Cannabis and dementia: Weeding through the evidence

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Sunnybrook
HURVITZ BRAIN SCIENCES PROGRAM

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Learning objectives

- There is increasing interest in the use of cannabinoids as a therapeutic intervention in dementia, particularly for agitation.
- By the end of this presentation learners will be aware that
  - agitation is a common and persistent symptom in those with Alzheimer's disease
  - current pharmacotherapies have modest efficacy and/or poor safety
  - there is a pharmacologic rationale for use of cannabinoids
  - limited literature has evaluated the efficacy of THC and related compounds for agitation
  - a pilot study of a cannabinoid for agitation has recently been completed

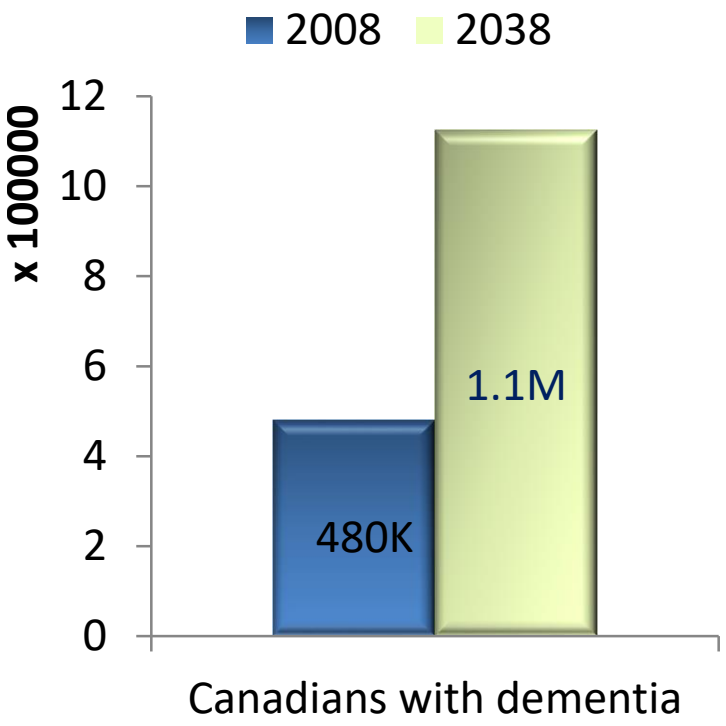
AGITATION IN ALZHEIMER'S DISEASE

Dementia—major neurocognitive disorder

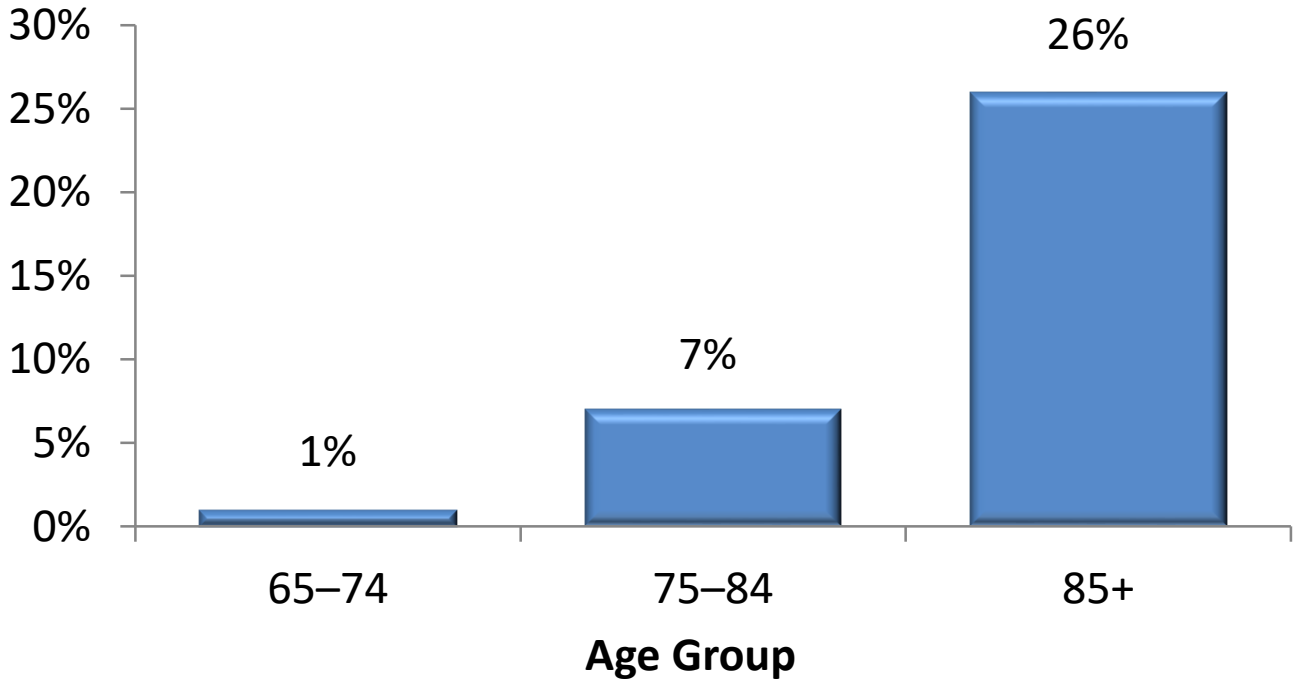
- sustained deterioration of cognitive ability sufficiently severe to impair occupational or social functioning (DSM-5)
- Major cause of disability and death in developed countries
- 4th leading cause of death in the US and Canada

The Rising Tide

- The number of Canadians with Alzheimer's disease and related dementias will more than double over 30 yrs
  - 2008 - 1.5% of Canada's population
  - 2038 - 2.8% of Canada's population



Prevalence of Alzheimer's Disease Increases with Age



Canadian Study of Health and Aging, *Can. Med. Assoc. J.*, 1994

ABC's of Dementia

Activities of daily living

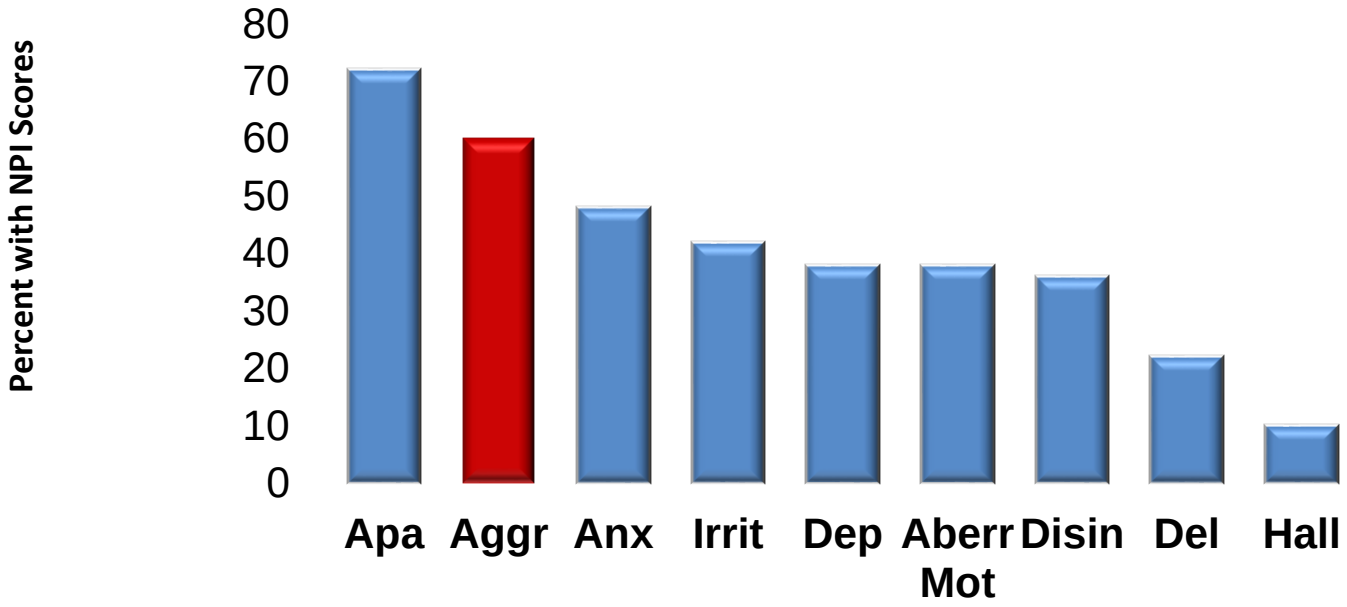
Behaviour

Cognitive deficits

Behavioural or Neuropsychiatric Symptoms (NPS):

A heterogeneous range of psychological reactions, psychiatric symptoms and behaviours resulting from the presence of dementia

Neuropsychiatric symptoms common in Alzheimer's Disease



Mega et al, Neurology 1996; 46: 130-135

Agitation in AD

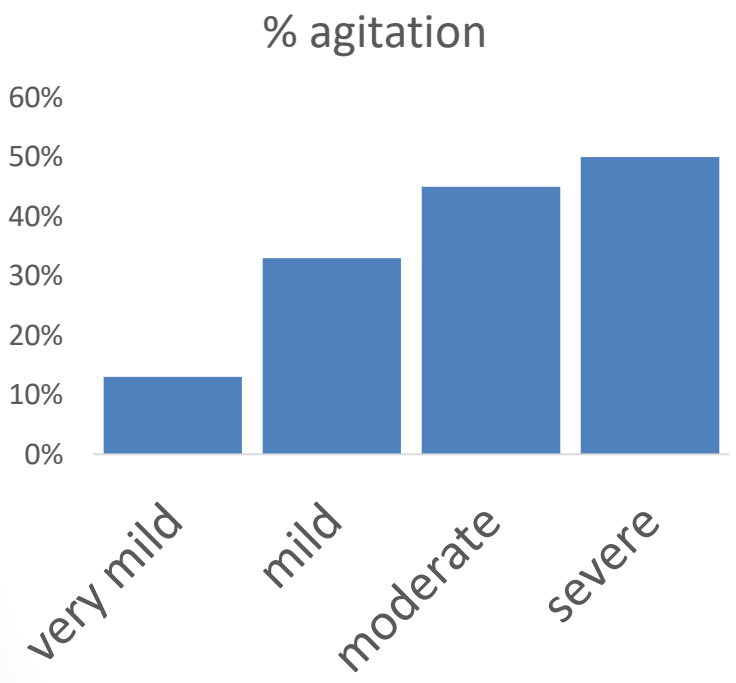
- IPA Criteria:
  - occurring in patients with cognitive impairment or dementia
  - behavior consistent with emotional distress
  - manifesting excessive motor activity, verbal aggression, or physical aggression
  - cause excess disability and are not solely attributable to another disorder (psychiatric, medical, or substance-related)

IPA Consensus Criteria, 2015

Agitation is common in AD

- 10% in people with mild cognitive impairment [Ryu et al 2011]
- 15% in people with dementia presenting to memory clinics [Brodaty et al 2015]
- 30% in those living in the community [Borsje et al 2015, Lyketsos et al 2002]
- 20%–50% of those with moderate-to-severe AD experience agitation [Lyketsos et al 2002, McKeith & Cummings 2004, Pitalka et al 2004]

