Interventions for Neuropsychiatric Symptoms with a Focus on Apathy and Agitation

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Disclosures

- Krista L. Lanctôt – Consultant or Advisory Board
  - BioXcel Therapeutics
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  - Eisai Co., Ltd.
  - Exciva
  - Ironshore Pharmaceuticals
  - Kondor Pharma
  - H Lundbeck A/S
  - Novo Nordisk
  - Otsuka
  - Praxis Therapeutics
  - Sumitomo Pharmaceuticals

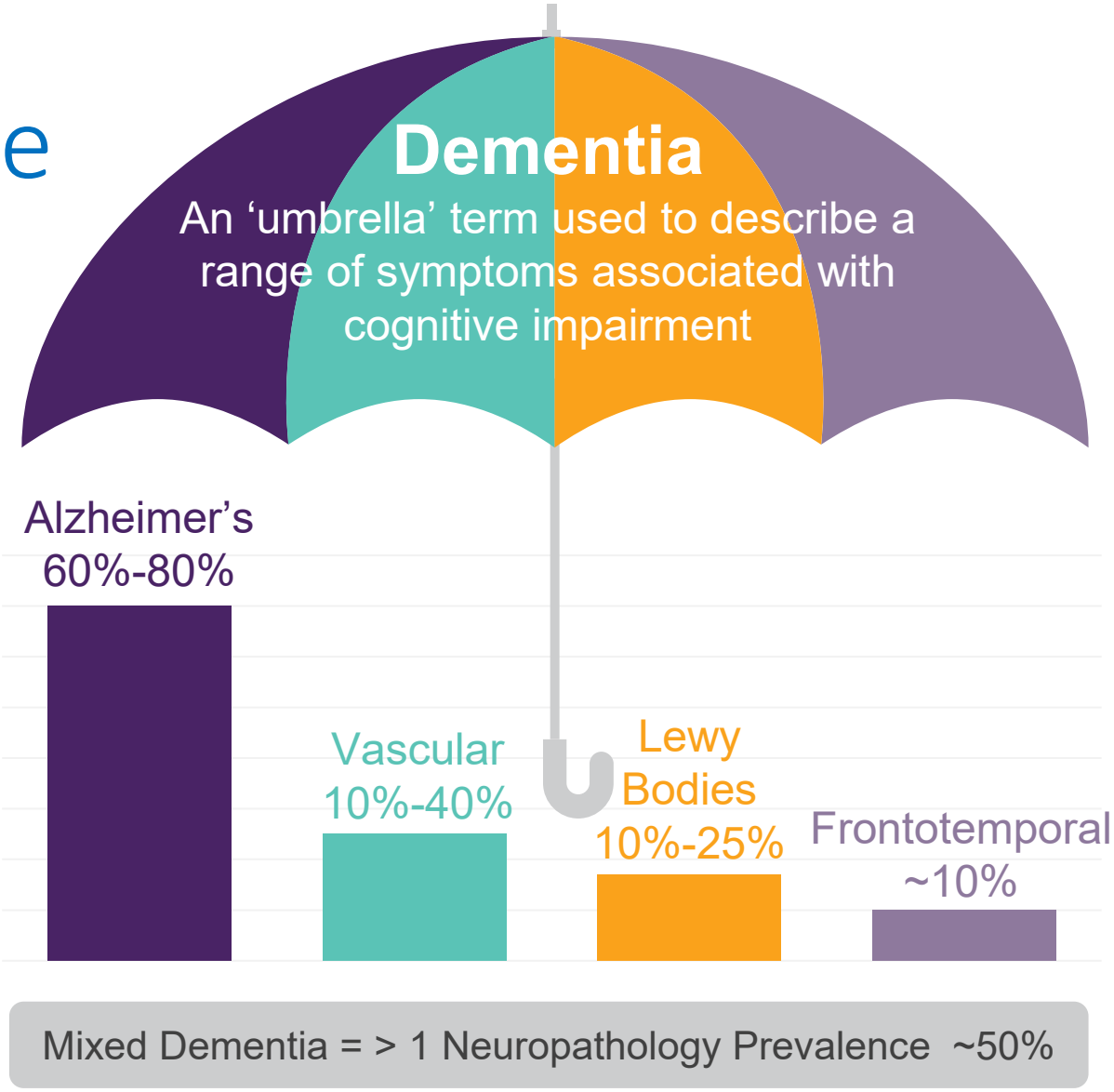
Learning objectives

By the end of this presentation, learners will know

- the symptoms of agitation and apathy
- nonpharmacologic interventions that have been shown help
- new medications that may help

Dementia is a syndrome

- Dementia is a collection of symptoms related to cognitive decline
  - memory loss, which is usually noticed by someone else
  - difficulties communicating or finding words
  - difficulties visual and spatial abilities, such as getting lost while driving
  - difficulties reasoning or problem-solving
  - difficulties handling complex tasks
  - difficulties planning and organizing
- **Alzheimer's** is most common cause



ABC's of Alzheimer's disease (AD)

