Cannabis and dementia: Weeding out the evidence

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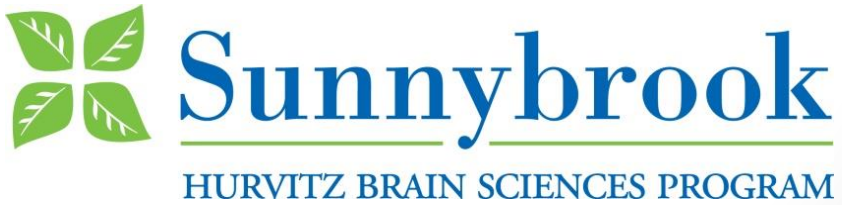

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CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- No medications discussed in this presentation are endorsed for clinical use
- Cannabinoids are not approved in dementia

Learning objectives

- At the end of this presentation learners will:
  - be aware of the major cannabinoid receptors and their functions
  - know the strength of evidence supporting use in Alzheimer’s disease
  - describe new results on efficacy and safety of nabilone for treatment of agitation in dementia

Endocannabinoid system (ECS)

- cannabinoid receptors and their endogenous lipid ligands identified
- triggered exponential growth of studies exploring ECS as a possible therapeutic target

Stimulation of the ECS has psychotropic effects

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

ECS may be relevant 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

Possible benefits of CB1 and CB2 activation for agitation in AD

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

Cannabinoids trials in AD

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)

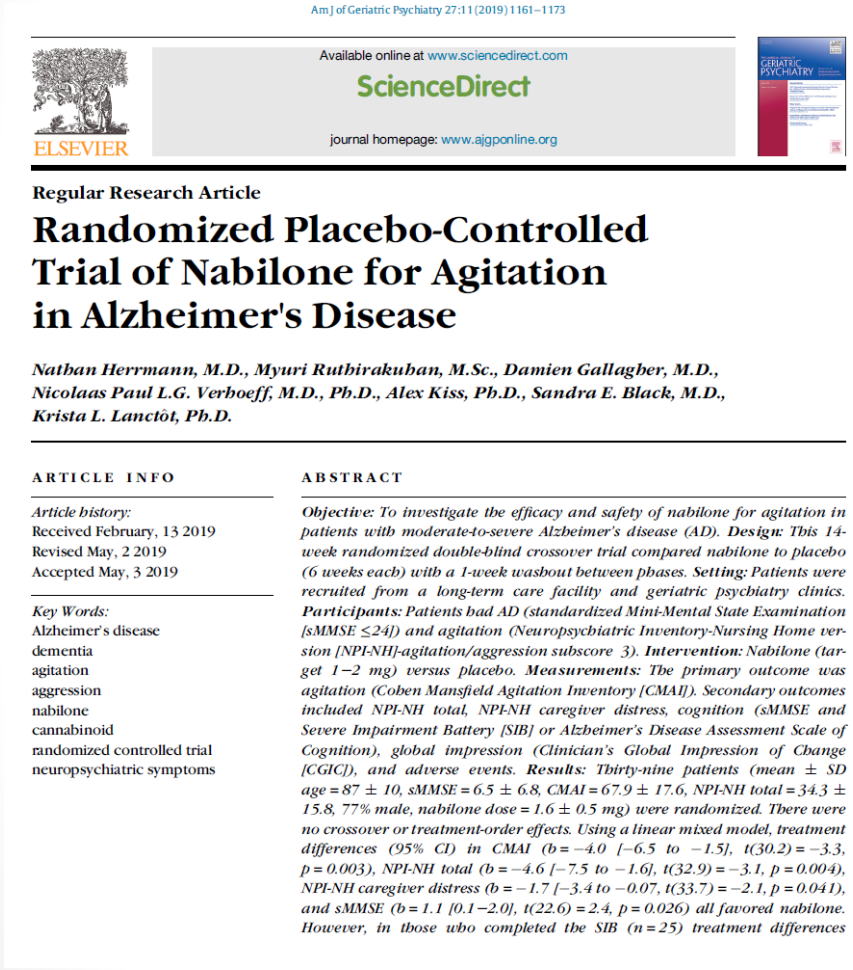
Dronabinol (synthetic THC)—positive trials, few study participants/short duration

