Cannabis and dementia: clearing the smoke

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HURVITZ BRAIN SCIENCES PROGRAM

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

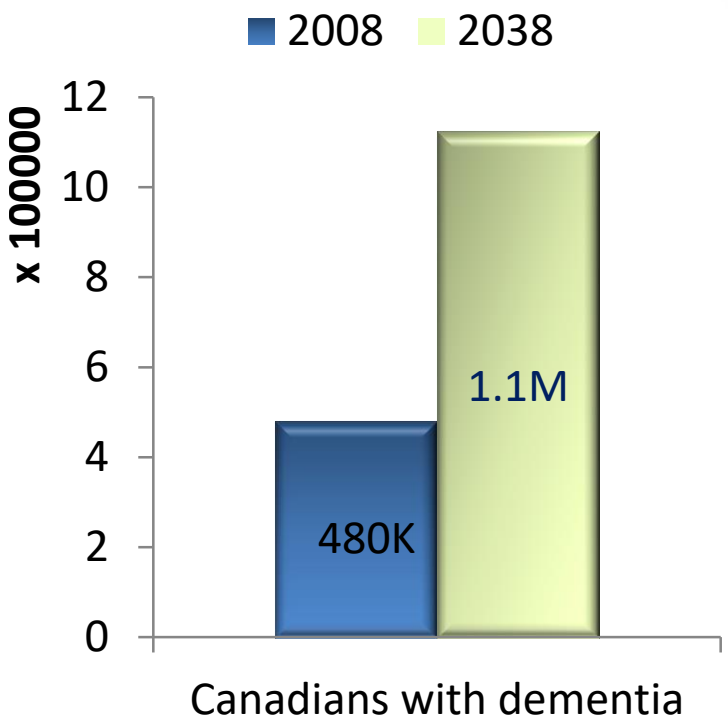
AGITATION IN ALZHEIMER'S DISEASE

Dementia-the facts

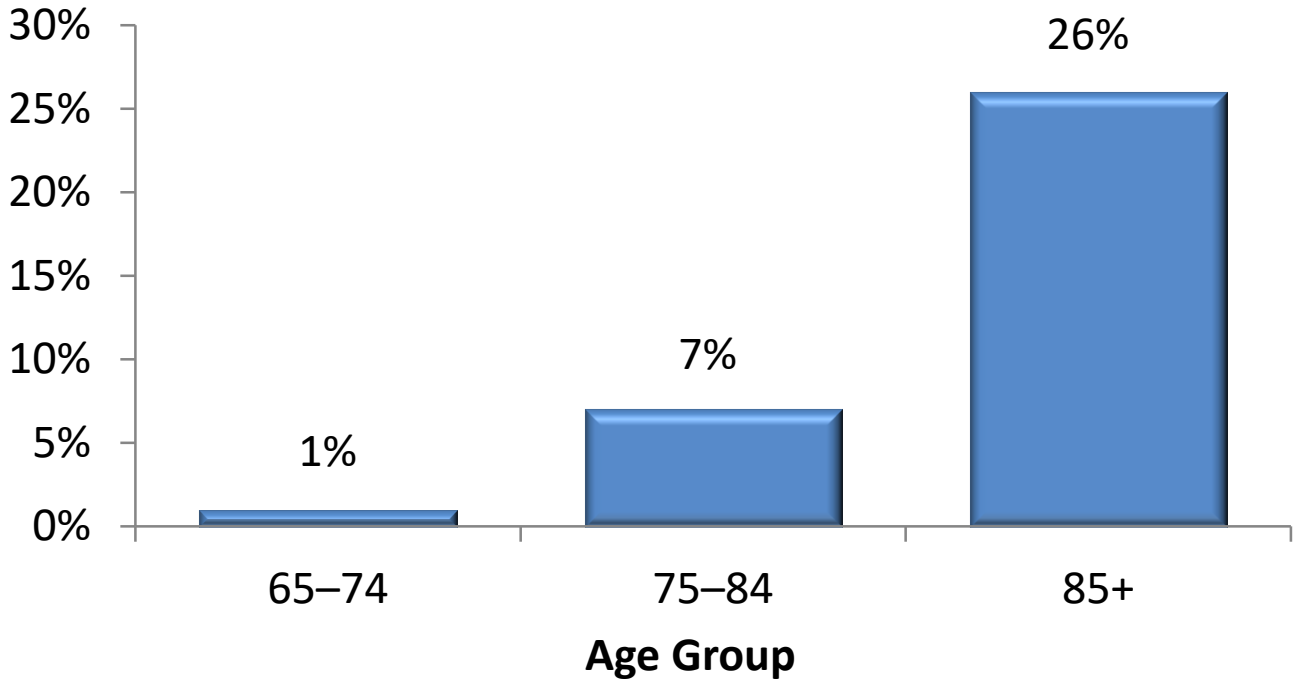
- sustained deterioration of cognitive ability sufficiently severe to impair occupational or social functioning (DSM-5)
- Major cause of disability and death in developed countries
- 4th leading cause of death in the US and Canada