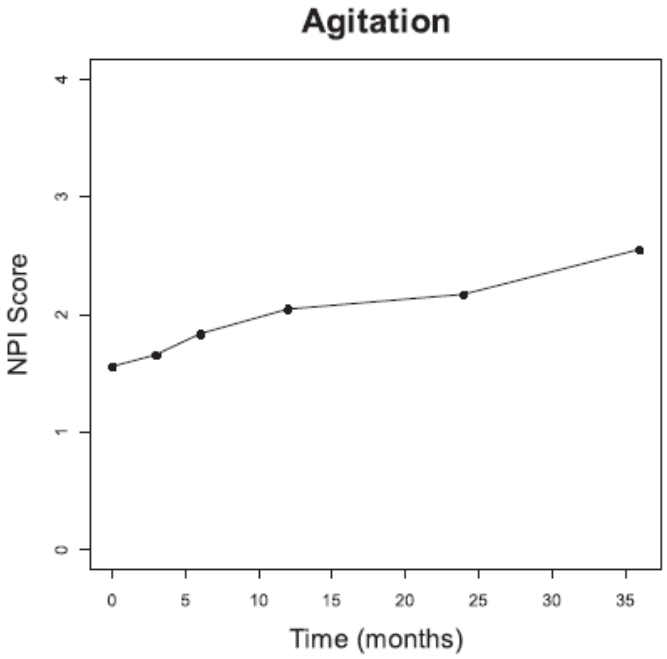
Prevalence of agitation increases with severity



- significantly greater odds of agitation (odds ratios [95% CI]):
  - mild 4.5 [2.3 to 8.7]
  - moderate 7.0 [3.6 to 13.3]
  - severe 6.2 [3.2 to 11.94]
- random effects logistic regression model adjusted for resident's age, gender, care home type

Livingston et al, 2017

Agitation is persistent



- % any agitation (score of at least 4)
- Baseline 51.7 (15.3)
- 3 months 53.0 (14.1)
- 6 months 54.7 (17.8)
- 1 year 54.6 (18.5)
- 2 years 59.1 (20.6)
- 3 years 59.6 (23.1)

Brodaty et al 2015

agitation—Impact

Caregivers

- 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]

Patients

- 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]

Agitation is associated with weight loss and pain

Weight loss

- common in AD
  - About 1/3 of patients with AD, with risk increasing as the disease progresses
- consequences
  - loss of muscle mass and strength, greater risk of falls, more functional dependence and lower quality of life
- associated with agitation

Pain

- common in AD [Pickering et al 2000] but difficult to identify [Herr 2001]
- may be undertreated [Pickering 2000, Herr 2001]
- associated with agitation [Husebo et al 2011, 2013]

CURRENT THERAPIES UNSATISFACTORY

Non-pharmacological treatments for agitation in Alzheimer's or mixed vascular dementia

Table 1. Non-pharmacological treatments for agitation and aggression in Alzheimer's or mixed vascular dementia.

Category	Treatment
Social contact	Pet therapy, one to one visits
Sensory enhancement/relaxation	Hand massage, individualized music, individualized art, sensory modulation, multi-sensory environments (e.g. snoezelen)
Purposeful activity	Helping tasks/volunteer roles, inclusion in group activity programs, access to outdoors
Physical activity	Exercise groups, indoor/outdoor walks, individual exercise programs
Neurocognitive intervention technology	Therapeutic robot (e.g. Paro seal), tablet computer, gaming console
Caregiver interventions	Caregiver education, caregiver support, connection to external organizations and services

Note. This table is provided for reference only, an appraisal of the evidence base underpinning these treatment strategies and their suitability depending on behavioural and psychological symptoms of dementia (BPSD) severity is outside of the scope of this paper.

Davies et al, 2018, DOI: (10.1177/0269881117744996)

Nonpharmacologic interventions

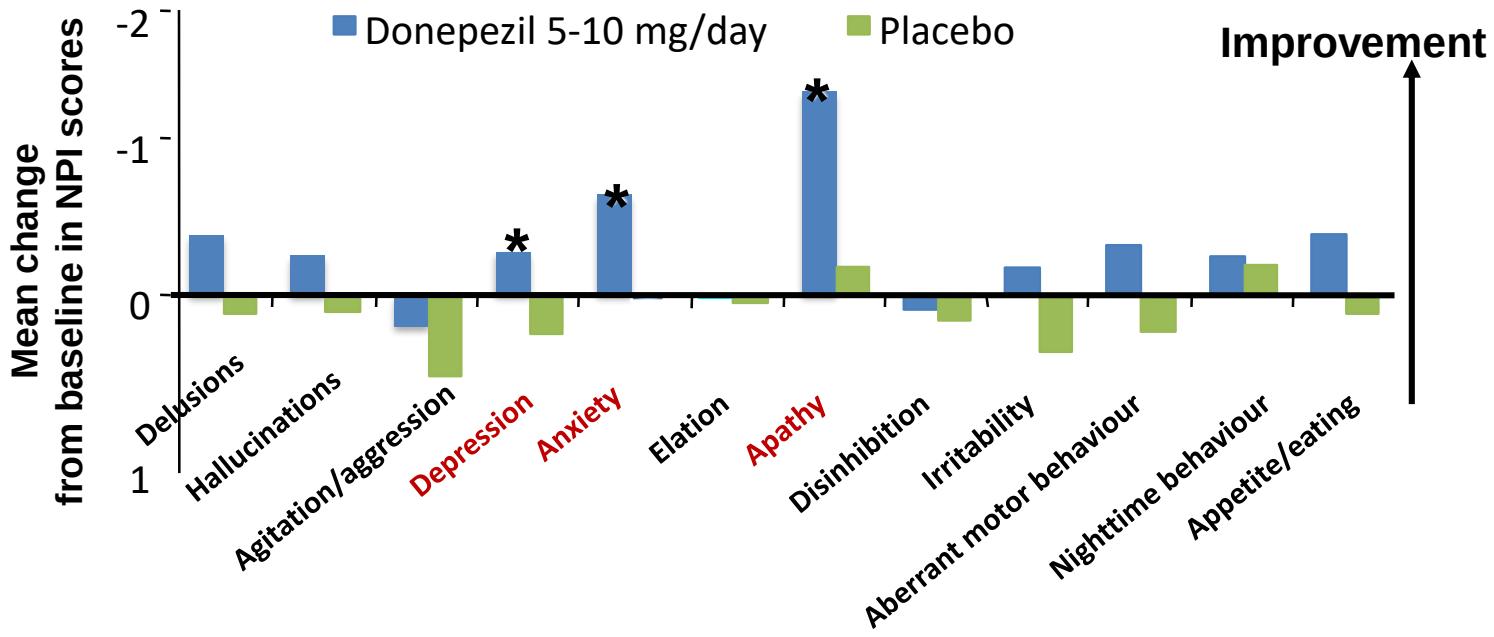
- systematic review of 160 studies of non-pharmacological interventions
- agitation in dementia people over 50 years of age in care facility settings
- various activities may help to reduce mild-to-moderate agitation
  - music therapy and sensory interventions (massage, therapeutic touch and multisensory stimulation)
- lacked significant long term benefits
- no beneficial effects on severe agitation symptoms.

Livingston et al. 2014

interventions for agitation

- Psychotropic medications
  - cholinesterase inhibitors (ChEIs)
  - memantine
  - antipsychotics
  - antidepressants