- 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 (THC analogue)—no trials

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

Nabilone trial



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Regular Research Article

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

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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*

- Double blind, placebo-controlled, cross-over trial in 38 patients with agitation and AD
- efficacy and safety of nabilone (1-2 mg/d) versus placebo (6 weeks each)

Société Alzheimer Society CANADA

Alzheimer's Drug Discovery Foundation

intervention

- nabilone:
  - synthetic derivative of THC
  - CB1 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

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Study Participants (n=39)

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

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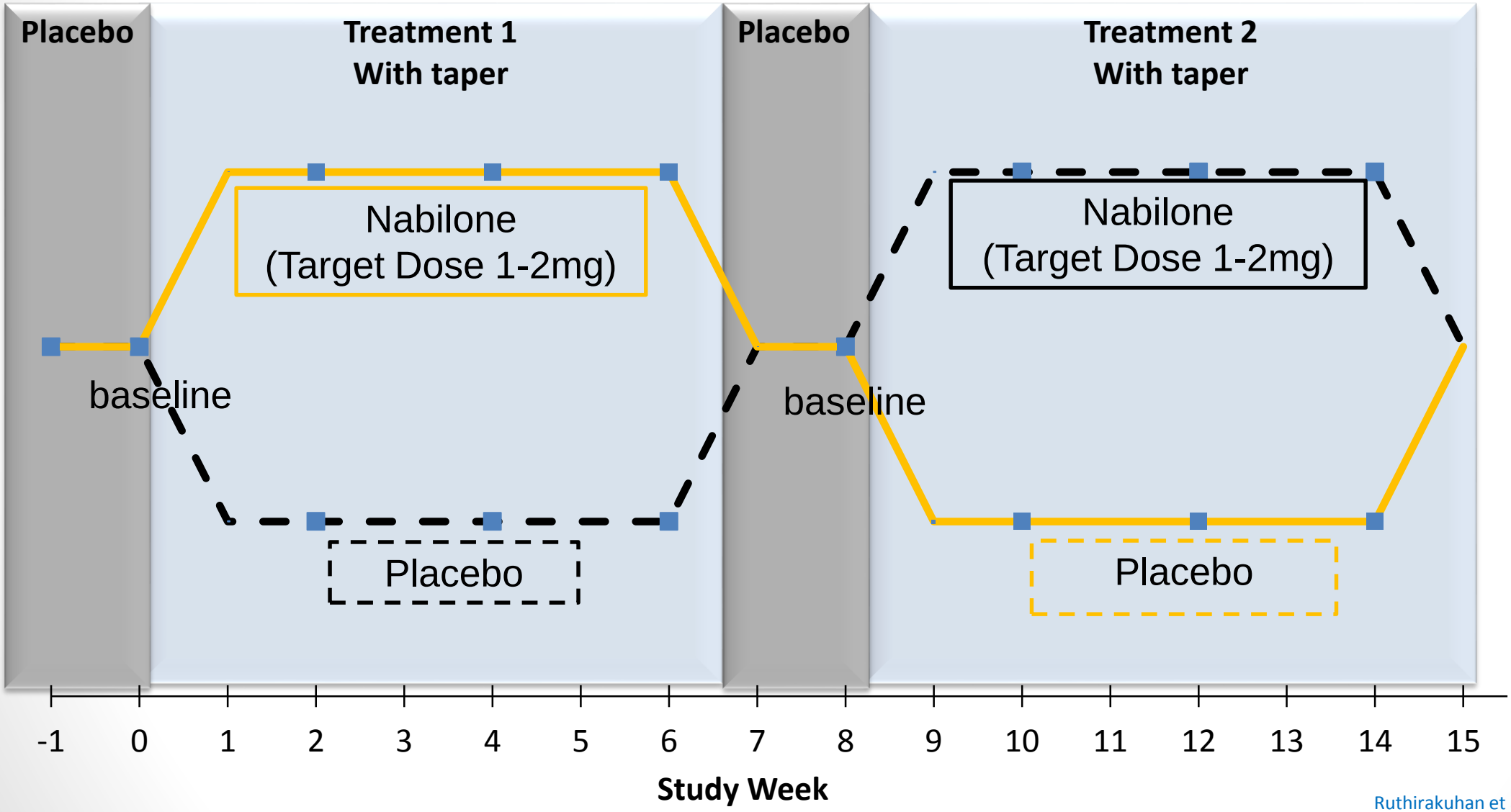
Study Design