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

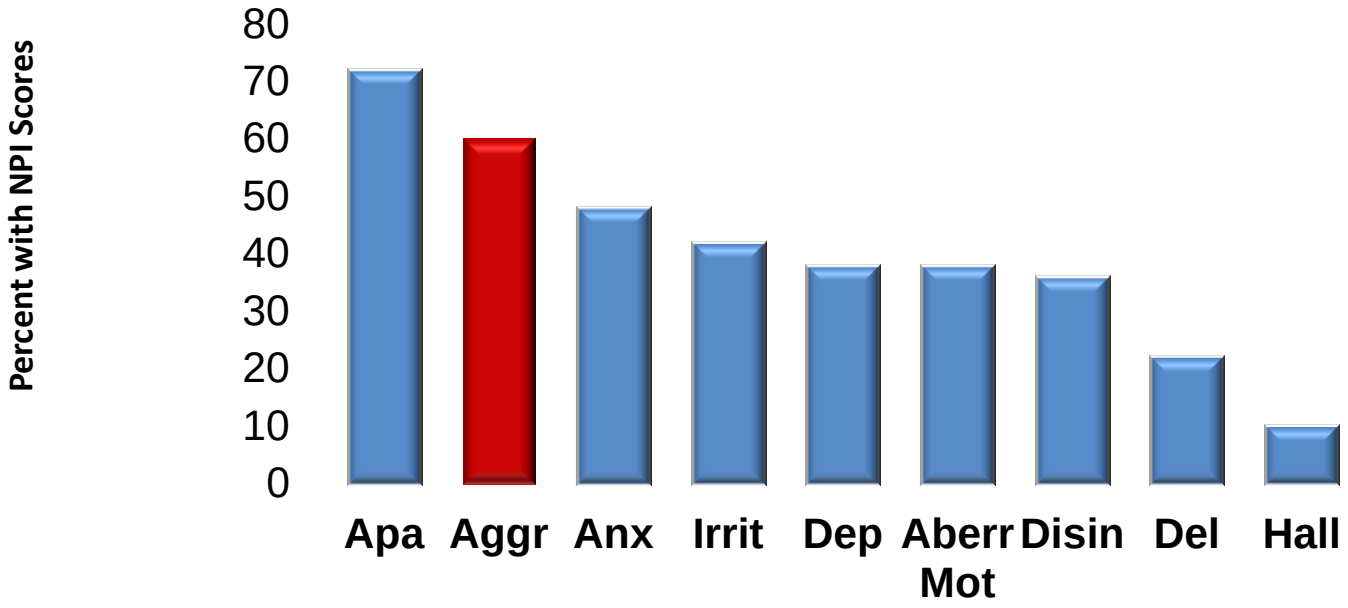
Behaviour

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

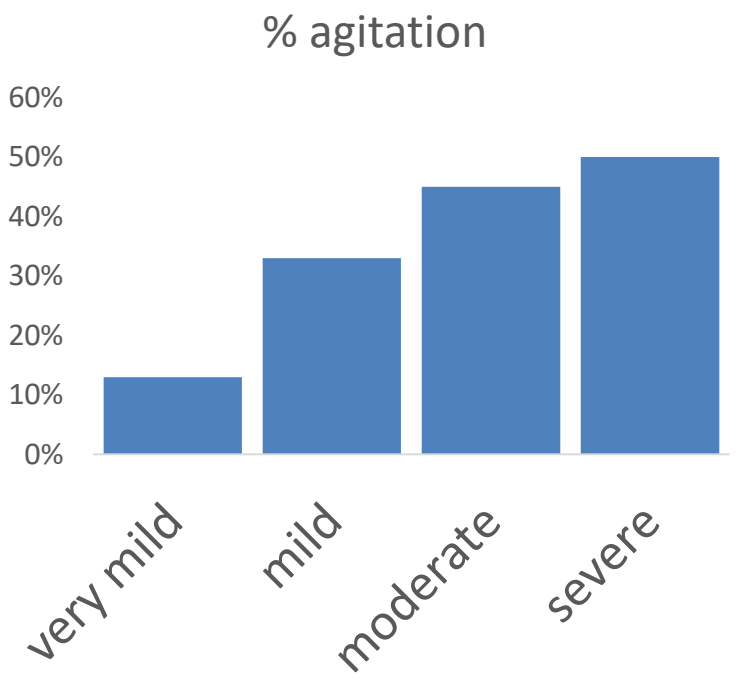
- IPA Criteria:
  - occurring in patients with cognitive impairment or dementia
  - behavior consistent with emotional distress
  - manifesting excessive motor activity, verbal aggression, or physical aggression
  - cause excess disability and are not solely attributable to another disorder (psychiatric,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

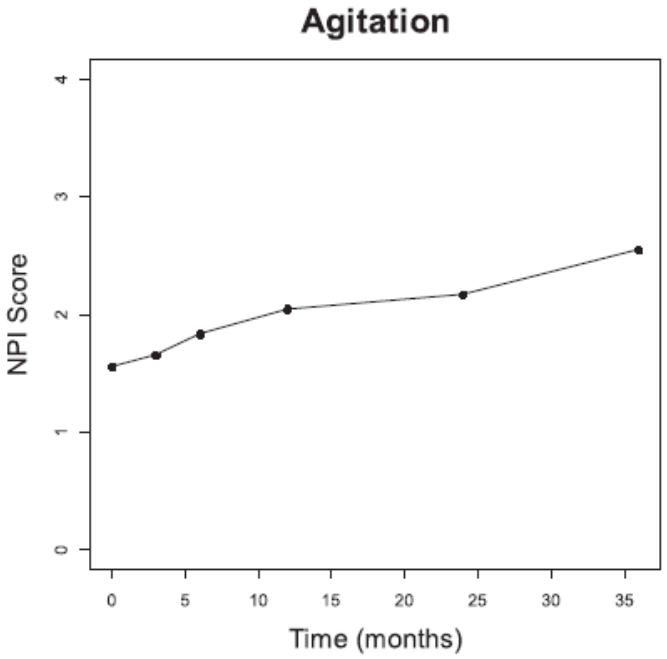
Prevalence of agitation increases with severity