Activities of daily living

Behaviour

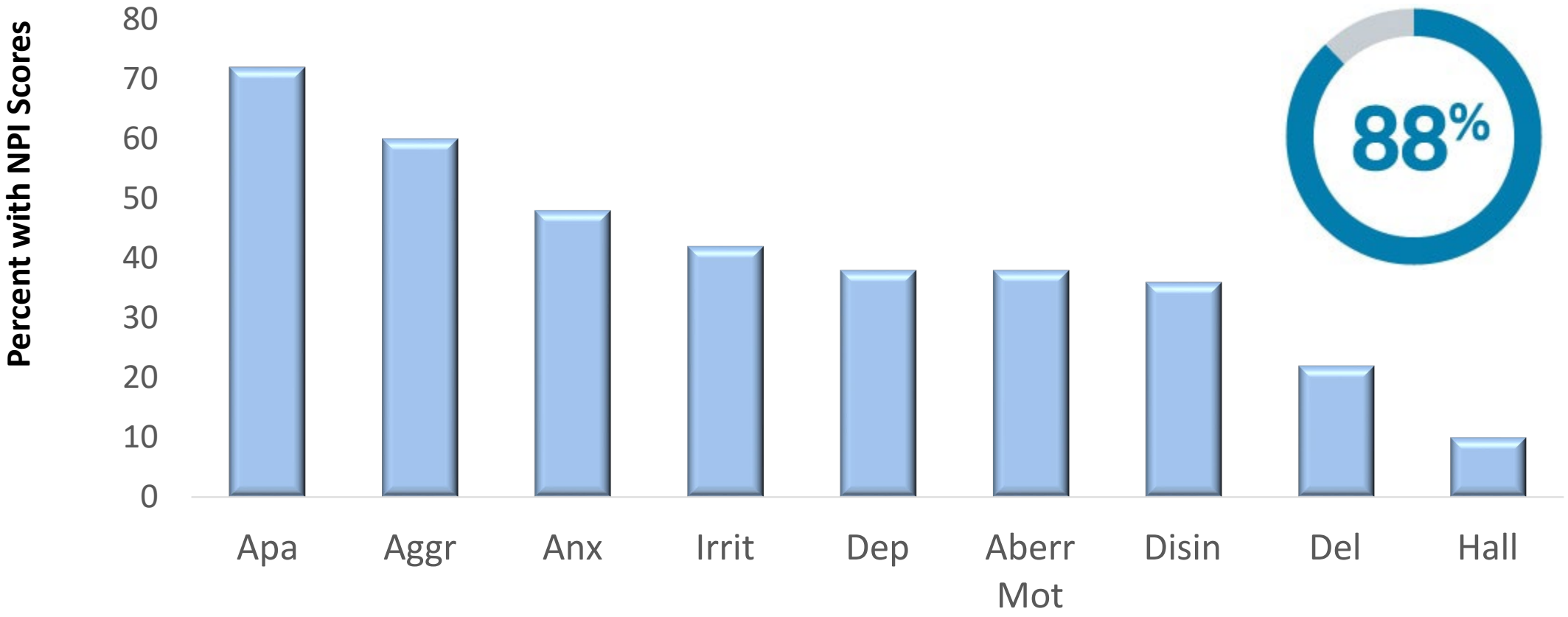
Cognitive deficits

Neuropsychiatric Symptoms (NPS):

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

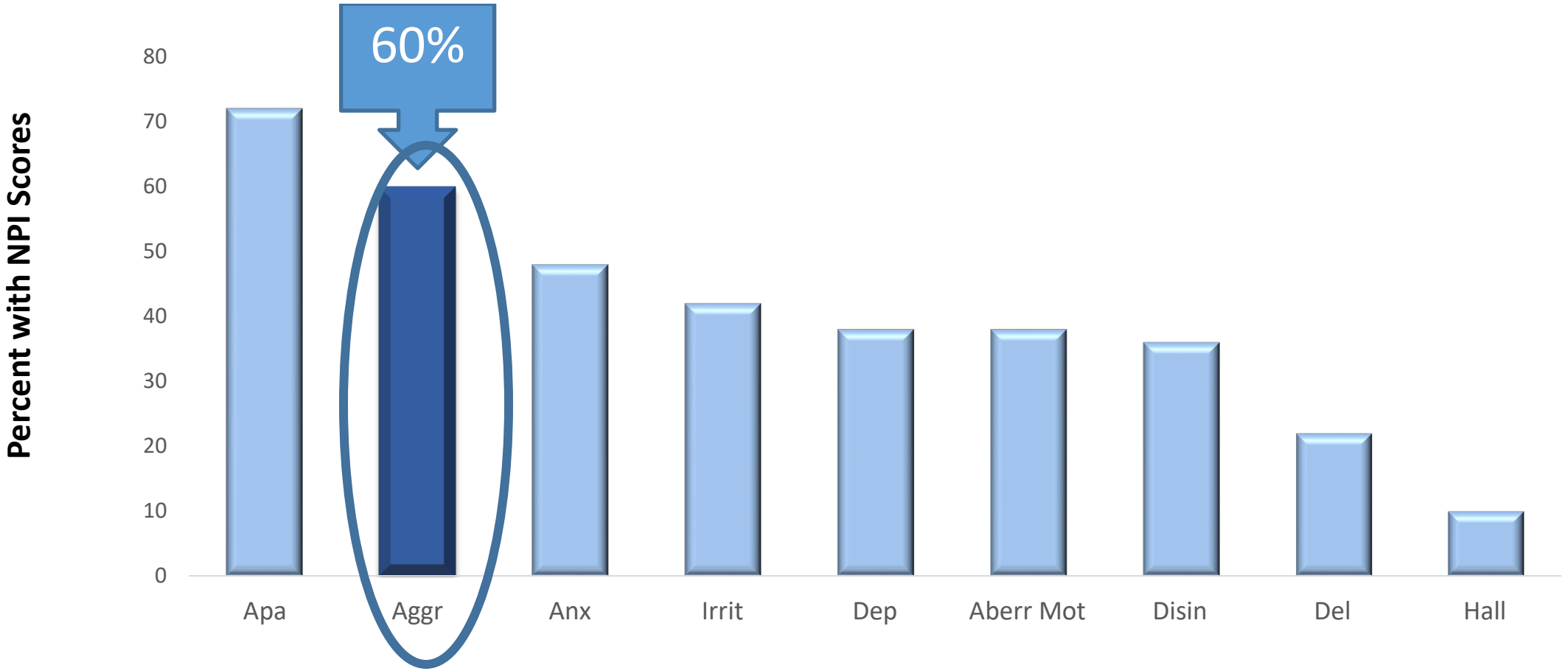
In 2020, it was estimated that there were 597,300 individuals living with dementia in Canada.
By 2030, we can expect this number will reach close to 1 million
[ASC Landmark Study, 2023]

