease
  - Multi-centre, randomized, placebo-controlled cross-over study (n=60)
  - Cannabinoid (CBD predominant, THC, +) versus placebo over 6 weeks
  - Biomarkers potentially related to response
  - recruitment beginning

- CBD
  - enhances endocannabinoid signaling
  - interacts with many non-endocannabinoid signaling systems: It is a "multi-target" drug.
  - potent antioxidant
  - antipsychotic properties
  - anxiolytic
- anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties [Scuderi et al 2009]

CCNA Canadian Consortium on Neurodegeneration in Aging
CCNV Consortium canadien en neurodégénérescence associée au vieillissement
WESTON BRAIN INSTITUTE

What would you do?

CASE STUDIES

Case studies

Case 1- from the chronic pain clinic

- Elderly woman with mixed dementia, paranoia agitation and bad chronic back pain from 5 years ago who benefitted from nabilone (pre study and off label use) who needed too much fentanyl + risperidone to settle otherwise.
- Did you want to know anything more? What would you do?

- Treated with nabilone titrated slowly to 2mg bid, risperidone reduced from 2mg to 0.5mg and Fentanyl tapered from 75ug to 25ug and stopped.
- Managed with 24h slow release morphine 30mg daily vs fentanyl 75ug (180mg morphine equivalent) with recommended "safe" maximum now 80mg daily.

Case studies

Case 2-- Nabilone study patient

- ~80 year old woman with advanced Alzheimer's
- Osteoarthritis of back moderate and significant yelling out, insomnia, resistive to care and not ambulating.
- Treated during COVID from home with remote visits from me only (risperidone for paranoia? stopped, escitalopram no success, trazodone too sedating) was fighting off homecare, husband and private caregiver.
- Did you want to know anything more? What would you do?

- Entered NBA-IT study and improved by week 4
- Post-study prescribed nabilone- transitioned to home palliative care

Case studies

Case 3: Nabilone study patient

- ~70 year old woman with rapidly progressive Alzheimer's moderately severe, depression and sundowning agitation with insomnia causing hired caregiver distress.
- Depression helped prior to sundowning for 2 years with mirtazapine (was eating poorly, not sleeping). Sundowning not settling with trazodone, melatonin, GP used zopiclone, lorazepam.
- Did you want to know anything more? What would you do?

- Entered study and settled at week 4 then became drowsy, less responsive, family decision maker withdrew consent though believed she benefitted initially from study drug. Post-study assessed by ER because of persisting drowsiness and found to have COVID.

Summary

- Agitation common and persistent symptom in those with Alzheimer's disease
  - current pharmacotherapies have modest efficacy and/or poor safety
- Increasing interest in the use of cannabinoids as a therapeutic intervention in dementia, particularly for agitation
- Pharmacologic rationale exists for use of cannabinoids
- Limited studies assessing the efficacy of THC and related compounds for agitation
- Recent trials of cannabinoids for agitation show promise
  - Efficacy, but concerns around sedation and other dose-related effects
- Further research needed
  - When to use, what to use, how to use, effective doses versus safety

CCSMH CANADIAN COALITION FOR SENIORS' MENTAL HEALTH

CCSMPA LA COALITION CANADIENNE POUR LA SANTÉ MENTALES DES PERSONNES ÂGÉES

E-learning Modules for Cannabis and Older Adults

- E-learning for physicians, other healthcare providers and healthcare students
- Project funded by Health Canada
- Modules developed by clinical experts
- MainPRO and MOC Accredited

Topics covered include;

- History of cannabis and legalization
- Neuropharmacology of cannabis
- Drug interactions
- How to talk to patients about cannabis
- Prescribing/authorizing cannabis
- Safety and risks of cannabis
- Cannabis use disorder/harm reduction

For more information contact info@ccsmh.ca or visit
https://ccsmh.ca/cannabis-and-older-adults-project/

Position statement published in 2020, updated from 2014 and 2018

POSITION STATEMENT:

USE OF MEDICAL CANNABIS FOR NEUROLOGIC DISORDERS

AMERICAN ACADEMY OF NEUROLOGY®

Currently, the AAN does **not** support the use of, nor any assertion of therapeutic benefits of, cannabis products as medicines for neurologic disorders in the absence of sufficient scientific peer-reviewed research to determine their safety and specific efficacy.