- 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 impacts patients and caregivers

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

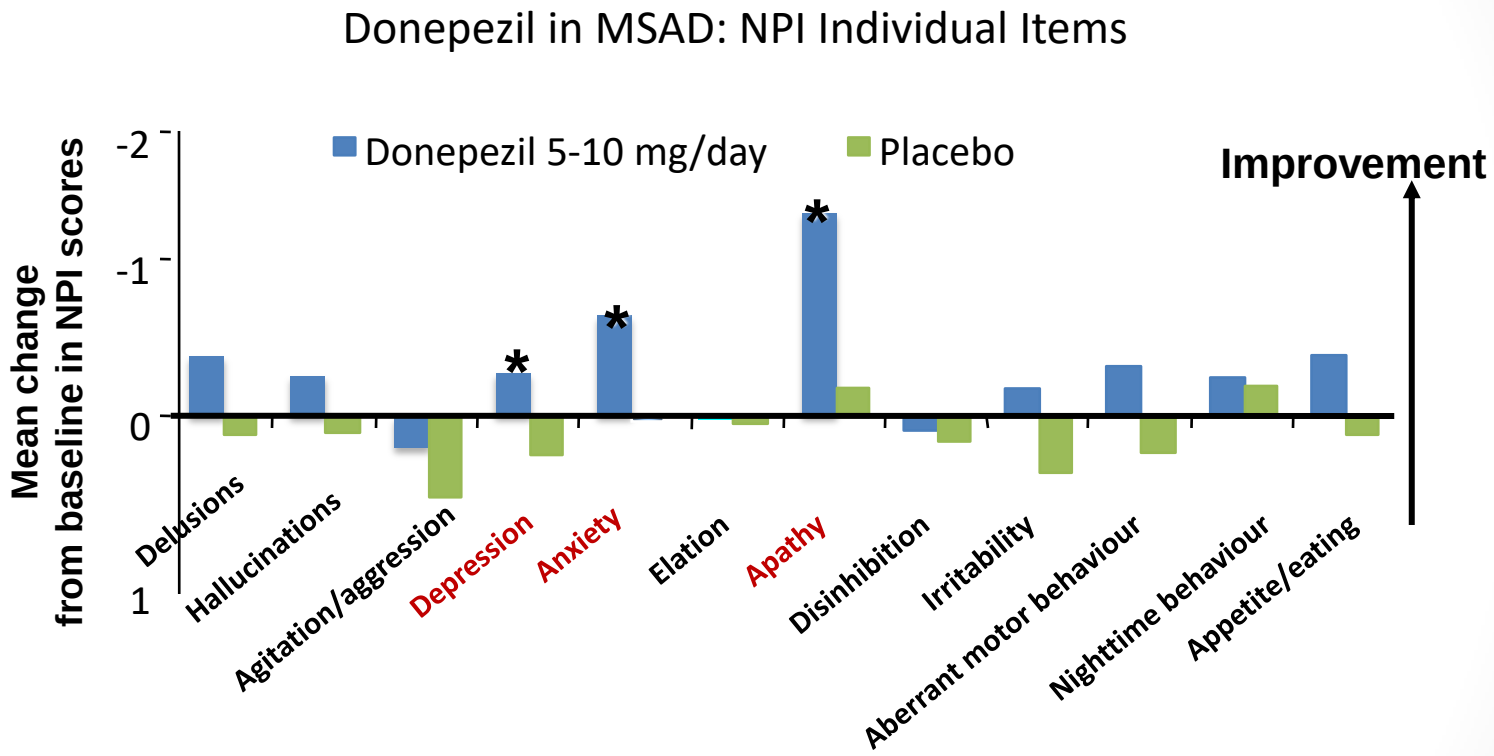
- systematic review of 160 studies of non-pharmacological interventions
- agitation in dementia people over 50 years of age in care facility settings
- various activities may help to reduce mild-to-moderate agitation
  - music therapy and sensory interventions (massage, therapeutic touch and multisensory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