NPS common in Alzheimer's Disease



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

Agitation is particularly common in Alzheimer's Disease



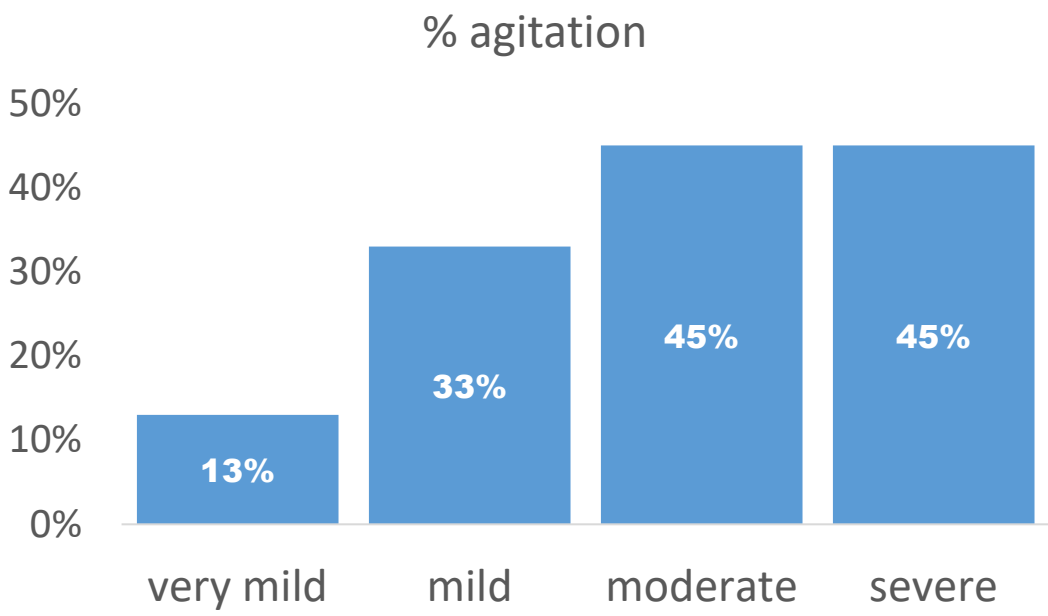
Mega et al, Neurology 1996; 46: 130-135

Frequency of agitation 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]
  - In home-dwelling participants with mild to moderate/severe dementia, prevalence of agitation as defined by a clinician ranged from 8.3% to 48.9% (Sano et al., 2022).
- 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]) [Livingston et al 2017]
  - mild 4.5 [2.3 to 8.7]
  - moderate 7.0 [3.6 to 13.3]
  - severe 6.2 [3.2 to 11.94]
- severity and prevalence equal in males and females [Eikelboom et al 2022]



Livingston et al, 2017

random effects logistic regression model adjusted for resident's age, sex, care home type

The Patient with Agitation: A Triad of Symptoms

- ✓ Behaviour consistent with distress
- ✓ Persistent or frequently recurrent for a minimum of two weeks

Cummings et al, 2015; Sano et al 2023

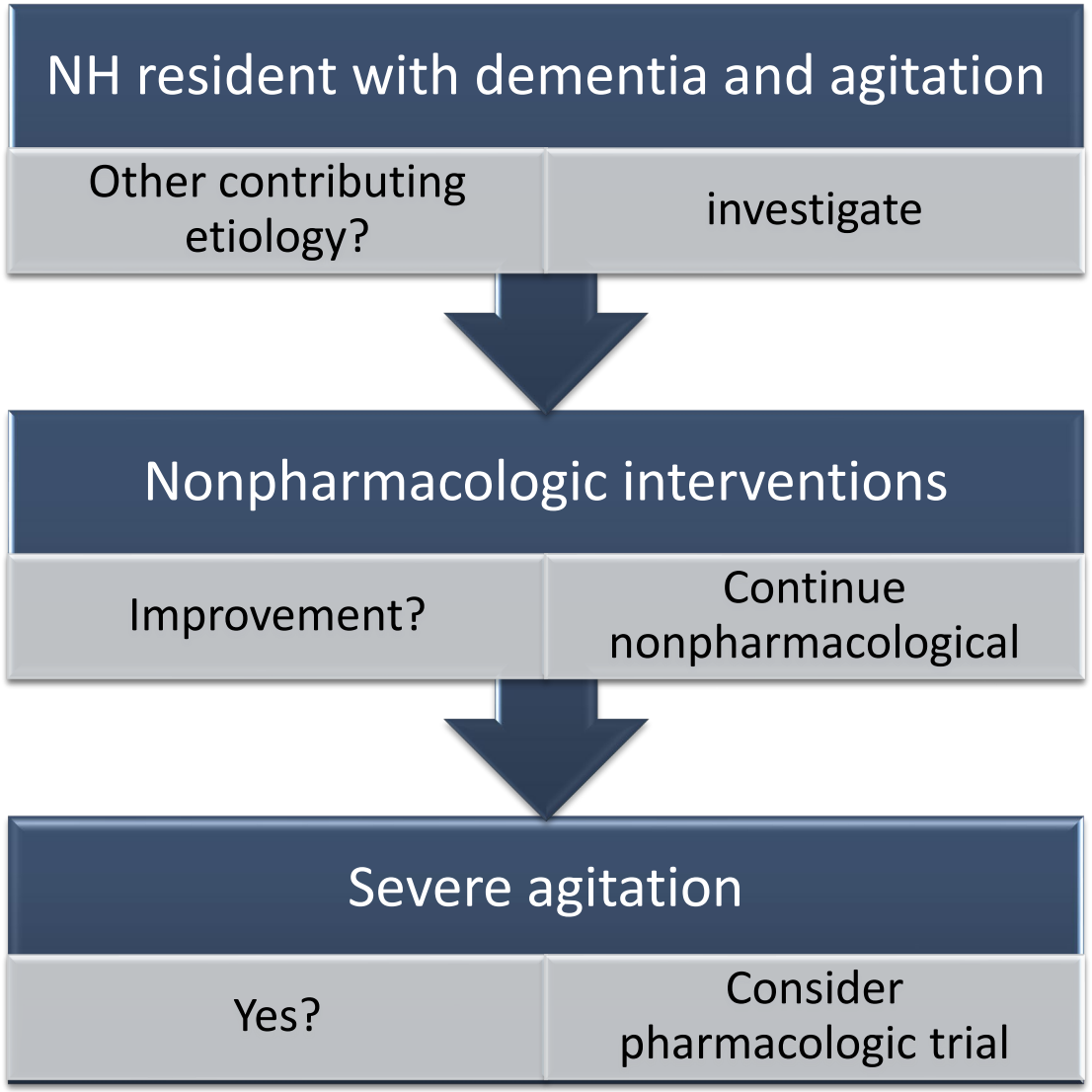
Agitation in Alzheimer's Disease (AD)

- 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], decreased quality of life [Schmüdderich et al 2021]
- Target for nonpharmacologic and pharmacologic intervention

Algorithm for treatment of agitation in LTC

Individualized selection

- based on feasibility (site and patient factors), patient preference and availability of resources
- Theories include progressively lower stress threshold