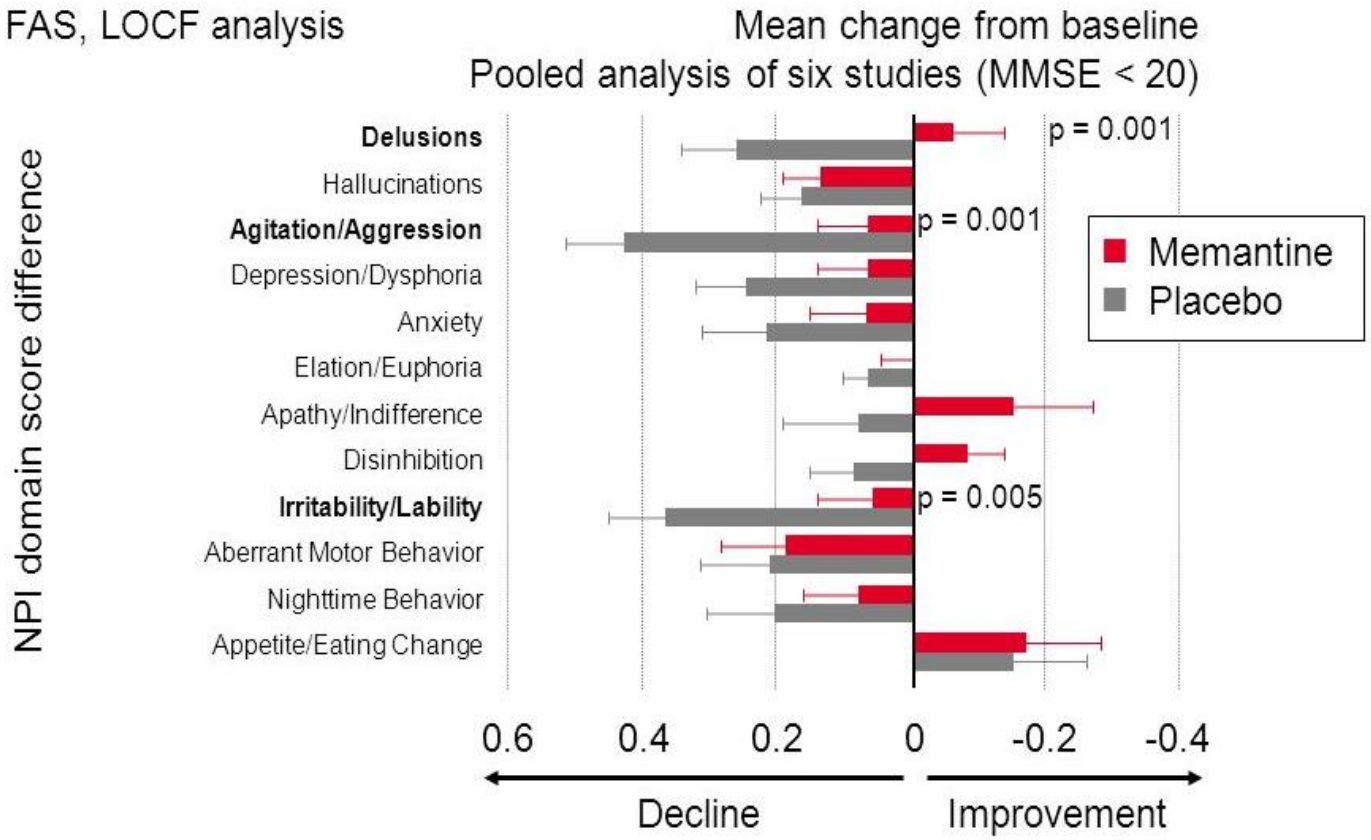
Donepezil in MSAD: NPI Individual Items



*$p < 0.02$ *vs.* placebo; n = 290; Week 24 LOCF analysis

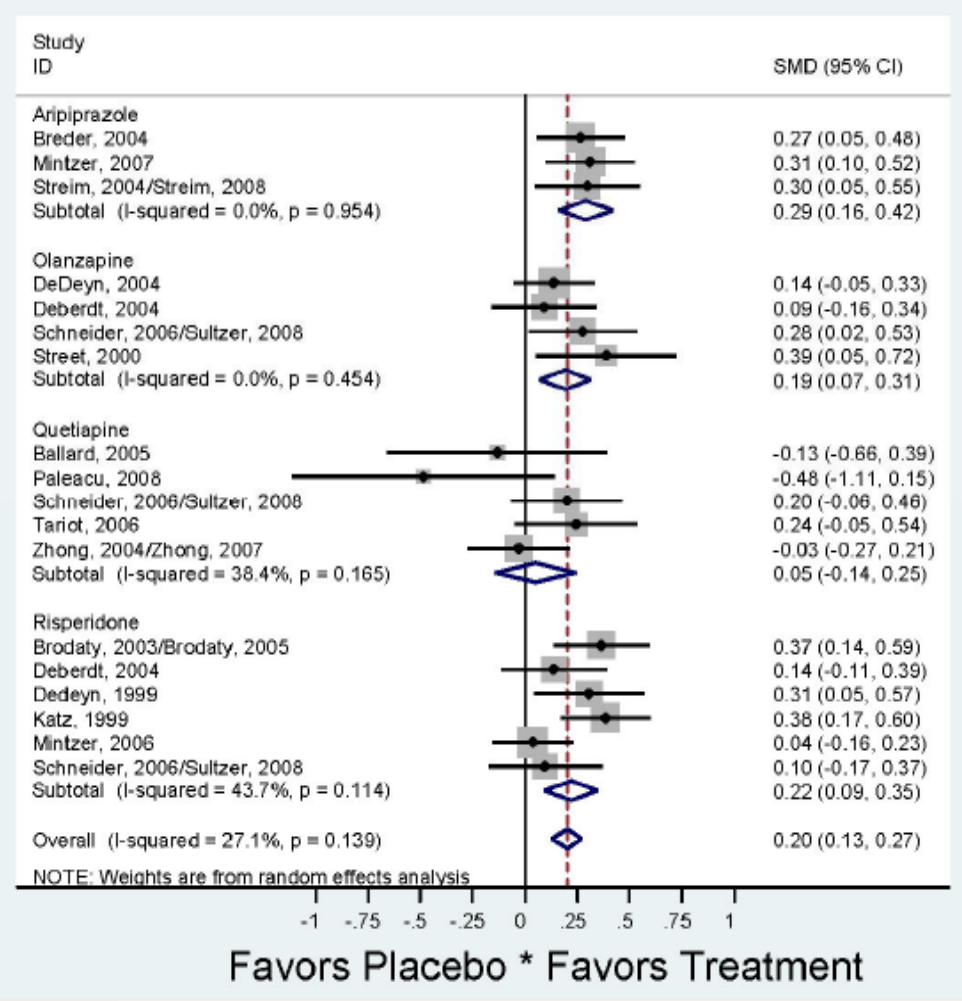
Gauthier et al. 2002

Benefits of memantine



Gauthier et al., Int J Geriar Psychiatry 2008

Effect of antipsychotic treatment on agitation



- NNT: ranges from 5 to 14
- NNH: for every 100 treated with an atypical antipsychotic, 1 death due to atypical drug
- for every 9 to 25 persons helped, there would be 1 death

AHRQ Comparative Effectiveness Review 2011

Citalopram and Agitation--CiTAD Trial

Original Investigation

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

- Design:
  - AD + agitation
  - Randomized to psychosocial intervention plus
    - citalopram (n = 94) (10 mg/d to 30 mg/d)
    - placebo (n = 92)
- significant benefits on agitation
  - 40% of citalopram improved vs 26% placebo
- significant worsening of cognition and QT interval prolongation (18.1 ms)

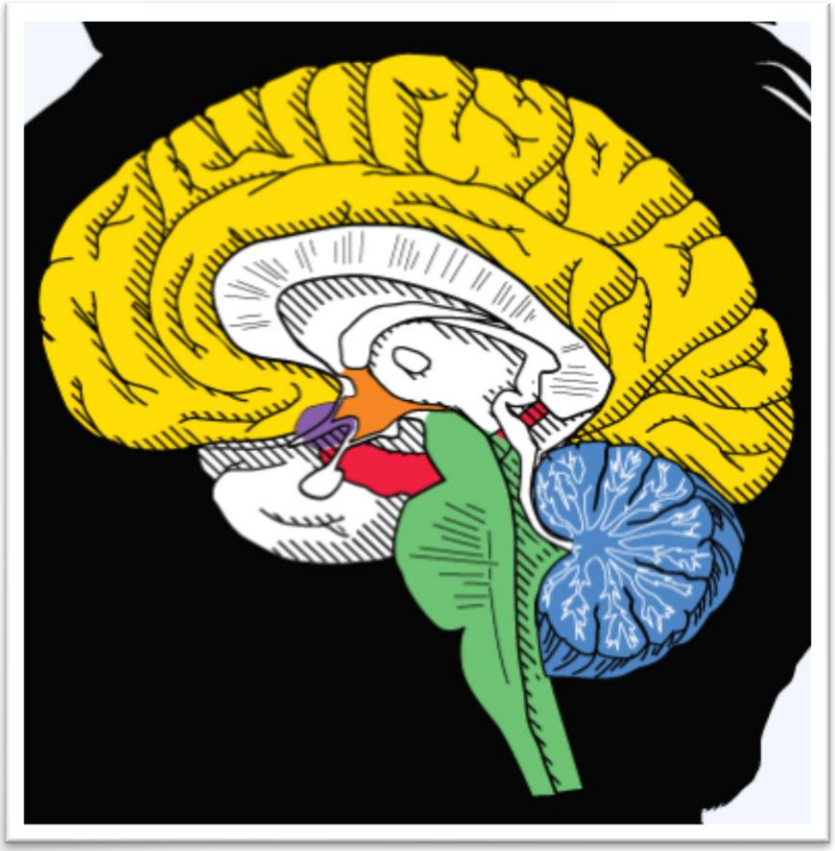
Porsteinsson et al JAMA 2014

The unmet need

- Nonpharmacologic interventions
  - Limited efficacy for severe agitation
  - Difficult to implement
- Pharmacotherapy
  - No medications that are both safe and efficacious

RATIONALE FOR USE OF CANNABINOIDS

Endocannabinoid system (ECS)



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

the data

- Liu CS, Chau SA, Ruthirakuhan M, Lanctôt KL, Herrmann N: Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease. CNS Drugs 29:615-623, 2015.
- Sherman C, Ruthirakuhan M, Vieira D, Lanctôt KL, Herrmann N: Cannabinoids for the treatment of neuropsychiatric symptoms, pain and weight loss in dementia. Current Opinion in Psychiatry 2018 Mar;31(2):140-146.
- Ruthirakuhan M, Lanctôt KL, Vieira D, Herrmann N. Natural and synthetic cannabinoids for agitation and aggression in Alzheimer's disease: A Meta-Analysis. J Clin Psychiatry 2019 Jan 29;80(2).

Possible benefits of CB1 and CB2 activation

Clinically

- Mild sedation
- Anti-anxiety
- Increase appetite
- Decrease pain

Pathological processes

- Endocannabinoid signaling modulates numerous AD pathological processes [Aso & Ferrer 2014]
  - neuroinflammation
  - excitotoxicity
  - mitochondrial dysfunction
  - oxidative stress
- Loss of endogenous cannabinoids in AD leads to loss of protection from excitotoxicity

Reviewed by Liu et al, 2016

Cannabis

- 2 major neuroactive components in cannabis
  - psychoactive Δ9-tetrahydro-cannabinol (Δ9-THC)
  - non-psychoactive cannabidiol (CBD)
  - non-psychoactive indicates lack of psychotropic effects that produce a 'high'
- *C. sativa* usually has higher Δ9-THC:CBD ratios than *C. indica.*
- *Sativa* strains often have more psychotropic effects, and are more stimulating, while *indica* strains are typically more sedating.
- Δ9-THC activates the endocannabinoid system
- CBD can have some anti-anxiety and other behavioral effects

Devinsky et al 2014

Cannabidiol (CBD)

- CBD enhances endocannabinoid signaling
- CBD interacts with many non-endocannabinoid signaling systems: It is a “multi-target” drug.
- CBD is a potent antioxidant
- CBD has antipsychotic properties
  - It is active in laboratory models of schizophrenia symptoms, and the prevalence of cannabis-linked psychosis is lower when street cannabis contains higher proportions of CBD.
- CBD is anxiolytic
- anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties [Scuderi et al 2009]

Devinsky et al 2014

CBD and THC

- CBD may potentiate some of Δ9-THC's beneficial effects
  - reduces Δ9-THC's psychoactivity to enhance its tolerability and widen its therapeutic window
  - counteract some functional consequences of CB1 activation in the brain, possibly by indirect enhancement of adenosine A1 receptors activity through ENT inhibition
- preparations with high CBD:Δ9-THC ratios are less likely to develop psychotic symptoms than those who consume preparations with low CBD:Δ9-THC ratios

Devinsky et al 2014

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
THC and cannabidiol (Sativex ®)	• Cannabis extract • CB1/CB2 agonist + CB1 antagonist	Neuropathic pain in multiple sclerosis
THC (Namisol ®)	• pure natural THC (>98%)	n/a

Double-blind, placebo controlled trials

THC—2 negative trials

- N=22 dementia and NPS, double-blind, repeated cross-over, 2 wks, no change NPS (van Den Elsen 2015a)
- N=24 dementia and NPS, double-blind 6 wk RCT, no change NPS (Van den Elsen 2015b)

Dronabinol—positive trials, few study participants/short duration

- 11 anorexic + AD, cross over 2.5 mg/d for 6 weeks, ⇓ CMAI agitation 2°, tolerability issues (Volicer et al 1996)
- 24 AD + agitation, 2.5 mg/d for 2 weeks (n=7), ⇓ nocturnal motor activity, tolerated (Mahlberg et al, 2007)
- 2 AD + nighttime agitation, cross-over 2.5 mg/d for 2 weeks, ⇓ nocturnal motor activity, tolerance (Walther et al., 2011)

Nabilone

- Case study (N=1), AD + NPS, 0.5 mg BID x 6 wks, ⇓ agitation, well tolerated (Passmore, 2008)

- Findings suggest possible signal

Ruthirakuhan et al 2019

Alzheimer's
Drug Discovery
Foundation

Nabilone trial

K Lanctot, N Herrmann, M Ruthirakuhan, D Gallagher, C Sherman, Eleenor Abraham, NPLG Verhoeff, A Kiss, SE Black, AC Andreazza

Study Participants (n=38)