Livingston et al. 2014

Medications for agitation

- antidementia medications
- antipsychotics
- antidepressants

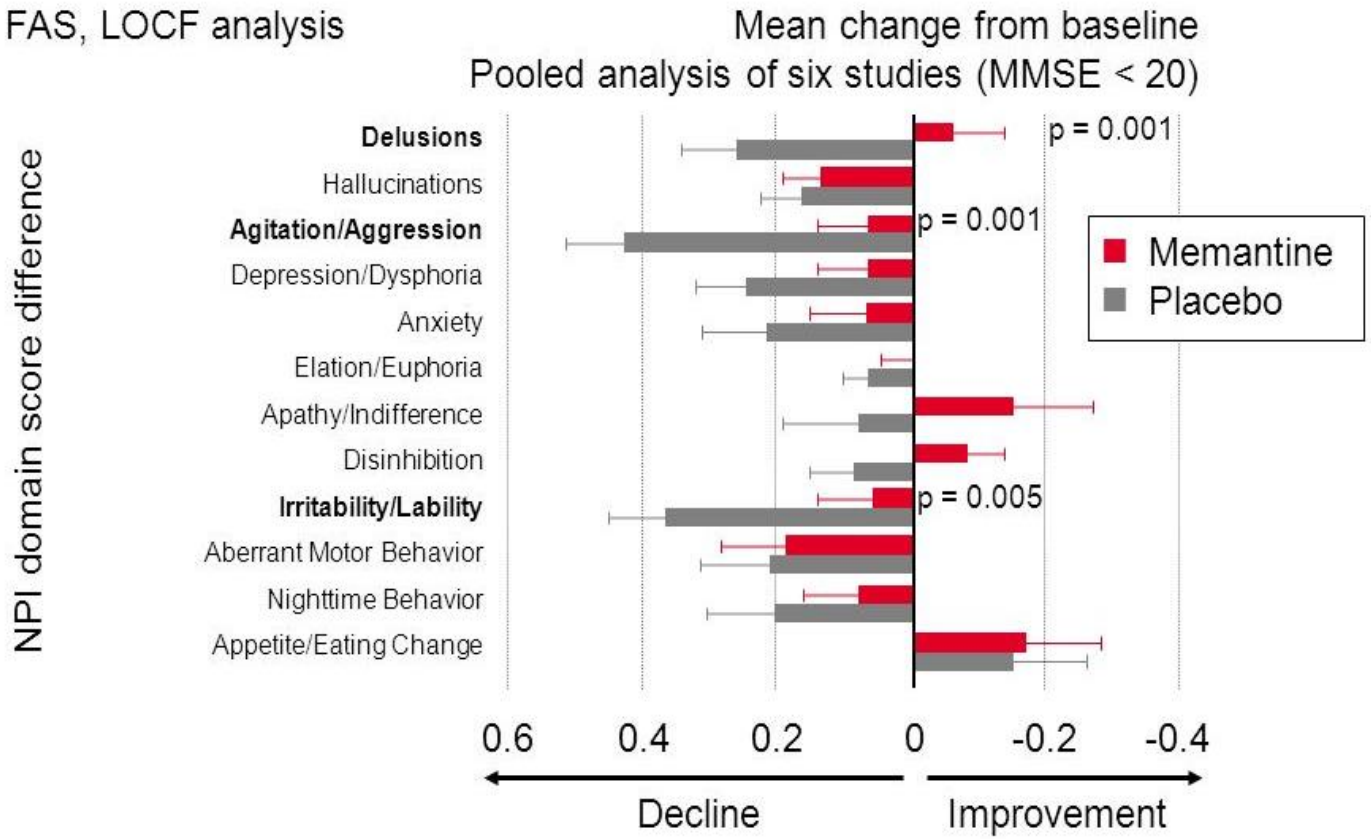
Anti-dementia medications may keep agitation from emerging