Cummings et al, 2023

Possible initial non-pharmacological approaches

- Reduce environmental clutter and noise
- Remove items that could be thrown or that upset patient
- Optimize lighting and give cues to heighten orientation
- Provide eyeglasses, hearing aids, mobility support, etc.
- Consider targeted nonpharmacologic approaches based on patient history/preferences
- Caregiver education: skills targeting behavioral challenges, and enhancing coping techniques

AMERICAN PSYCHIATRIC ASSOCIATION

Non-pharmacological interventions for agitation in dementia

Group activities

- structured group activities
- exercise
- dance
- horticultural therapy

Interventions

- animal-assisted therapy
- bright light therapy
- aromatherapy
- music
- simulated presence therapy
- therapeutic touch
- sensory (massage, snoezelen)

Caregiver training

- person-centred care
- dementia-care mapping

Non-Pharmacological Interventions for Agitation

- systematic review of RCTs with at least 45 participants that evaluated non-pharmacological interventions for agitation (33 studies)
  - ✓ activities-based interventions
  - ✓ music therapy, sensory interventions (massage, snoezelen, therapeutic touch),
  - ✓ caregiver training interventions (person-centred care, dementia care mapping) effective
  - x no evidence of efficacy for light therapy, aromatherapy
  - ○ insufficient evidence for exercise, simulated presence therapy, mixed psychosocial

G. Livingston, 2014, *British Journal of Psychiatry*, 205(06), 436–442

Caregiver Training Interventions

- **Person-Centred Care (PCC):** holistic care to help preserve personhood as disease progresses (Chenoweth et al., 2009)
  - Care techniques personalized according to individuals' preferences and needs
  - Less intensive training than dementia-care mapping
- **Dementia-Care Mapping (DCM)**: method of systematically identifying and responding to probable causes of agitation
  - Trained staff observe care, the environment, factors associated with resident well-being
  - Identify positive and negative aspects of care delivery
  - Provide feedback to untrained care staff to help with planning, implementation, and assessment of PCC

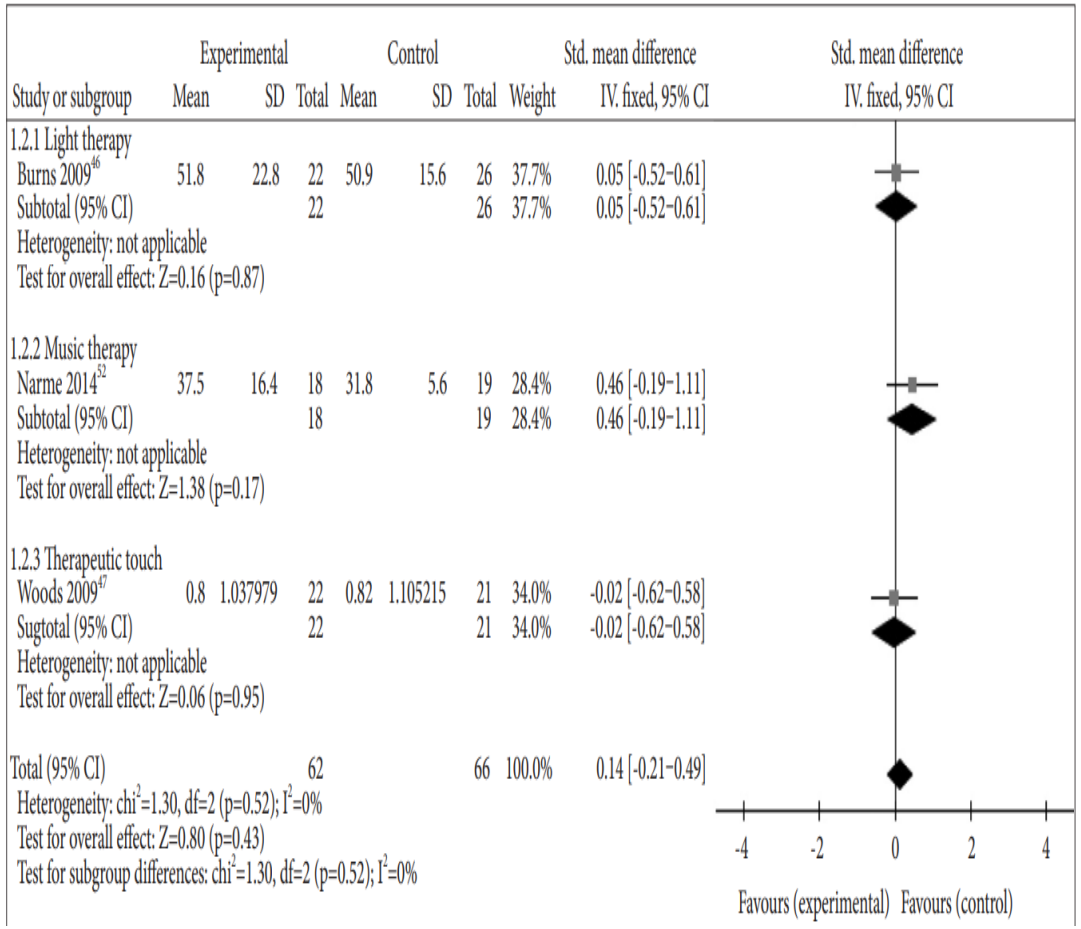
Efficacy in moderate to severe?

- meta-analysis of non-pharmacological interventions in moderate-to-severe dementia
- only 3 studies
  - light therapy, music therapy, therapeutic touch

x no effect on agitation (SMD=0.14, 95% CI= –0.21 to 0.49, p=0.43);