Inclusion	Exclusion
• ≥55 years of age • Diagnosis of AD or mixed AD (major NCD) • Moderate-to-severe stage dementia (sMMSE ≤24) • Clinically significant agitation (NPI A/A >3) • Stable dose of cognitive enhancer (≥ 3 months)	• Change in psychotropic medications (≤1 month) • Contraindications to nabilone (history of hypersensitivity to cannabinoid) • Delusions or hallucinations • Current significant cardiovascular disease • Other psychiatric/neurological conditions, previous or current abuse of/dependence on marijuana

Lanctôt et al 2019

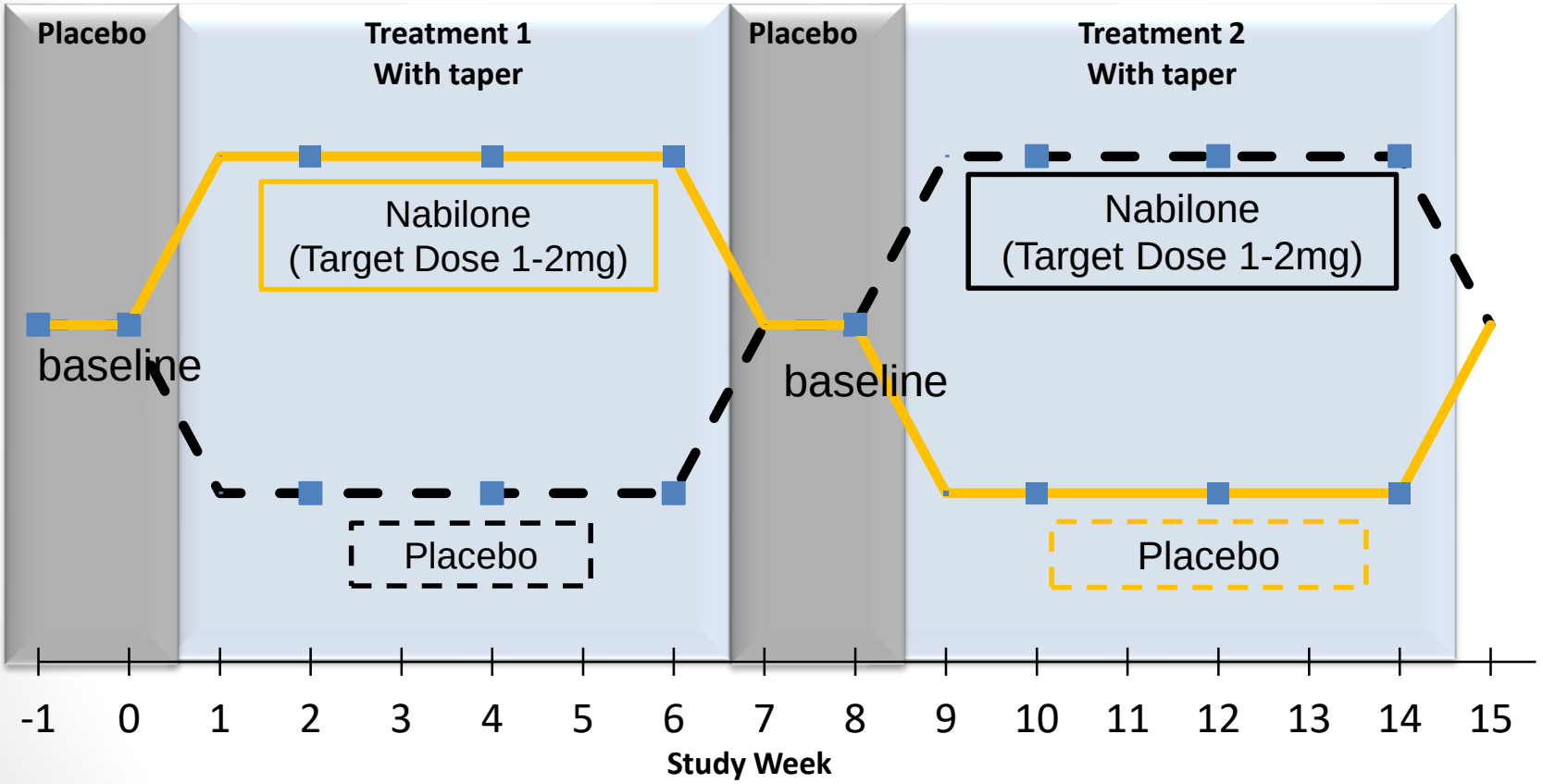
intervention

- nabilone:
  - synthetic derivative of THC
  - CB 1 and CB2 partial agonist
  - high oral bioavailability
  - duration of action 8-12 hours, given b.i.d.
  - marketed for nausea and vomiting associated with chemotherapy

- target dose 1-2 mg/d
  - Week -1: placebo run-in
  - Week 0: 0.25 mg qhs x 3 nights, then 0.25 mg BID for four days
  - Week 1: 0.5 mg once daily
  - Week 2: 0.5 mg BID (1 mg/d)
  - Weeks 3-4: dose increased to a maximum of 1 mg BID (2 mg/d total) or decreased based on tolerability
  - that dose maintained until down-titration

Lanctôt et al 2019

Study Design



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Primary Outcome

- Agitation (CMAI)

Secondary Outcomes

- Behaviour (NPI-NH)
- NPI-NH aggression/agitation
- Cognition (sMMSE, ADAS-cog or SIB)
- Global Change (CGIC)
- Caregiver distress (NPI-NH)
- Safety (TEAE and drop-outs)

Exploratory Outcomes

- Pain (PAIN-AD)
- Nutritional Status (Mini-Nutritional Assessment-SF)

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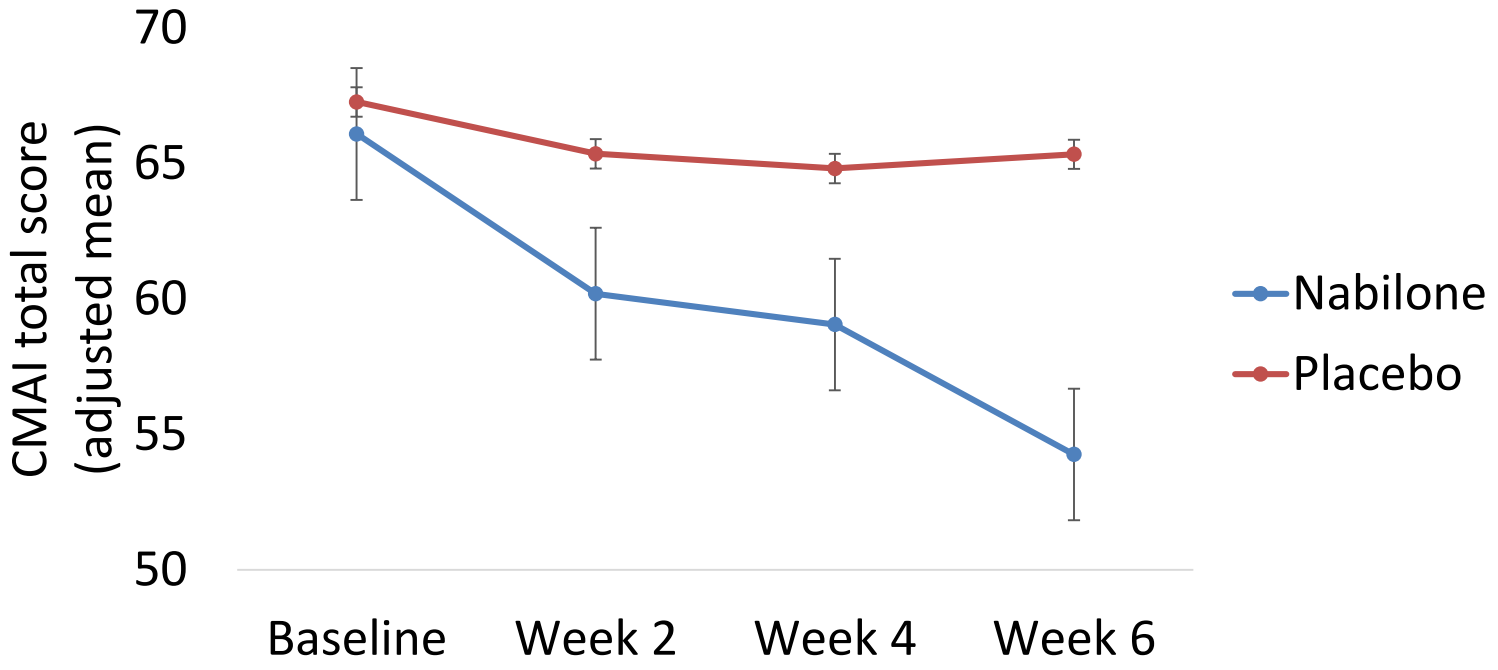
Agitation improved significantly during nabilone compared to the placebo phase



- estimated treatment difference [95% CIs] on CMAI was b= -4.0 [-6.5 to -1.5], p=0.003 favouring nabilone
- no cross-over effect (t(32)=1.6, p=0.11), no treatment order effect (t(31)=0.2, p=0.85)
- *significant differences
  - Week 2--nabilone: 62.5±19.2 versus placebo 68.3±16.3, (t(32)= -2.39, p=0.03);
  - Week 6/endpoint-- nabilone: 55.8±15.9 versus placebo: 65.9±13.7, (t(32)=-3.77, p=0.001).

secondary outcomes

- overall behaviours (NPI-NH) significantly lower (*b*= -4.6 [-7.5 to -1.6], p=0.004) during nabilone
- agitation/aggression (NPI) was significantly lower (*b*=-1.5 [-2.3 to -0.62], p=0.001) during nabilone
- total caregiver distress was significantly lower (b= -1.7 [-3.4 to =0.7], p=0.041) during nabilone

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inconsistent effect on cognition

- significant difference in cognition (MMSE) (*b*= 1.1 [0.1 to 2.0], p=0.026) that favoured nabilone
  - MMSE ≤15 (n=25), there was a significant difference in SIB score (b= -4.6 [-7.3 to -1.8], p=0.003), that favoured placebo
  - ADAS-Cog scores (n=3) not analyzed