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

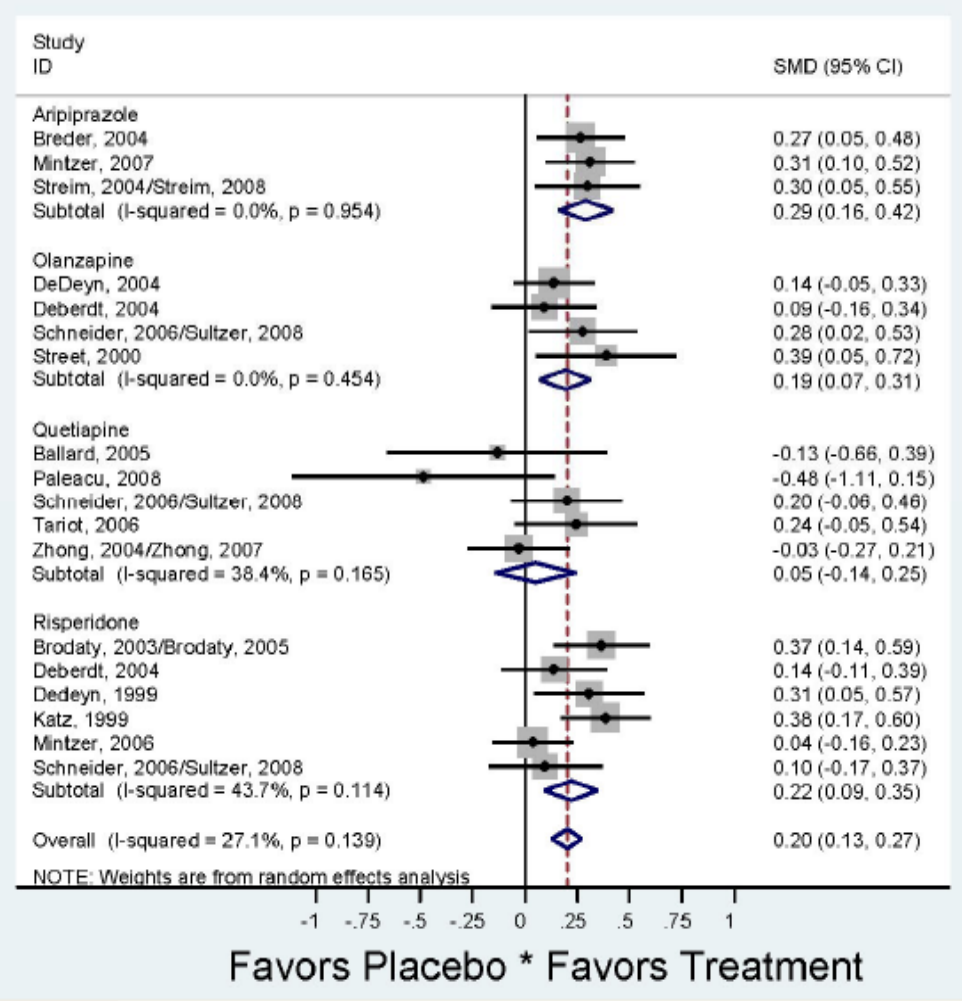
Gauthier et al. 2002

Memantine may help agitation from emerging



Gauthier et al., Int J Geriar Psychiatry 2008

Antipsychotics help agitation, but with risks



- 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

Certain antidepressants can help-more effective in early AD

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)

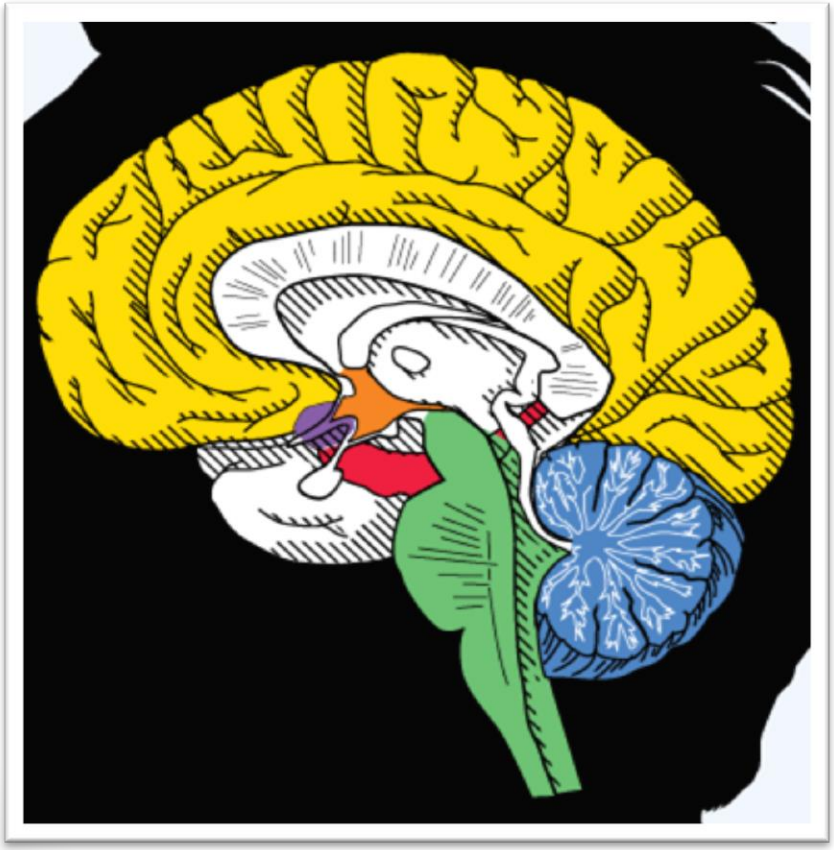
Porsteinsson et al JAMA 2014

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

Drugs related to marijuana work on the 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

Possible benefits of CB1 and CB2 activation

Clinically

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

Pathological processes

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

Reviewed by Liu et al, 2016

Cannabis

- 2 major neuroactive components in cannabis
  - psychoactive Δ9-tetrahydro-cannabinol (Δ9-THC)
  - non-psychoactive cannabidiol (CBD) (no '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 directly activates the endocannabinoid system

Devinsky et al 2014

Cannabidiol (CBD)

- CBD enhances endocannabinoid signaling
- CBD interacts with many non-endocannabinoid signaling systems: It is a “multi-target” drug
- 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
- preparations with high CBD:Δ9-THC ratios are less likely to cause psychotic symptoms

Devinsky et al 2014

Medications related to cannabis

Cannabinoid	MOA	Indication
dronabinol (Marinol ®)	• synthetic THC	Antiemetic Appetite and weight loss (AIDS)
nabilone (Cesamet ®)	• THC derivative	Antiemetic
THC and cannabidiol (Sativex ®)	• Cannabis extract	Neuropathic pain in multiple sclerosis
THC (Namisol ®)	• pure natural THC (>98%)	n/a
Cannabidiol (Epidiolex®)	• CBD oil	anticonvulsant

Double-blind, placebo controlled trials

THC—2 negative trials, low dose, not in agitation

- 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—no clinical trials

- ⇓ agitation, well tolerated in single patient (Passmore, 2008)