- no heterogeneity (I^2 =0%) and low certainty of evidence

Figure 1 Meta-analysis on agitation

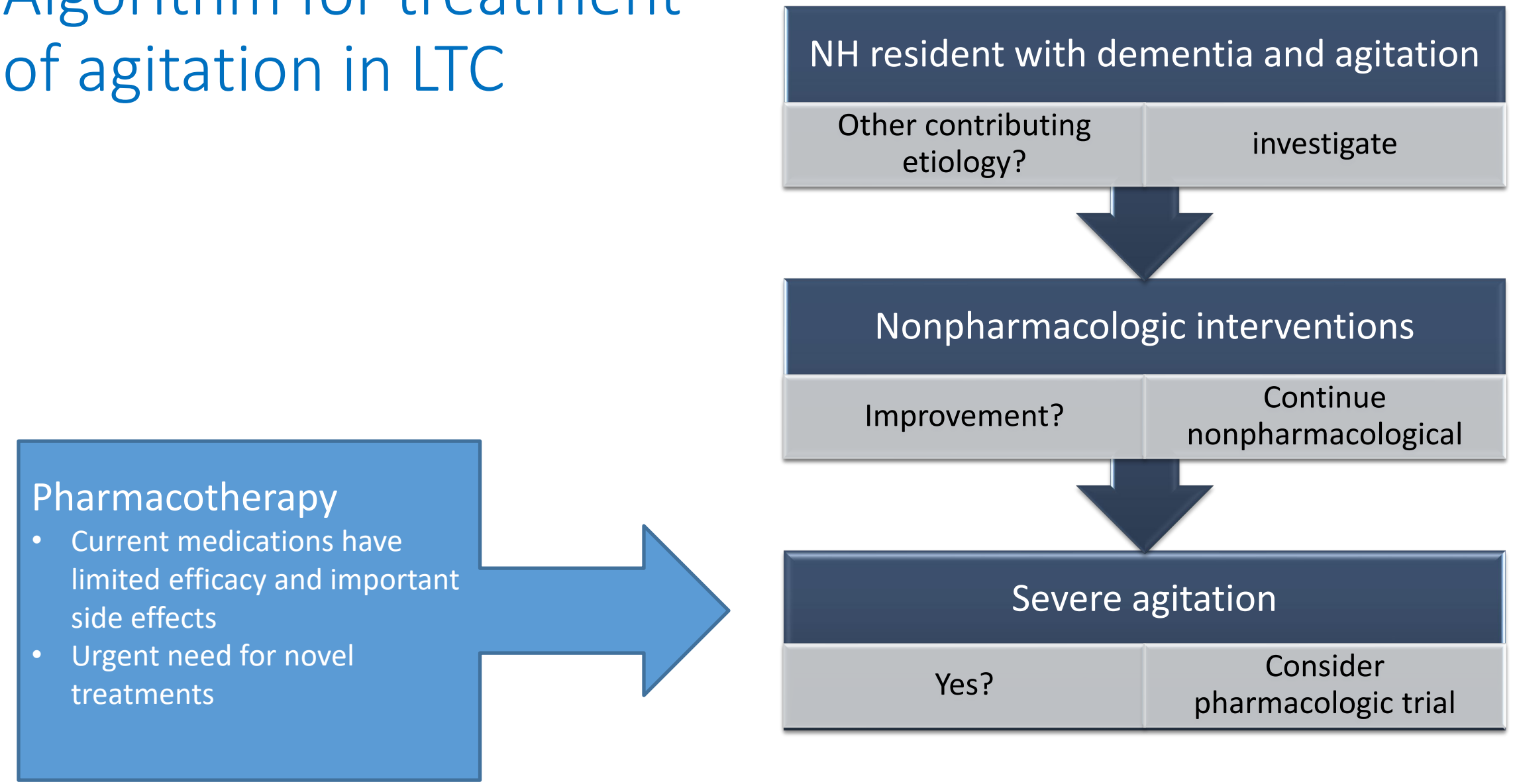


R. Na et al., 2019, *Psychiatry Investigation*, 16(5), 325–335

Non-pharmacologic interventions

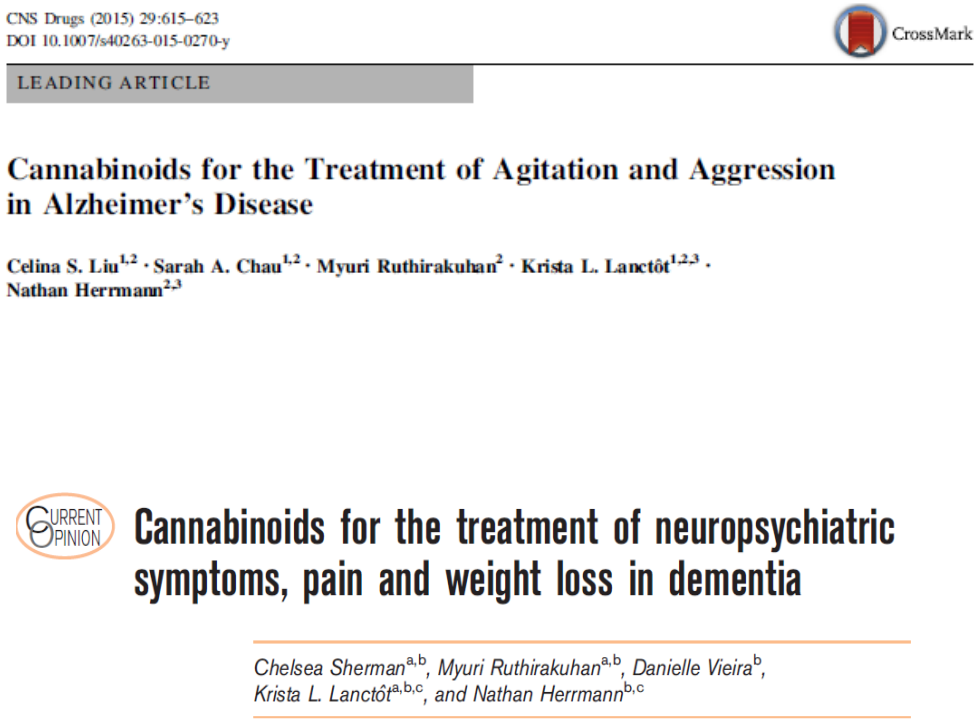
- In general, activity-based interventions, music therapy, and massage have consistently shown benefits for agitation in nursing home residents with dementia
- Music therapy and exercise are the most feasible; low costs and low time commitment for training and implementation
- Feasibility considerations in LTC settings
  - Need for specialized staff
  - Declines in sensory capabilities (i.e. hearing, vision, taste, smell, touch) limits sensory
  - Physical limitations e.g., capacity to exercise
- Further research on long-term effects, multi-component interventions and efficacy for severe agitation

Algorithm for treatment of agitation in LTC



Cummings et al, 2023

✓ Identify treatment targets for agitation in dementia: Endocannabinoid system



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]