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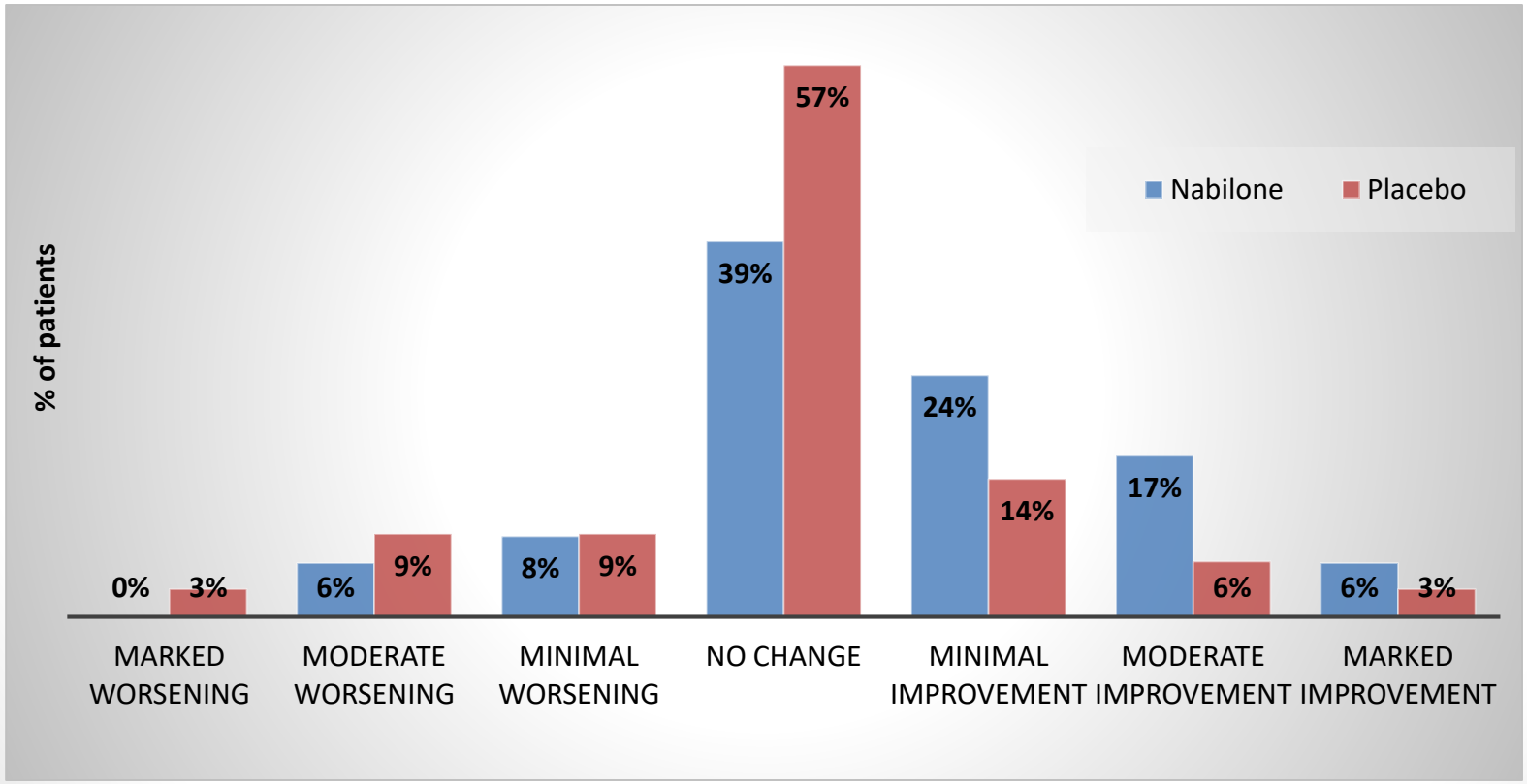
CGIC during nabilone versus placebo phases

- CGIC “minimal” to “marked” improvement (McNemar’s test, p=0.09)
  - 47% improved during nabilone
  - 23% improved during placebo



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No detectable difference in pain

- There were no treatment differences on the PAINAD scale (b= 0.03 [-0.22 to 0.27], p=0.82)
- PAINAD: The total score ranges from 0-10 points
  - 1-3=mild pain; 4-6=moderate pain; 7-10=severe pain.
  - These ranges are based on a standard 0-10 scale of pain, but have not been substantiated in the literature for this tool.
- Baseline average 2.6±1.4

nutrition and weight

- significant differences on nutrition (MNA-SF) (b= 0.2 [0.02 to 0.4], p=0.03), favouring nabilone
- MNA-SF: Max 14 points.
  - 0-7 Malnourished; 8-11 At risk of malnutrition; 12-14 Normal
- Baseline average 8.7±2.9

- No significant difference in weight change (kg) (b=0.01 [-0.69 to 0.71], p=0.97)
- Average baseline weight: 67.9±14.1 kg

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=0.02)
  - no differences in treatment-limiting sedation (5 vs. 1 McNemar's test, p=0.22)
  - 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=0.69)
  - study discontinuations (3 vs. 2 McNemar's test, p=0.08)
  - deaths (1 vs. 1)

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Study summary

- placebo controlled double-blind cross-over trial
  - no significant carry-over or treatment order effects detected
  - nonpharmacological interventions before trial, placebo run-in and washout, variable dose
- nabilone treatment was associated with a significant reduction in agitation over 6 weeks
- Tolerability good
  - increased sedation warranting cautious dosing
  - questions remain regarding cognitive effects
- pilot study with a relatively small sample size
- signal and feasibility support future studies

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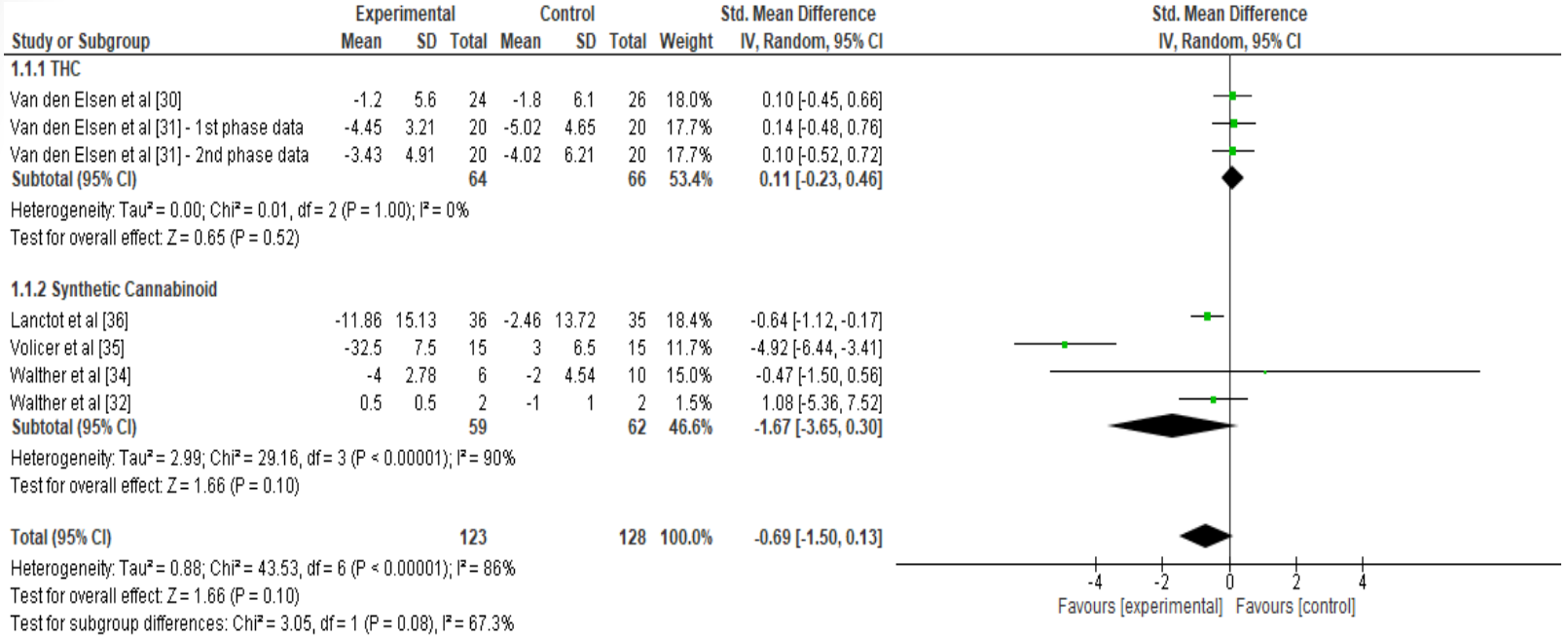
Meta-Analysis of Cannabinoids for Agitation



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 as a group on agitation (standard mean difference: -0.69, P = .10)
- significant heterogeneity ($\chi^2_6 = 43.53$, $P < .00001$, $I^2 = 86\%$)
- 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).

Ruthirakuhan et al 2019

Current Studies

Drug	Study
Namisol (Netherlands) (pure natural THC)	Phase 1 cross-over study, dosing: 3, 5, or 6.5 mg or placebo
Dronabinol (John's Hopkins)	Phase II
Nabilone (Sunnybrook)	Phase III

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 trial of a nabilone for agitation shows promise
  - Efficacy, but concerns around sedation

The Cannabis Act

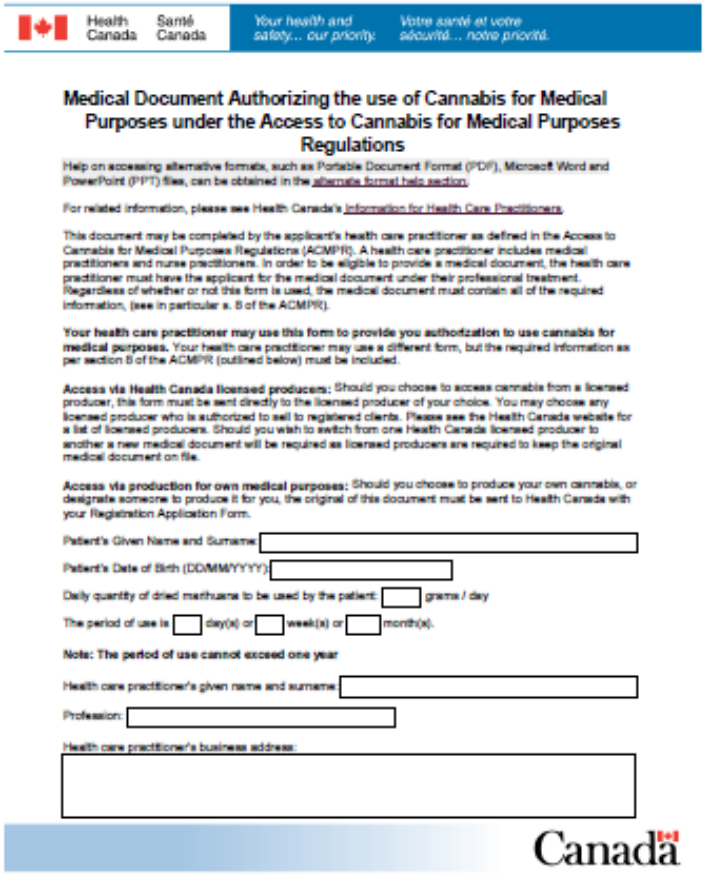
- Since legalization, the methods have changed and become more streamlined. The Cannabis Act came into play October 17, 2018
- Patients authorized by their health care provider (either a medical practitioner or nurse practitioner) are still able to access cannabis for medical purposes by:
  1. buying directly from a federally licensed seller
  2. registering with Health Canada to produce a limited amount of cannabis for their own medical purposes
  3. designating someone to produce it for them.