CBD—no clinical trials

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

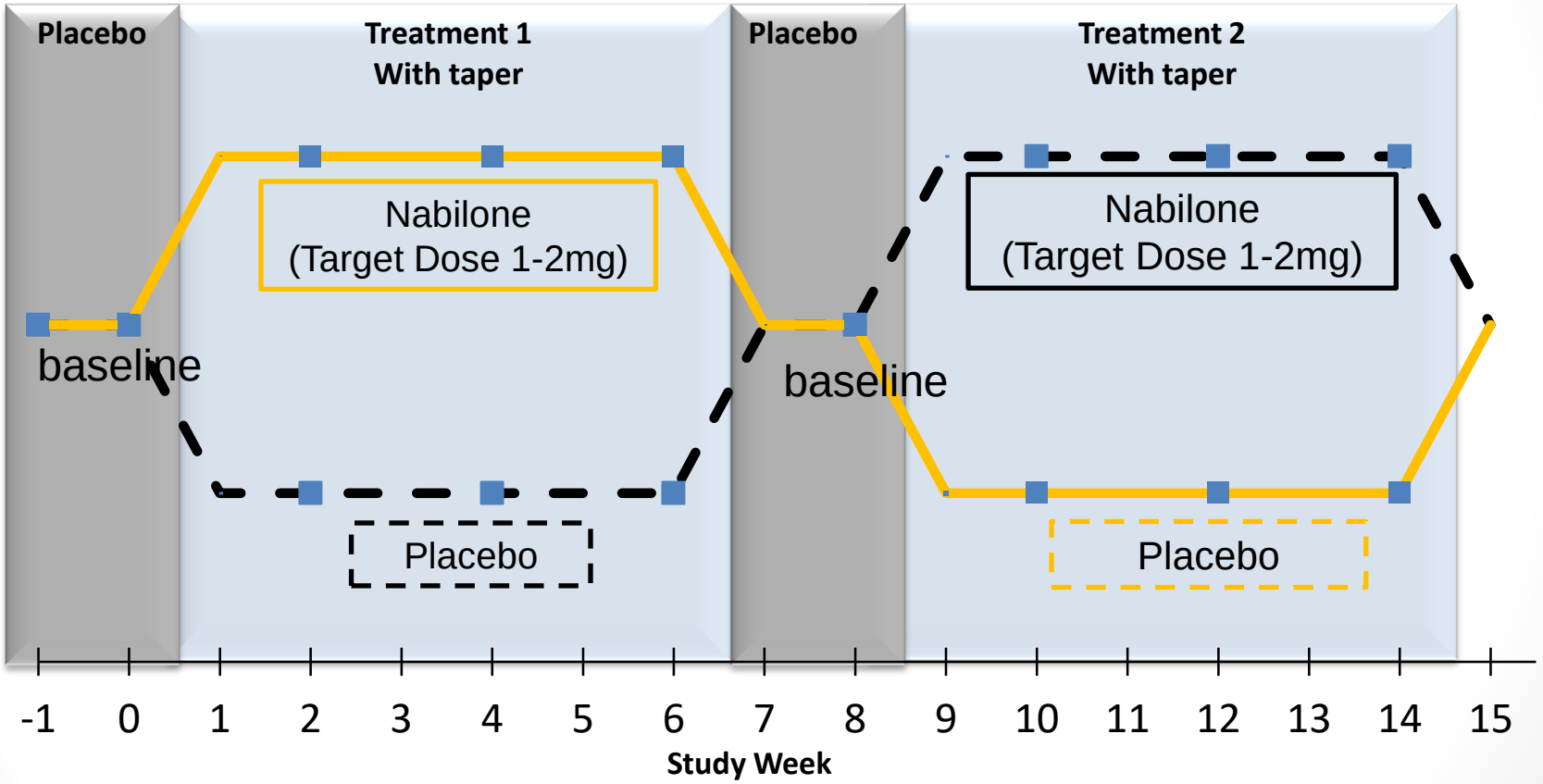
Nabilone in agitation trial

- nabilone:
  - synthetic derivative of THC
  - high oral bioavailability
  - duration of action 8-12 hours, given b.i.d.
  - marketed for nausea and vomiting
  - target dose 1-2 mg/d

- Participants
  - N=38 with moderate to severe Alzheimer's disease and agitation
  - No delusions or hallucinations