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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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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%

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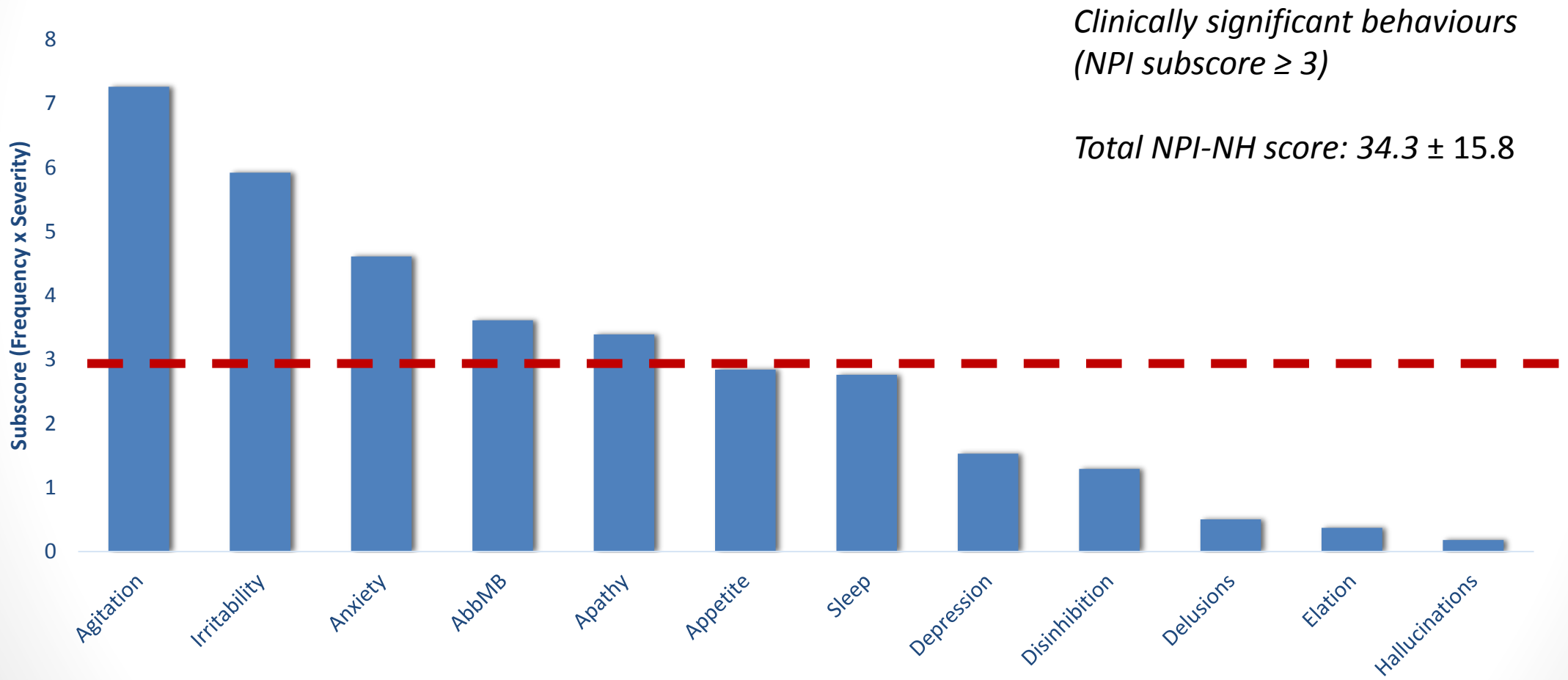
Patient characteristics (n=38)

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%

Neuropsychiatric Symptoms (NPI-NH)



Clinically significant behaviours (NPI subscore ≥ 3)