Ontario Cannabis Store site

- Dried Flowers
  - sativa, indica, and hybrid strains
- Pre-Rolled Joints
  - sativa, indica, and hybrid strains
- Oils/ Tinctures/ Topical ointments
  - bottled, sprays, and capsules containing all or isolated components of various strains
- Edibles
  - contain components, mostly CBD and/or THC, that is infused with any food that contains a fat-soluble component i.e.,- if using butter to make brownies, the butter would contain CBD and/or THC

Access to cannabis-medical practitioner

Medical Practitioners must provide this form to Health Canada for patients to obtain legally regulated medical cannabis.



Health Canada / Santé Canada — Your health and safety... our priority. / Votre santé et votre sécurité... notre priorité.

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations

Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the alternate format help section.

For related information, please see Health Canada's Information for Health Care Practitioners.

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 8 of the ACMPR).

Your health care practitioner may use this form to provide you authorization to use cannabis for medical purposes. Your health care practitioner may use a different form, but the required information as per section 8 of the ACMPR (outlined below) must be included.

Access via Health Canada licensed producers: Should you choose to access cannabis from a licensed producer, this form must be sent directly to the licensed producer of your choice. You may choose any licensed producer who is authorized to sell to registered clients. Please see the Health Canada website for a list of licensed producers. Should you wish to switch from one Health Canada licensed producer to another a new medical document will be required as licensed producers are required to keep the original medical document on file.

Access via production for own medical purposes: Should you choose to produce your own cannabis, or designate someone to produce it for you, the original of this document must be sent to Health Canada with your Registration Application Form.

Patient's Given Name and Surname:

Patient's Date of Birth (DD/MM/YYYY):

Daily quantity of dried marihuana to be used by the patient: ☐ grams / day

The period of use is ☐ day(s) or ☐ week(s) or ☐ month(s).

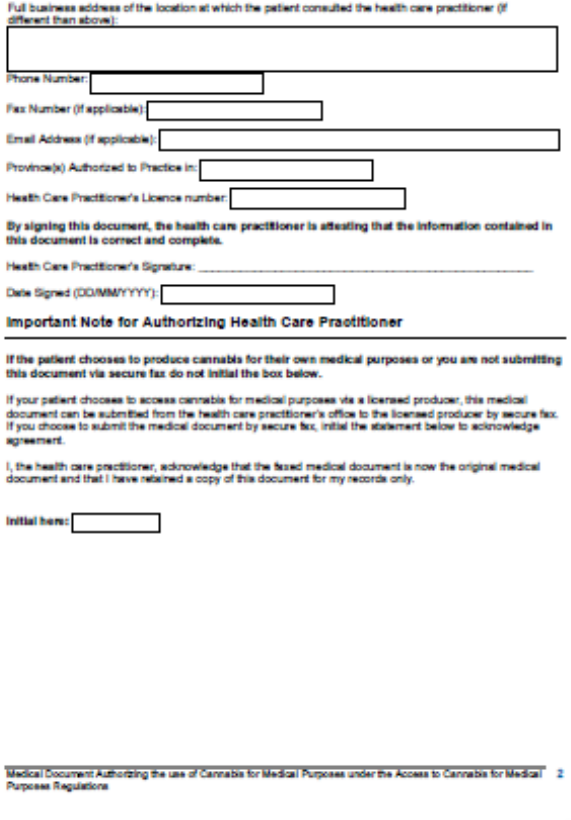
Note: The period of use cannot exceed one year

Health care practitioner's given name and surname:

Profession:

Health care practitioner's business address:

Canada



Full business address of the location at which the patient consulted the health care practitioner (if different than above):

Phone Number:

Fax Number (if applicable):

Email Address (if applicable):

Province(s) Authorized to Practice in:

Health Care Practitioner's Licence number:

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: _____

Date Signed (DD/MM/YYYY):

Important Note for Authorizing Health Care Practitioner

If the patient chooses to produce cannabis for their own medical purposes or you are not submitting this document via secure fax do not initial the box below.

If your patient chooses to access cannabis for medical purposes via a licensed producer, this medical document can be submitted from the health care practitioner's office to the licensed producer by secure fax. If you choose to submit the medical document by secure fax, initial the statement below to acknowledge agreement.

I, the health care practitioner, acknowledge that the faxed medical document is now the original medical document and that I have retained a copy of this document for my records only.

Initial here: ☐

Medical Document Authorizing the use of Cannabis for Medical Purposes under the Access to Cannabis for Medical Purposes Regulations 2

Access to Cannabis-provide by self

Health Canada / Santé Canada

Your health and safety... our priority. / Votre santé et votre sécurité... notre priorité.

Access to Cannabis for Medical Purposes Regulations

Production for Own Medical Purposes and Production by a Designated Person Registration Form

Questions

Please contact the Office of Medical Cannabis:
Toll-Free: 1-866-337-7705
Email: amo-bom@hc-sc.gc.ca

Mailing

Once completed and signed, your form is to be sent to Health Canada at the following mailing address:

Health Canada
Registration Process
Address Locator: 0302B
Ottawa, ON K1A 0K9

Privacy Notice

The personal information you provide to Health Canada is governed in accordance with the Privacy Act. We only collect the information we need to administer the Production for Own Medical Purposes and Production by a Designated Person Program authorized under the Access to Cannabis for Medical Purposes Regulations.

Purpose of collection: We require your personal information to process your request for registration as per sections 177(3) to 177(7) and 181(2) of the *Access to Cannabis for Medical Purposes Regulations*.

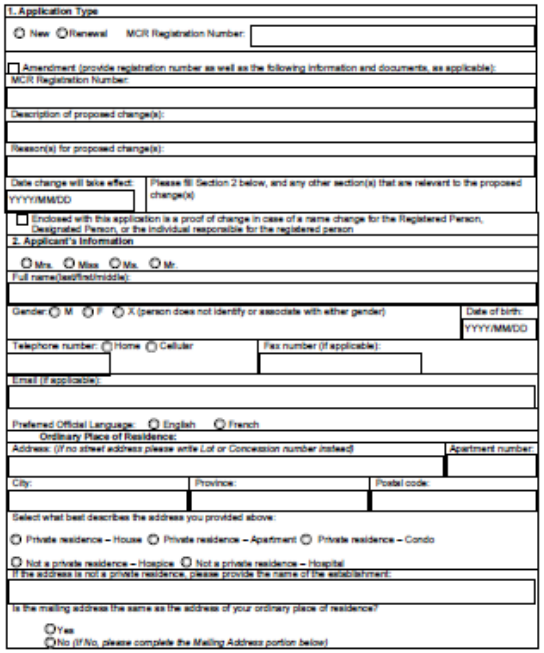
Other uses or disclosures: Your personal information may be shared with law enforcement entities to confirm your lawful possession and production of cannabis. In limited and specific situations, your personal information may be disclosed without your consent in accordance with subsection 8(2) of the *Privacy Act*.

Refusal to provide the information: Failure to provide the requested information will result in your request not being processed and your registration form and accompanying documents being returned.

For more information: This personal information collection is described in Info Source, available online at infosource.gc.ca. A Personal Information Bank (PIB) is under development and will be included in infosource.gc.ca.

Your rights under the Privacy Act: In addition to protecting your personal information, the *Privacy Act* gives you the right to request access to and correct your personal information. For more information about these rights, or about our privacy practices, please contact Privacy Coordinator at 613-946-3179 or privacy-vie.privee@hc-sc.gc.ca. You also have the right to file a complaint with the Privacy Commissioner of Canada if you think your personal information has been handled improperly.

Canada



1. Application Type

○ New ○ Renewal MCR Registration Number:

☐ Amendment (provide registration number as well as the following information and documents, as applicable):

MCR Registration Number:

Description of proposed change(s):

Reason(s) for proposed change(s):

Date change will take effect: YYYY/MM/DD

Please fill Section 2 below, and any other section(s) that are relevant to the proposed change(s)

☐ Enclosed with this application is a proof of change in case of a name change for the Registered Person, Designated Person, or the individual responsible for the registered person

2. Applicant's Information

○ Mrs. ○ Miss ○ Ms. ○ Mr.

Full name(last/first/middle):

Gender: ○ M ○ F ○ X (person does not identify or associate with either gender) Date of birth: YYYY/MM/DD

Telephone number: ○ Home ○ Cellular Fax number (if applicable):

Email (if applicable):

Preferred Official Language: ○ English ○ French

Ordinary Place of Residence:

Address: *(If no street address please write Lot or Concession number instead)* Apartment number:

City: Province: Postal code:

Select what best describes the address you provided above:

○ Private residence – House ○ Private residence – Apartment ○ Private residence – Condo

○ Not a private residence – Hospice ○ Not a private residence – Hospital

If the address is not a private residence, please provide the name of the establishment:

Is the mailing address the same as the address of your ordinary place of residence?

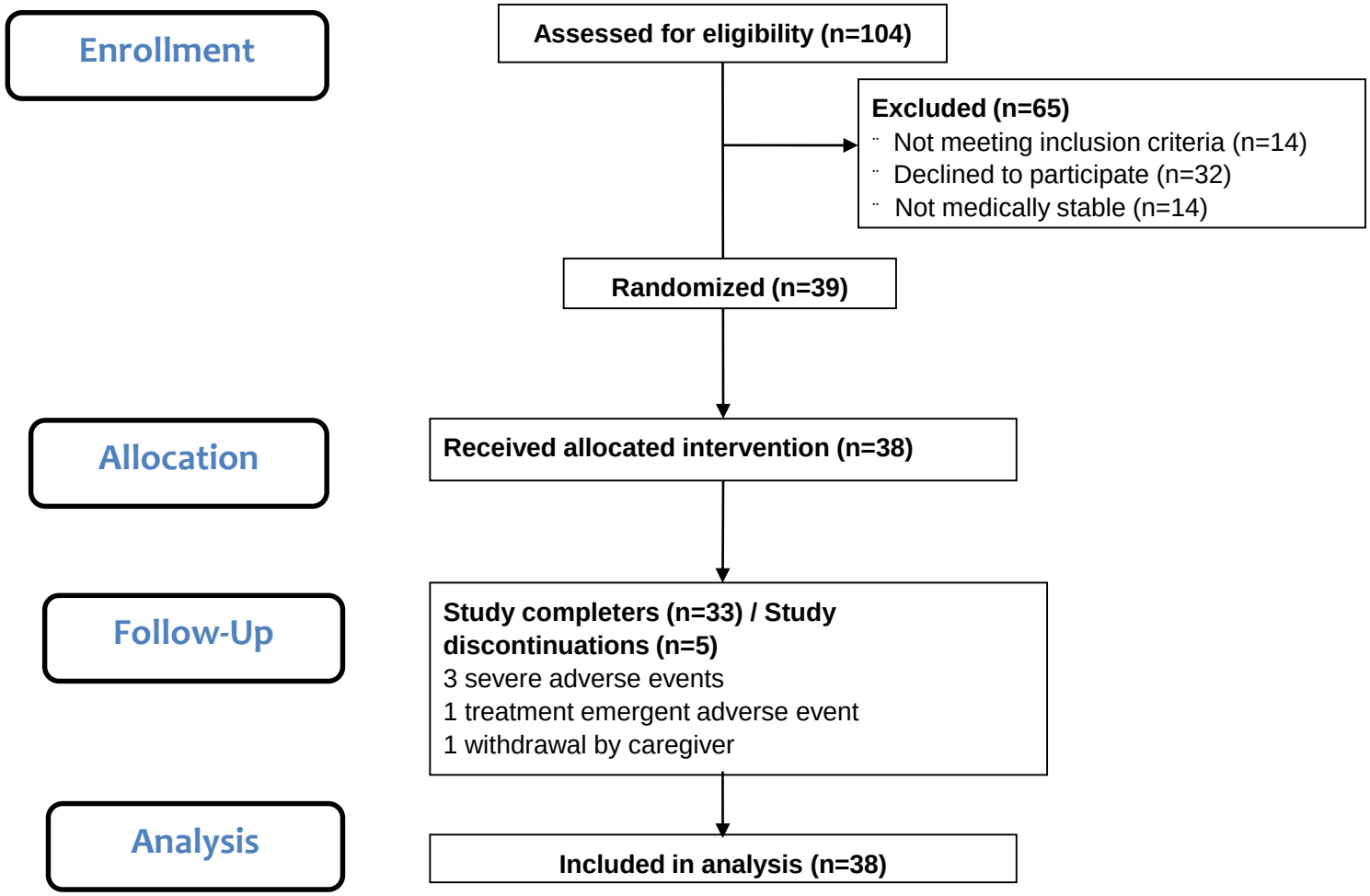
○ Yes
○ No *(If No, please complete the Mailing Address portion below)*