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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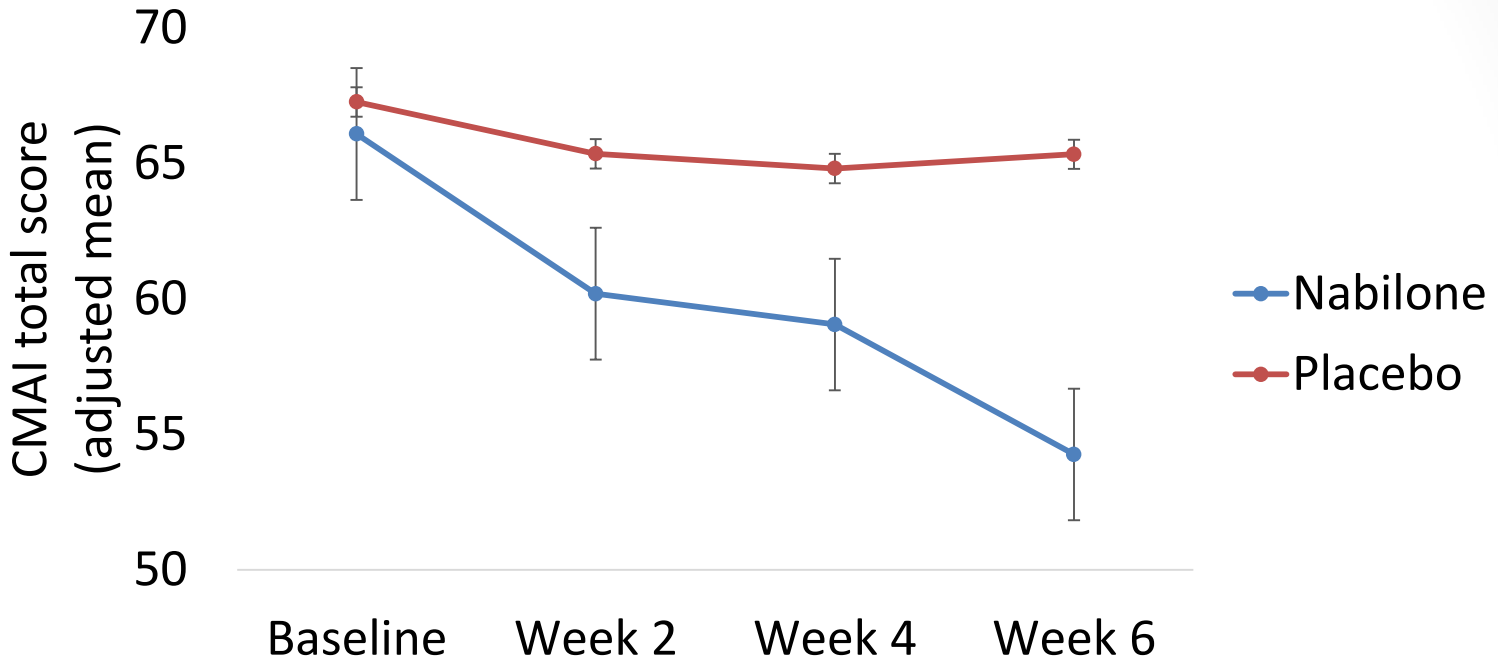
Agitation improved significantly during nabilone compared to the placebo phase



- estimated treatment difference [95% CIs] on CMAI was b= -4.0 [-6.5 to -1.5], p=0.003 favouring nabilone
- *significant differences
  - Week 2—nabilone 5 points lower(t(32)= -2.39, p=0.03);
  - Week 6/endpoint– nabilone 10 points lower, (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

Lanctôt et al 2019

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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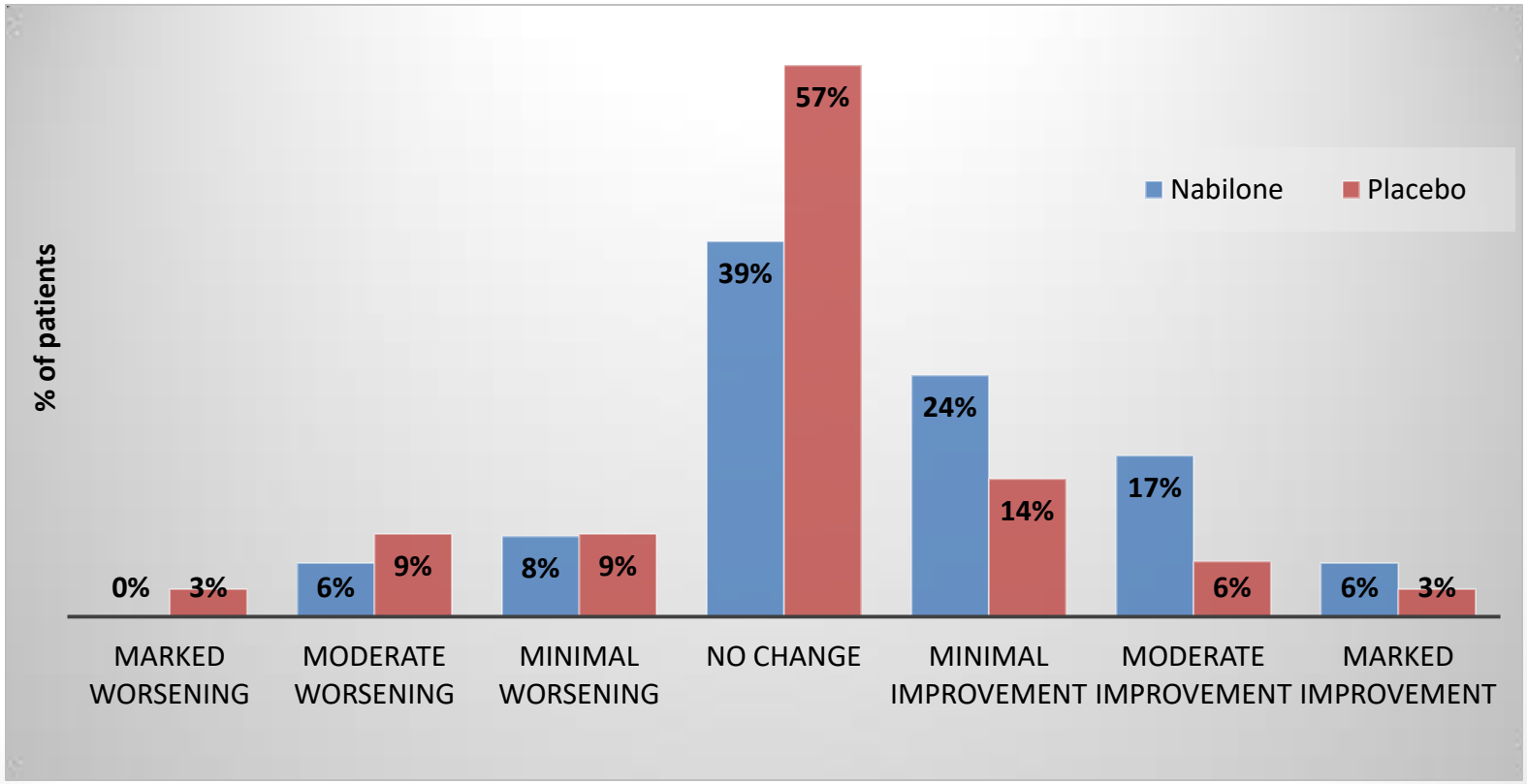
Clinical significance