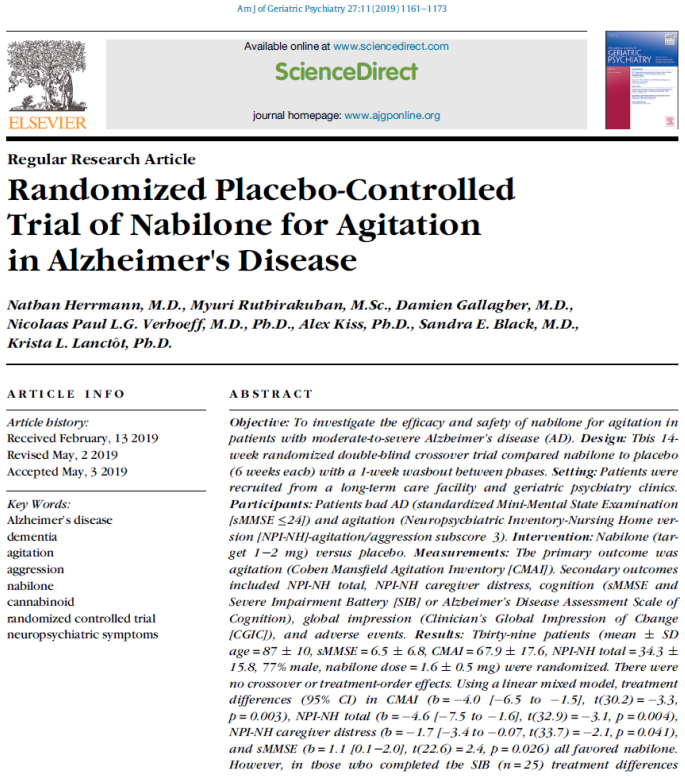
Cannabinoids for the treatment of neuropsychiatric symptoms, pain and weight loss in dementia

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

- Clinically
  - Mild sedation, anti-anxiety, increase appetite, decrease pain
- Possible benefits of CB1 and CB2 activation
  - Endocannabinoid activity modulates numerous pathological processes [Aso & Ferrer 2014]

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

Pilot study of nabilone for agitation in AD



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Regular Research Article

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

Nathan Herrmann, M.D., Myuri Ruthirakuhan, 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

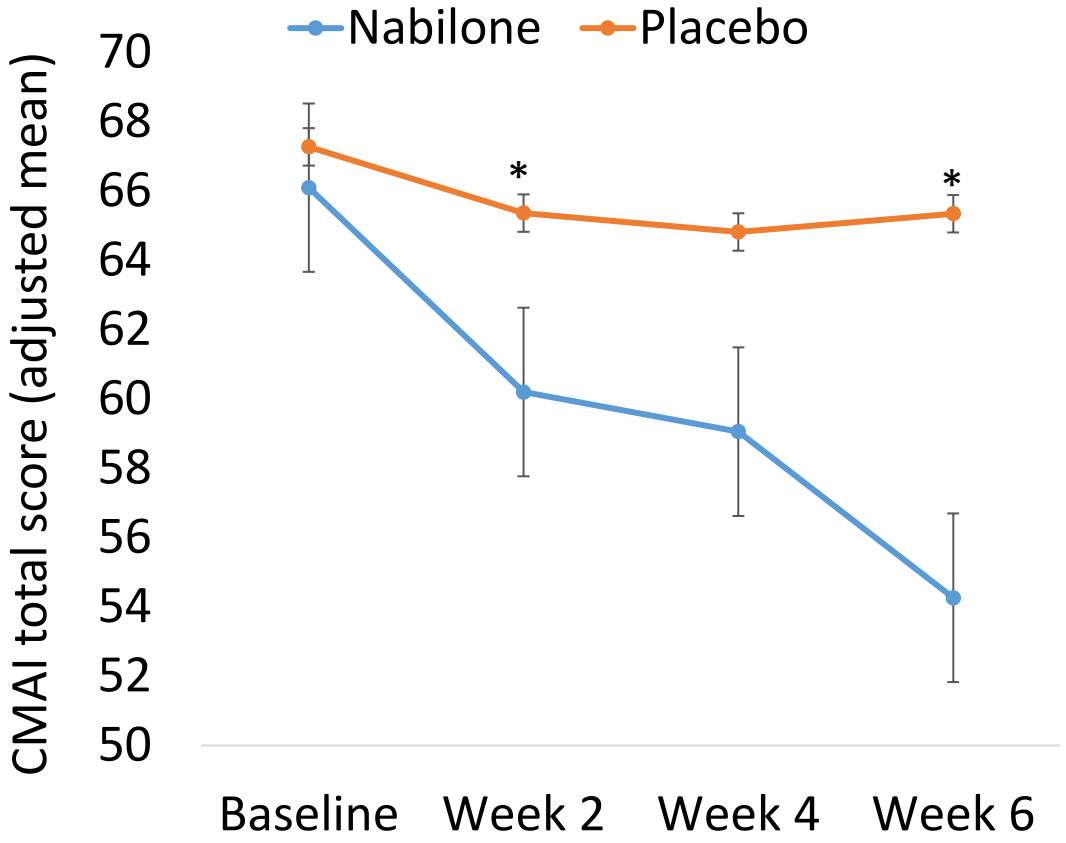
- nabilone
  - synthetic derivative of THC
  - marketed for nausea and vomiting associated with chemotherapy
- double blind, placebo-controlled, cross-over trial in 38 patients with agitation and AD
- efficacy and safety of nabilone (1-2 mg/d) versus placebo (6 weeks each)

Société Alzheimer Society CANADA

Alzheimer's Drug Discovery Foundation

Herrmann N, et al . Am J Geriatr Psychiatry. 2019

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
  - Week 6/endpoint-- nabilone 55.8±15.9 vs placebo 65.9±13.7, (t(32)=-3.8, p=0.001)
- CGIC "minimal" to "marked" improvement (McNemar's test, p=0.09)
  - 47% improved during nabilone
  - 23% improved during placebo

Herrmann N, et al . Am J Geriatr Psychiatry. 2019

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)

Herrmann N, et al . Am J Geriatr Psychiatry. 2019

✓ Evaluate new and innovative treatments: Nabilone for Agitation Blinded Intervention Trial

- Treating agitation in patients with Alzheimer's disease
  - Multi-centre, randomized, parallel-group placebo-controlled study (n=108)
  - 1-2mg of nabilone over 8 weeks
  - Biomarkers potentially related to agitation and response
- Investigators
  - K Lanctôt (PI), G Marrotta (QI), SE Black, A Burhan, C Fischer, D Gallagher, N Herrmann (co-PI), Z Ismail, S Kumar, D Seitz, T Rajji
- 5 sites: Toronto (3), Whitby, Calgary
  - CCNA Team 11 LTC Facilities
- recruitment ongoing