Medical marijuana dispensing concerns

- form, contents, dosage, and type may not be specified,
- type of marijuana and mode of delivery determined by dispensary employees
- growing and cultivation are largely unstandardized
  - Contents may still vary even when standardized
- safety concerns: incidents of pesticides, molds, and other contaminants, the consumption of which could lead to serious health problems, being found on plants
- facilitate recreational use of the drug

Intoxication and withdrawal

- Abrupt cessation of chronic or excessive cannabinoid use can results in a withdrawal syndrome
- features similar to those associated with cessation of plant cannabis use
- Typical symptoms include anxiety, depression, insomnia, increased drug craving, increased muscle tone or muscle twitching, chills and sweating, decreased appetite and headache.
- Treatment of intoxication and withdrawal is supportive and symptomatic, as no specific antidotes are available
  - intravenous fluids for dehydration
  - a short-acting benzodiazepine for agitation or anxiety
  - acetaminophen for pain or headache
  - antidepressant treatment reserved for depression persisting several days or a known independent comorbid mood disorder


Enrollment
Assessed for eligibility (n=104)
Excluded (n=65)
Not meeting inclusion criteria (n=14)
Declined to participate (n=32)
Not medically stable (n=14)
Randomized (n=39)
Allocation
Received allocated intervention (n=38)
Follow-Up
Study completers (n=33) / Study discontinuations (n=5)
3 severe adverse events
1 treatment emergent adverse event
1 withdrawal by caregiver
Analysis
Included in analysis (n=38)

Treatment difference on CMAI

- Cannabinoid
  - nabilone -4.0 [-6.5 to -1.5] NNT 4, NNH treatment limiting sedation 10
- Atypical antipsychotics
  - risperidone -1.17 [-2.02 to -0.32] (Ballard et al., 2006 Cochrane)
  - olanzapine -0.4 [-0.9 to 0.1] (Deberdt et al., 2005)
- Antidepressants
  - citalopram −2.38 [−4.13 to −0.63] (Porsteinsson et al., 2014 CitAD)
  - trazodone 5.18 [-2.86 to 13.22] (Martinón-Torres et al., 2004 Cochrane)
  - fluoxetine 2.80 [-5.84 to 11.44] (Seitz et al., 2011 Cochrane)

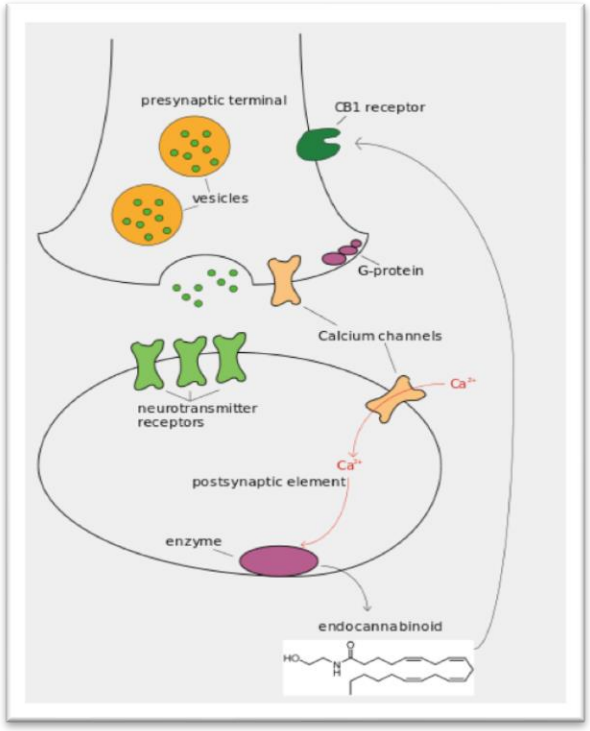
TEAEs

	N in Nabilone	N in Placebo
Total	31	14
Sedation (including lethargy)	17	6
Treatment limiting sedation	5	1
Falls	8	7
Bradycardia	1	0
Myoclonic Jerk	1	0
Elevated Urea Levels	1	0
Rash	1	0
Significant increase in NPS	1	2
Dizziness	1	0
Shakiness	0	1

SAEs

	N in Nabilone	N in Placebo
Total	5	4
Lethargy	2	0
Death	1	1
Critically high INR	1	0
Myocardial infarction	1	0
Cancer diagnosis	0	1
Pneumothorax	0	1
Sepsis due to UTI	0	1

endocannabinoids



- serve as neuromodulators via retrograde signaling
- Synthesized on demand from membrane phospholipids
- Inactivated by transport back into cell or hydrolysis by fatty acid amide hydrolase (FAAH)

Medical marijuana

- 2015 the government introduced new 'marijuana for medical purposes regulations', which allow physicians to 'authorize' medical marijuana use for virtually any health condition for which this is considered beneficial; supply is facilitated by licensed commercial producers.
- Dispensing concerns
  - form, contents, dosage, and type cannot be specified, as they would be in a typical drug prescription
  - type of marijuana and mode of delivery determined by dispensary employees
  - growing and cultivation are largely unstandardized
  - safety concerns: incidents of pesticides, molds, and other contaminants, the consumption of which could lead to serious health problems, being found on plants
  - facilitate recreational use of the drug

Patient demographics (n=38)

Baseline Demographics	
Age	87±10
Sex (%M)	77%
% inpatient	72%
No. concomitant psychotropic medications	1.8±0.7
antidepressant	87 %
cholinesterase inhibitor	53%
atypical antipsychotic	45%
memantine	29%
benzodiazepine	5%

Patient characteristics (n=38)

Baseline Characteristics	
CMAI	67.9±17.6
Met IPA criteria for agitation	97%
NPI-NH total	34.3±15.8
NPI-NH agitation/aggression	7.1±3.3
NPI-NH total caregiver distress score	12.7±7.9
MMSE	6.5±6.8
CGI severity	3.7±0.9
Moderately ill	50%
Markedly ill	29%
Severely ill	18%
Extremely ill	3%

ECS in AD

CB1—excitotoxicity

- CB1 possibly reduced in AD (region specific?)
- CB1 receptors regulate neurotransmitters involved in excitotoxic neurodegenerative processes
- CB1 agonists in limbic system inhibit GABA release and modulate glutamate release
- CB1 agonists prevented Aβ - induced neurotoxicity in vitro [Milton 2002].
- ↓ nitric oxide production led to ↓ tau protein hyperphosphorylation [Esposito et al 2006].

CB2—neuroinflammation

- CB2 receptors upregulated with neuroinflammation in AD
- microglia activation and migration regulated by CB2 receptors
- CB2 agonists suppress the neuroinflammatory process in activated microglia [Ehrhart et al 2005]
- CB2 agonists may lead to β - amyloid removal [Tolon et al 2009; Ehrhart et al 2005]

CB_1/CB_2 agonists prevent microglial activation, led to improved memory performance in rat models of AD [Marchalant 2008] and normal aging

Drug	Authors, Year	Study Design/Intervention	Number of participants	Findings
THC	Van den Elsen et al, 2015	Double-blind, repeated cross-over .75 mg BID vs 1.5 mg BID vs placebo, 6 weeks	22 patients with dementia + NPS	-no change in NPS -well tolerated
	Van den Elsen et al., 2015	Double-blind, placebo-controlled RCT 1.5 mg TID vs placebo, 6 weeks	24 patients with dementia + NPS	-no change in NPS -well tolerated
Dronabinol (synthetic THC)	Woodward et al, 2014	Retrospective chart review 7.03 mg for 16 days	40 inpatients with dementia + NPS	-decrease in agitation/aggression -questionable tolerability
	Walther et al., 2006	Open-label 2.5mg for 2 weeks	6 (5 patients with AD, 1 patient with VAD)	-decrease in nocturnal motor activity and agitation -well tolerated
	Walther et al., 2011	Placebo-controlled RCT 2.5 mg for 2 weeks	2 patients with AD +nighttime agitation	-short-term decrease in nocturnal motor activity, before return to baseline
	Mahlberg and Walther, 2007	Placebo-controlled study 2.5 mg for 2 weeks	24 patients with AD + agitation	-decrease in nocturnal motor activity -well-tolerated
	Volicer et al, 1996	Placebo-controlled cross over study 2.5 mg for 6 weeks	11 anorexic patients with probably AD	-decrease in agitation -questionable tolerability
Nabilone (synthetic THC analogue)	Passmore, 2008	Case study (N=1) 0.5 mg daily, increased to 0.5 mg BID for 6 weeks	1 patient with AD + NPS	-decrease in agitation -well-tolerated

Trials with THC

Drug	Authors, Year	Study Design/ Intervention	Number of participants	Findings	Limitations
THC	Van den Elsen GA et al, 2015	Double-blind, repeated cross-over .75 mg BID vs 1.5 mg BID vs placebo, 6 weeks	22 patients with dementia + NPS	-no change in NPS -well tolerated	- Short duration (2 weeks per treatment phase)
	Van den Elsen GA et al., 2015	Double-blind, placebo-controlled RCT 1.5 mg TID vs placebo, 6 weeks	24 patients with dementia + NPS	-no change in NPS -well tolerated	-(Not agitated) -Placebo response