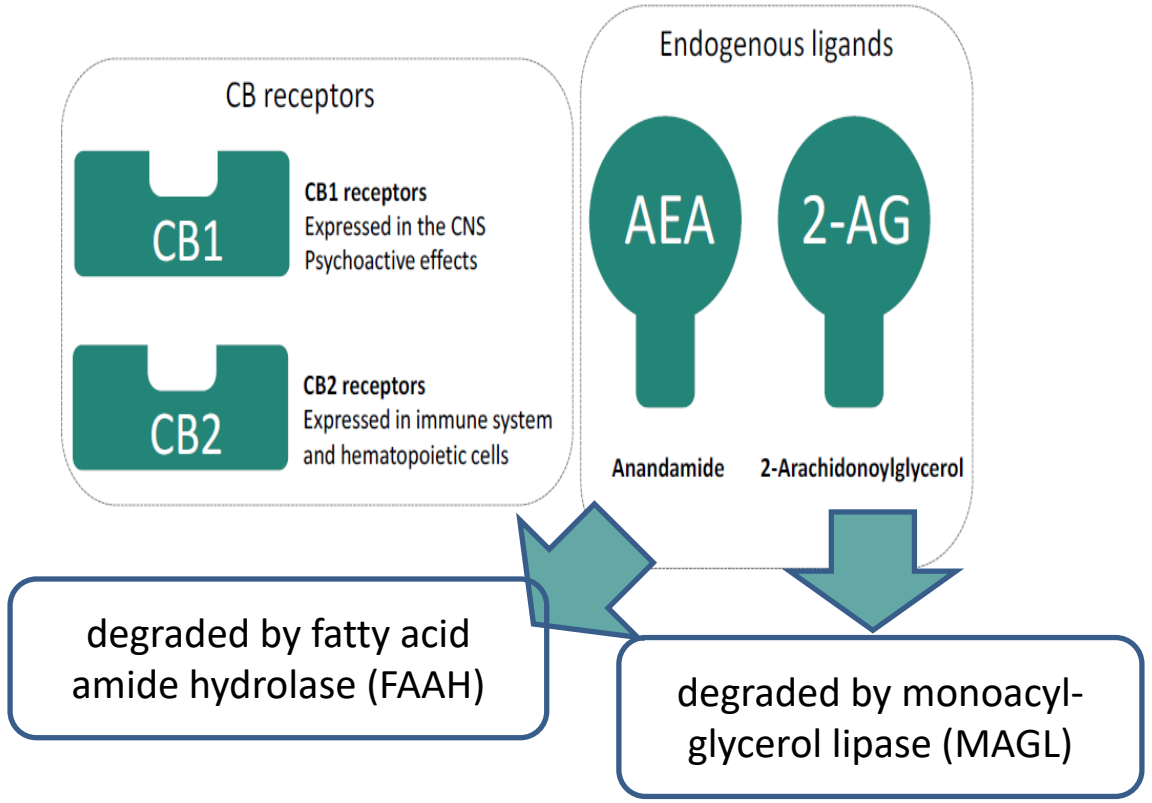
Endocannabinoid system in Alzheimer's Disease

Small number of studies

- CB1 upregulated in PFC in early AD, inversely correlated with Braak tau pathology [Farkas et al 2012]
- CB1 neurons greatly reduced in inflammatory areas of Ab-induced microglial activation [Ramirez et al 2005]
- CB2 and FAAH overexpressed in astrocytes near Ab plaques in entorhinal and parahippocampal regions of AD brain [Benito et al 2003]
- CB2 40% higher in frontal cortex of AD samples and positively correlated with increase in Ab [Solas et al 2013]
- CB2 agonist removed Ab deposits in vitro [Tolon et al 2009]

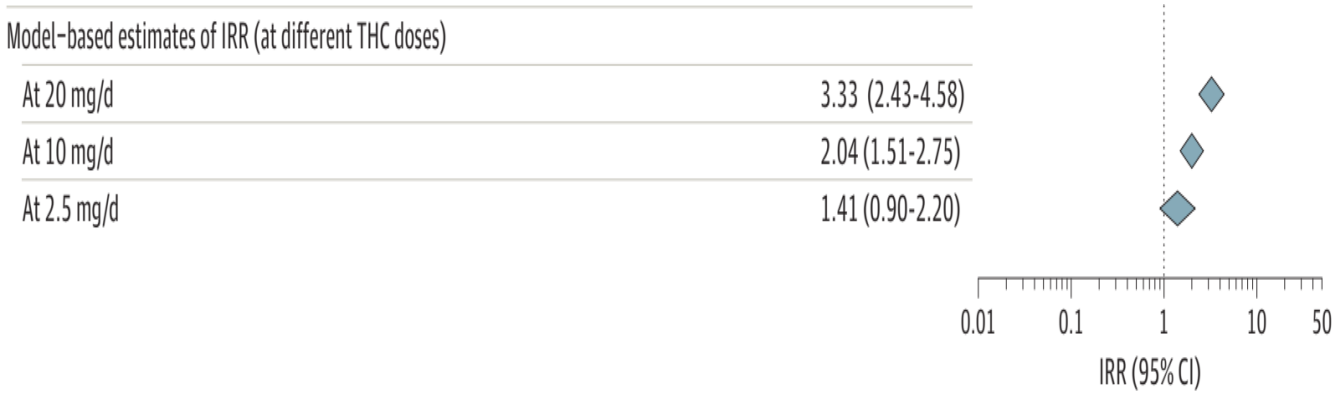
Endocannabinoid system (ECS)

- 2 receptors: CB1 (CNS) and CB2 (immune)
- 2 endocannabinoids: anandamide (AEA) and 2-arachidonoyl glycerol (2-AG)



EVALUATION OF THC-RELATED NEUROPSYCHIATRIC SYMPTOMS AMONG ADULTS AGED 50 YEARS AND OLDER: A SYSTEMATIC REVIEW AND META-REGRESSION ANALYSIS

- Meta-analysis of RCTs reporting the safety and tolerability of different CBMs (CBD and THC combinations, THC, or its analogues) in people older than 50 years of age
  - 30 RCTs analyzed 1417 patients, median age, 59.5 in intervention groups and, 1210 patients, median age 58.9, in control groups
- significant positive association between THC dose and IRR for
  - dizziness or light-headedness (estimate, 0.05; 95% CI, 0.02-0.08; P = .001)
  - and thinking or perception disorder (estimate, 0.07; 95% CI, 0.03-0.11; P < .001) for THC studies,
  - *no association with AEs for THC and CBD combination studies*



Conclusion: higher THC dose was associated with a higher incidence of thinking or perception disorder and dizziness or light-headedness

Velayudhan et al 2021