Alzheimer's Drug Discovery Foundation

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

CALM-IT

✓ Evaluate new and innovative treatments: Cannabidiol for Agitation Medication Intervention Trial

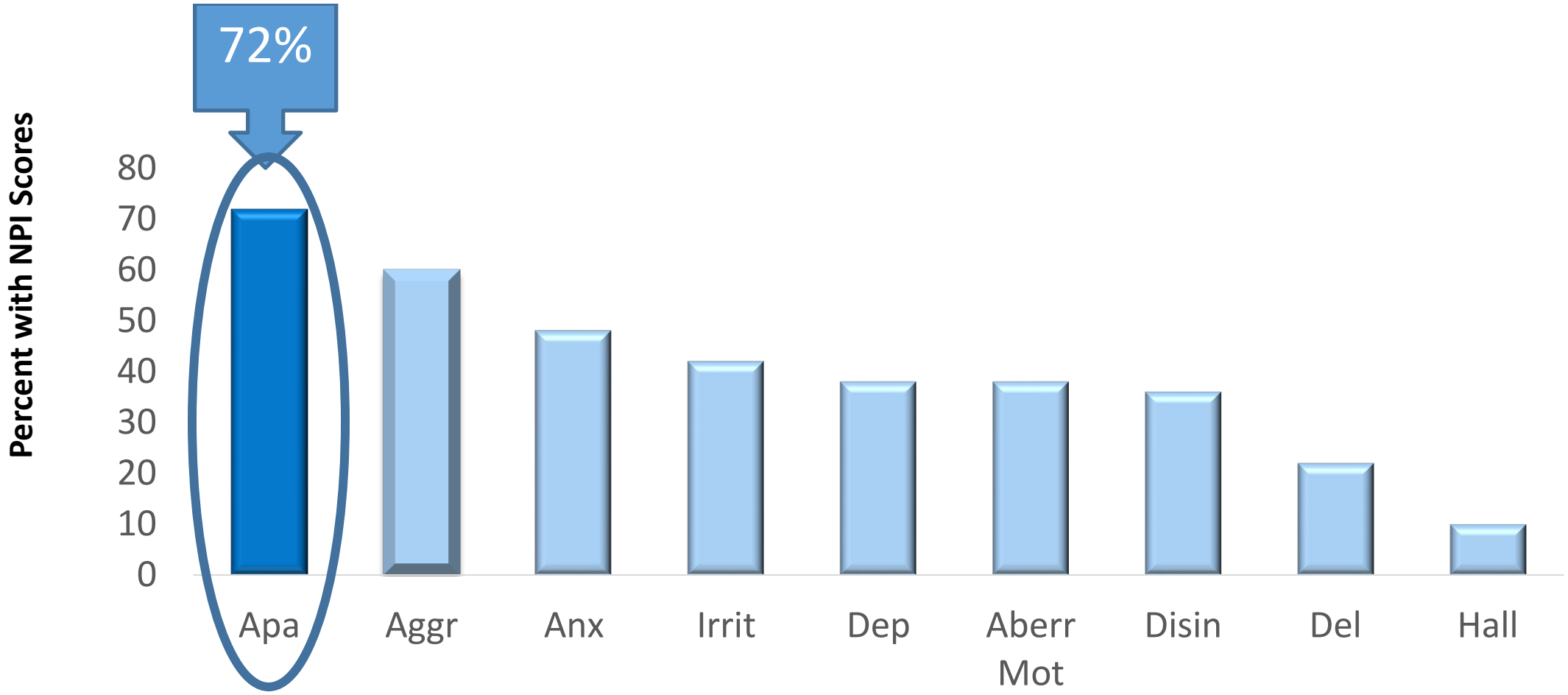
- Treating agitation in patients with Alzheimer's disease
  - Multi-centre, randomized, placebo-controlled cross-over study (n=60)
  - 400 mg CBD versus placebo over 6 weeks
  - Biomarkers potentially related to response
- Investigators
  - K Lanctôt (PI), G Marrotta (QI), SE Black, A Burhan, C Fischer, D Gallagher, N Herrmann (co-PI), Z Ismail, S Kumar, D Seitz, T Rajji
- 5 sites: Toronto (3), Whitby, Calgary
  - CCNA Team 11 LTC Facilities
- study start-up

WESTON BRAIN INSTITUTE

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

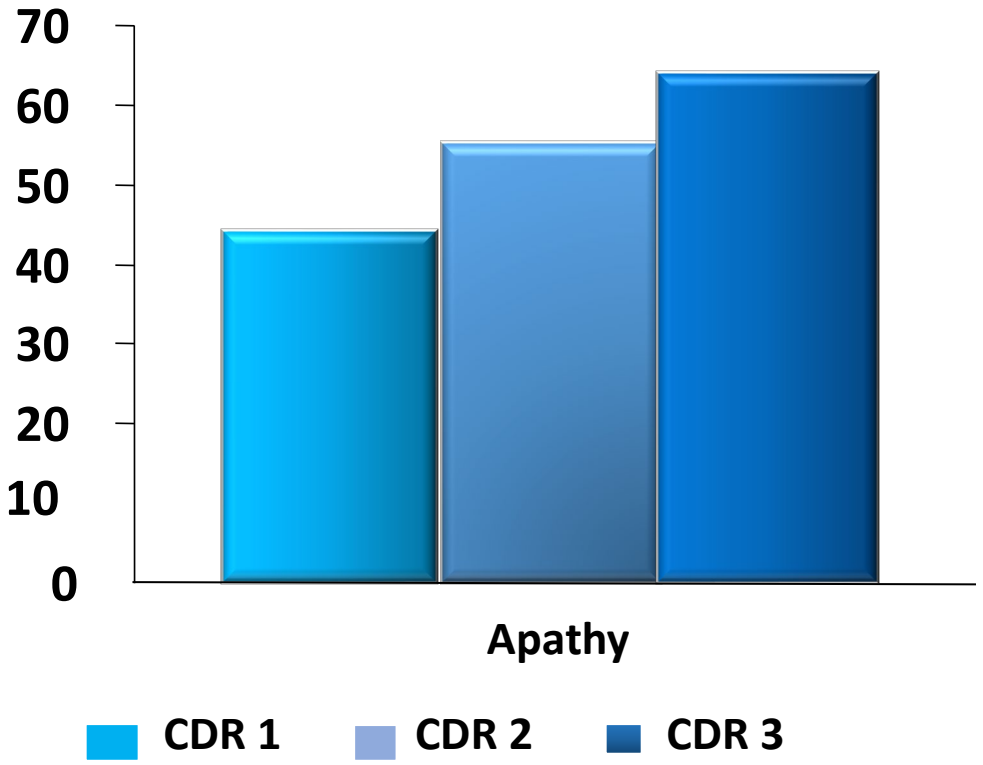
Apathy is the most common NPS in Alzheimer's Disease