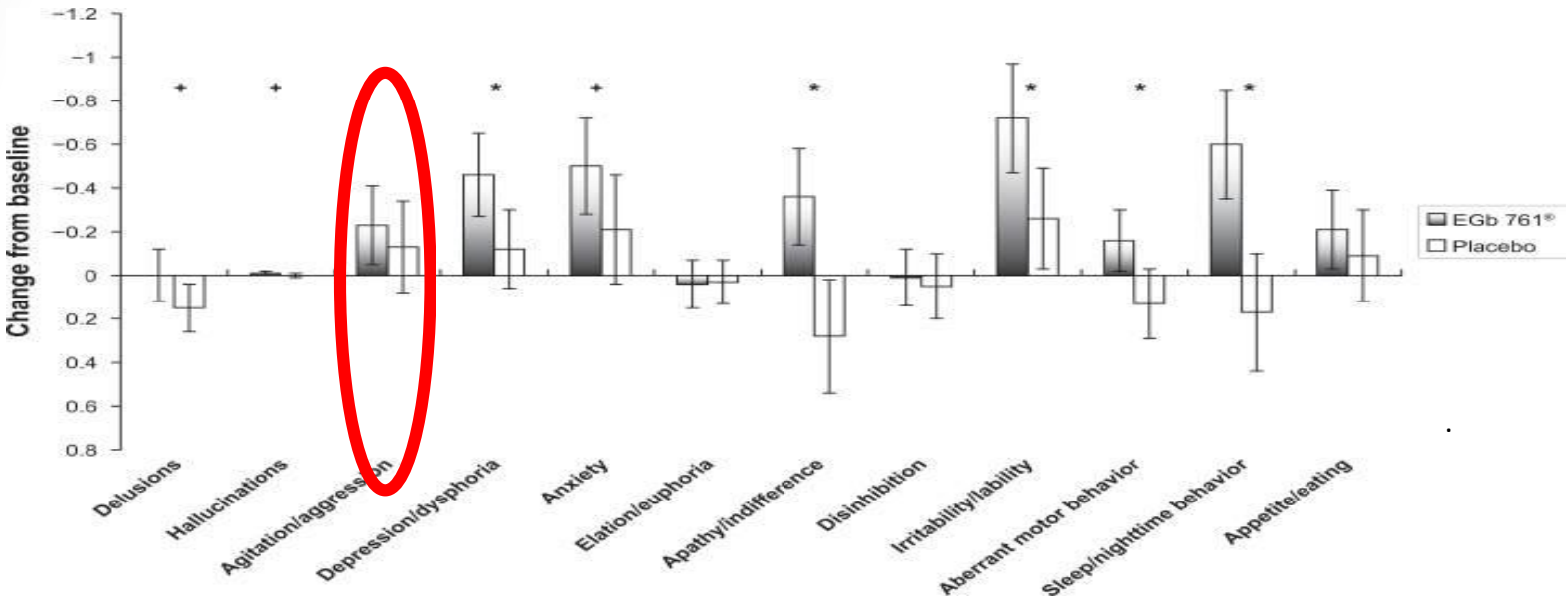
Ruthirakuhan et al 2019

Trials with Synthetic CB

Drug	Authors, Year	Study Design/ Intervention	Number of participants	Findings	Limitations
Dronabinol (synthetic THC)	Volicer et al, 1996	Placebo-controlled cross over 2.5 mg for 6 weeks	11 anorexic + AD	-⇓ agitation -questionable tolerability	- sample size
	Mahlberg, 2007	Placebo-controlled 2.5 mg for 2 weeks	24 AD + agitation	-⇓ nocturnal motor activity -well-tolerated	- duration
	Walther et al., 2011	Placebo-controlled cross-over 2.5 mg for 2 weeks	2 AD + nighttime agitation	-short-term ⇓ nocturnal motor activity, tolerance	- duration - sample size
Nabilone (synthetic THC analogue)	Passmore, 2008	Case study (N=1) 0.5 mg OD, increased to 0.5 mg BID x 6 wks	1 AD + NPS	-⇓ agitation -well-tolerated	- No placebo - sample size

Ruthirakuhan et al 2019

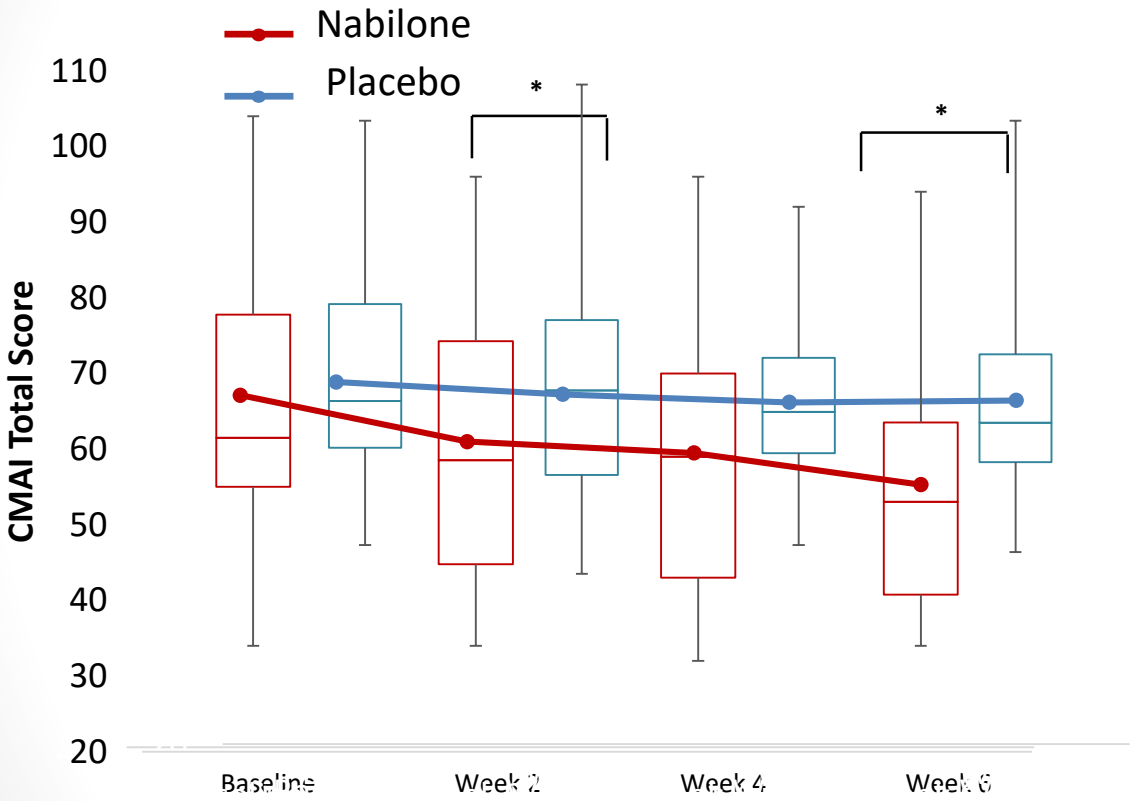
Ginkgo Biloba



- RCT in 410 outpatients with mild to moderate dementia (AD ± cerebrovascular disease, vascular dementia) with NPS (NPI>=5)
- Mechanisms of action include increasing cerebral blood flow, antioxidant and antiinflammatory effects, with antiplatelet effects

Bachinskaya, et al. Neuropsychiatr Dis Treat. 2011;7:209-215

Agitation (CMAI total) — primary outcome

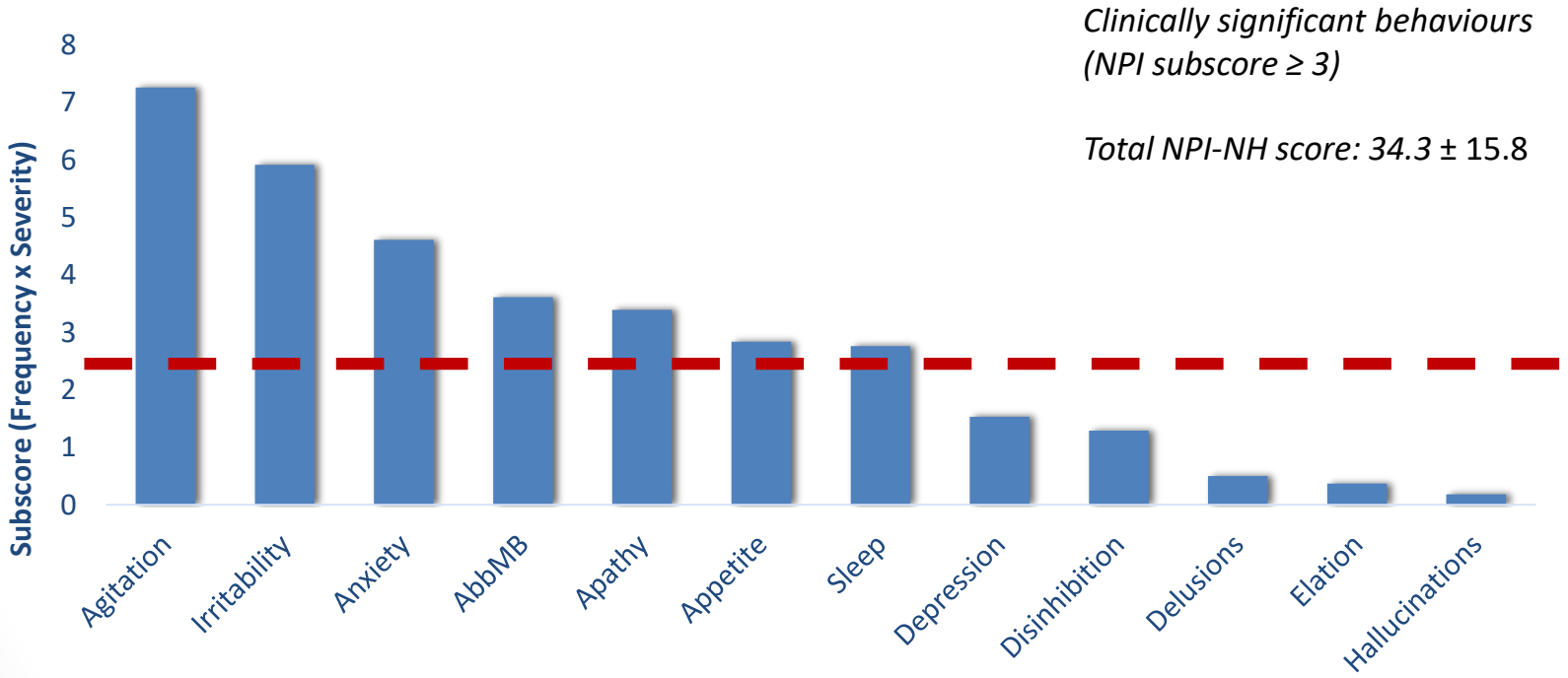


- estimated treatment difference [95% CIs] on CMAI was b= -4.0 [-6.5 to -1.5], p=0.003 favouring nabilone
- no cross-over effect (t(32)=1.6, p=0.11)
- no treatment order effect (t(31)=0.2, p=0.85)
- *significant differences
  - Week 2--nabilone: 62.5±19.2 versus placebo 68.3±16.3, (t(32)= -2.39, p=0.03);
  - Week 6/endpoint--nabilone: 55.8±15.9 versus placebo: 65.9±13.7, (t(32)=-3.77, p=0.001).

# in Nab.	37	33	30	30
# in Plb.	36	33	33	33

Lanctôt et al 2019

Neuropsychiatric Symptoms (NPI-NH)



Clinically significant behaviours (NPI subscore ≥ 3)

Total NPI-NH score: 34.3 ± 15.8

Lanctôt et al 2019