Total NPI-NH score: 34.3 ± 15.8

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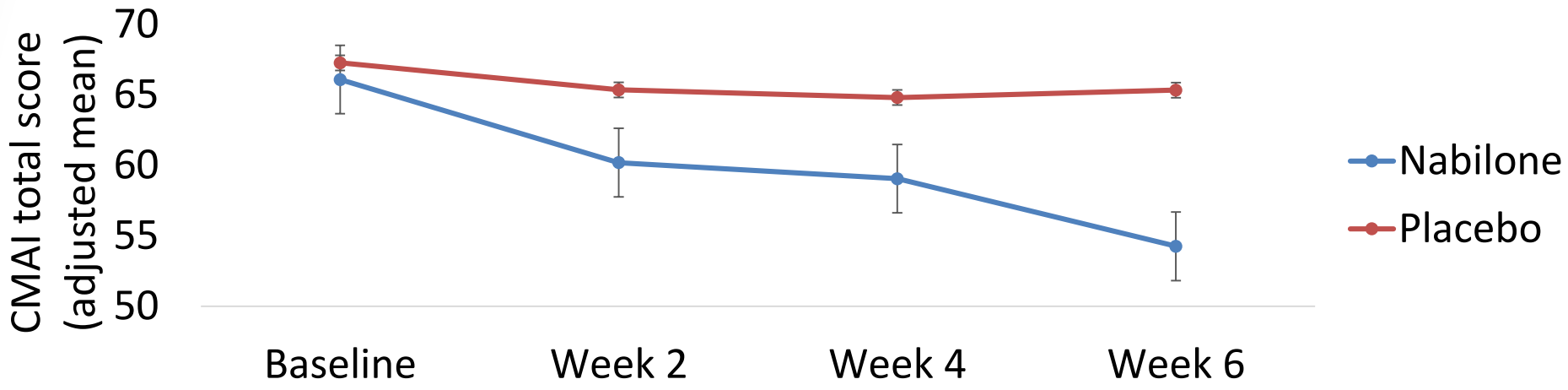
Agitation improved significantly during nabilone compared to placebo phase



- 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)=-3.8, p=0.001)

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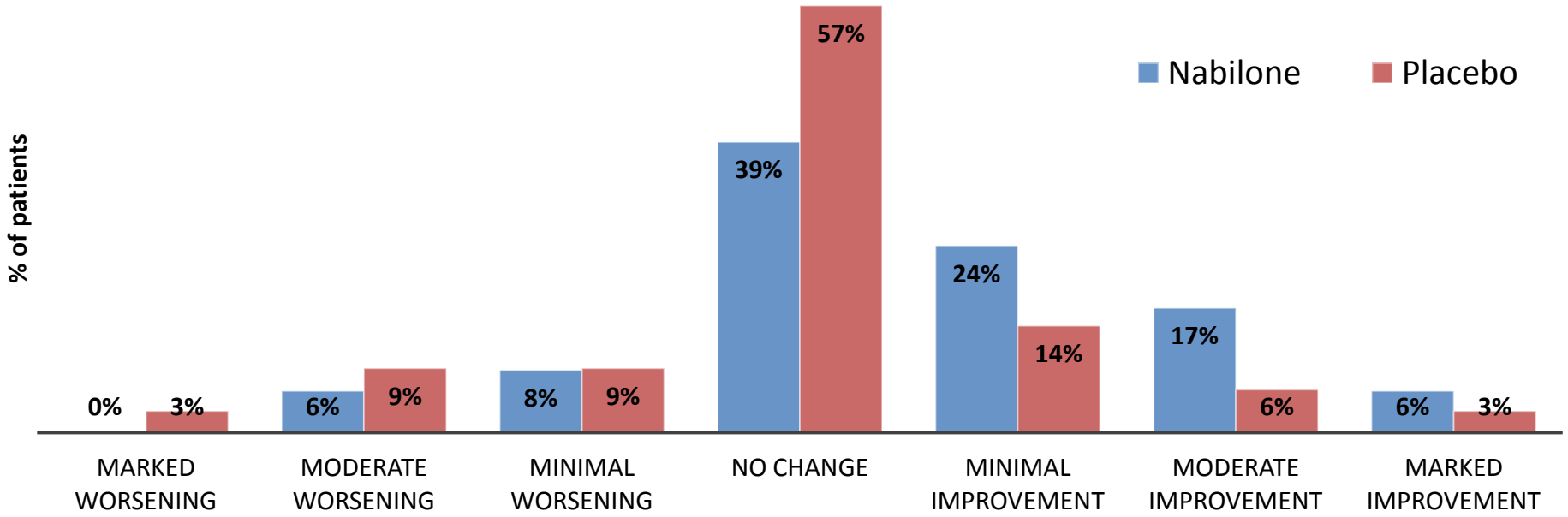
CGIC during nabilone versus placebo phases