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



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The pain outcome

- There were no treatment differences on the PAINAD scale
  - (b= 0.03 [-0.22 to 0.27], p=0.82)
- Participants had low pain
  - Baseline average 2.6±1.4
  - Total score ranges from 0-10 points, 1-3=mild pain
- Higher pain predicted improved agitation

nutrition and weight

- significant differences on nutrition favouring nabilone
  - (MNA-SF) (b= 0.2 [0.02 to 0.4], p=0.03),

- No significant difference in weight change
  - (b=0.01 [-0.69 to 0.71], p=0.97)
  - Average baseline weight: 67.9±14.1 kg (not underweight by BMI)

Well-tolerated

- 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 improved 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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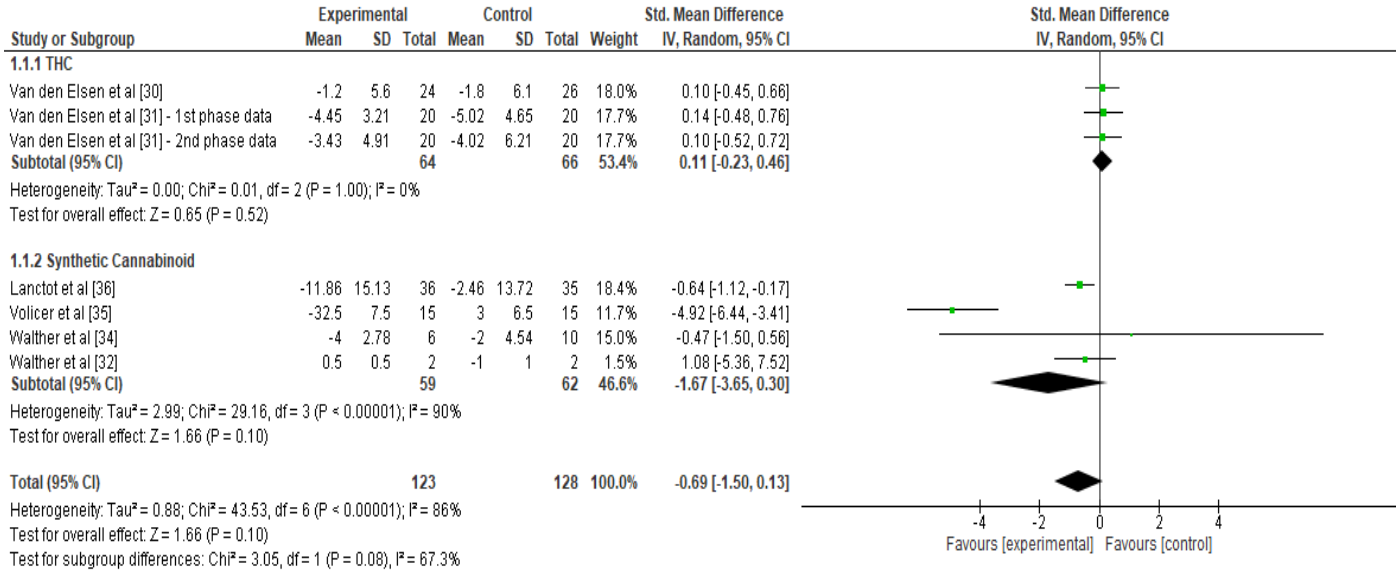
Meta-Analysis of Cannabinoids for Agitation



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—drug or dose?
  - (standard mean difference: -0.69, P = .10)
- significant heterogeneity
  - ($\chi^2_6 = 43.53$, $P < .00001$, $I^2 = 86\%$)
- Possible greater improvement with synthetic over THC
  - ($\chi^2_1 = 3.05$, $P = .08$)
- larger effect on agitation with greater cognitive impairment
  - ($B = 0.27$, $t_6 = 2.93$, $P = .03$)

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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