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



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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
- 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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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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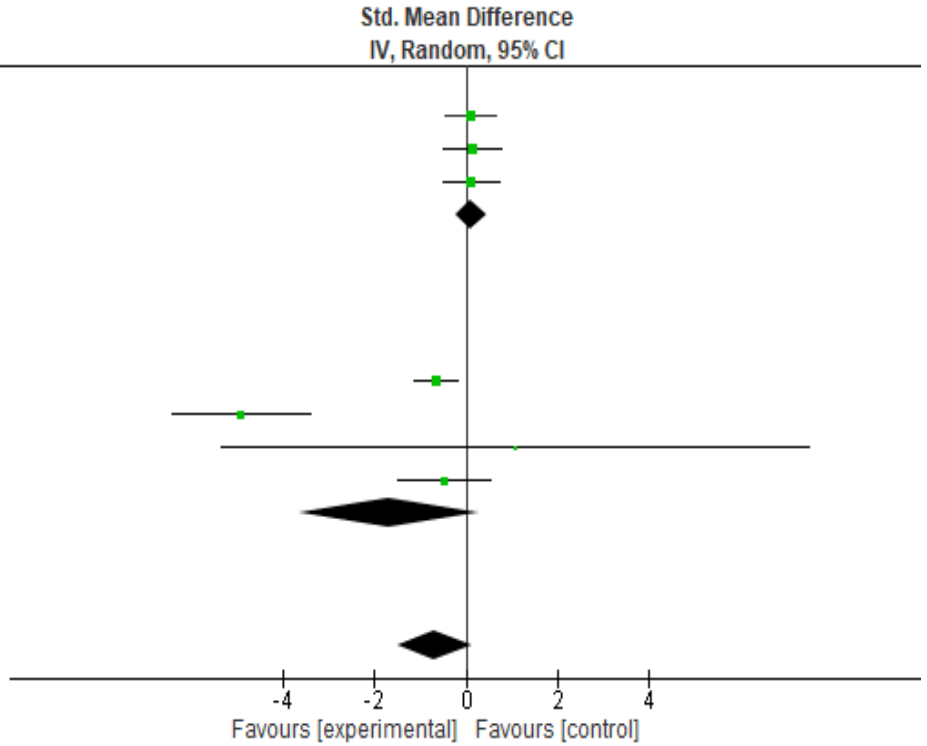
Meta-Analysis of Cannabinoids for Agitation

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 ($B = 0.27$, $t_6 = 2.93$, $P = .03$).

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Biomarkers of nabilone response

- Oxidative stress and neuroinflammation
  - Mechanistically relevant for ECS
  - cytokines previously associated with agitation [Ruthirakuhan et al 2018]
  - lower baseline TNF-α was associated with decreases in agitation severity in the nabilone phase only (b=1.14, p=.045)
- 24-S-hydroxycholesterol (cerebrocholesterol (Cchol))
  - Elevated brain cholesterol (reduced serum Cchol), associated with reduced membrane fluidity, preventing ligand binding to CB1
  - reduction in the production of Cchol due to neuronal cell death
  - Cchol associated with baseline agitation (CMAI IPA) ($F(1,36)=4.95$, $p=.03$)
  - Did not predict response to nabilone
- Clusterin (apolipoprotein-J)
  - Chaperone protein involved in Aβ fibrillation, clearance, and complement inhibition and increased in AD [Hsu et al 2017]
  - inconsistently correlated with agitation [Mukaetove-Ladinska et al 2014, Hsu et al 2017]
  - Did not predict response to nabilone

Ruthirakuhan et al 2019a, b

Current studies

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

Summary

- 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
- ongoing trials