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

Apathy in Alzheimer's disease

- apathy one of the most common syndromes with a 5-year prevalence estimate of 71% (Cache County Study) [Steinberg et al 2008]
- more frequent with disease progression [Mega et al, 1996]



Mega et al, 1996

The Patient with Apathy Syndrome: A Triad of Symptoms

Diminished goal-directed behaviour

Miller et al, J Alzheimer's & Dementia 2021

The Patient with Apathy Syndrome

Diminished goal-directed behavior 2/3

Initiative

- Less spontaneous and/or active than usual self
- Less likely to initiate usual activities
  - Hobbies
  - Chores
  - Self-care
  - Conversation
  - Work-related or social activities

Interest

- Less enthusiastic about usual activities
  - Less interested in, or less curious about events in their environment
  - Less interested in activities and plans made by others
  - Reduced participation in activities even when stimulated
  - Less persistence in maintaining or completing tasks or activities
  - Less interested in friends and family

Emotional Expression

- Less spontaneous emotions
  - Expresses less emotion in response to positive or negative events
  - Less affectionate compared to their usual self
  - Less concerned about the impact of their actions on other people
  - Less empathy

Miller et al, J Alzheimer's & Dementia 2021

Impact of apathy in Alzheimer's disease

- Persons with dementia
  - decreased quality of life [Hurt et al 2008]
  - greater cognitive decline [Starkstein et al 2006]
  - greater functional decline [Starkstein et al 2006]
  - increased mortality [Nijsten et al 2017]
- Care partners
  - increased care needs [Freels et al 1992]
  - increased caregiver burden [Kaufer et al 1998, Dauphinot et al 2015]
  - increased risk of institutionalization [Banerjee et al 2003]
  - higher costs of care [Herrmann, Lanctôt et al 2006]
- Target for nonpharmacologic and pharmacologic interventions

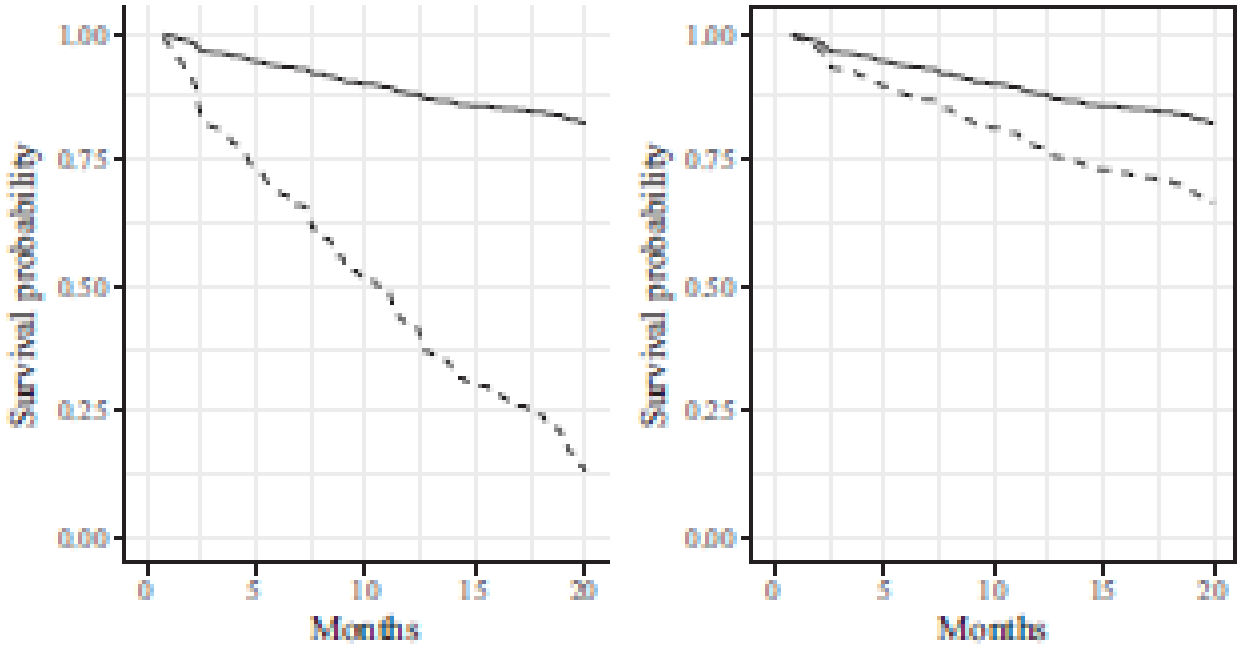
Impact of Apathy: outpatients

- Apathy impacts PWD
  - 354 consecutive outpatients with AD [Starkstein et al 2006]
  - follow up in 247 (70%) 1 and 4 years after the baseline
  - predicts cognitive and functional decline
    - MMSE (group x time ($F(2,236) = 7.4$, $p = 0.0007$)
    - Functioning Independence Measure (FIM)(group x time $F(2,216) = 5.2$, $p = 0.006$)
- Apathy impacts care partners
  - 548 memory clinic outpatients, predictors of ZBI [Dauphinot et al 2015]
  - correlated with caregiver perception of burden
    - severity of cognitive impairment (MMSE), IADL and NPI
    - apathy (multivariate linear regression coefficient B=1.11 (0.78, 1.43) p<.001) greatest

Dauphinot et al, J Alzheimer's Dis 2015; Starkstein et al, JNNP, 2006

Impact of Apathy in LTC

- Apathy associated with increased mortality in NH patients



- Survival probability in months for patients of somatic care (left) and dementia special care (right) units (n=713)
  - patients without apathy (black line)
  - patients with apathy (dotted line)
- 1 SD increase in AES-10 score associated with 62% increase in mortality (HR = 1.62, 95% CI = 1.40–1.88, P < .001).

Nijsten et al 2017

Non-pharmacological interventions for apathy in dementia

Group activities

- multisensory stimulation
- art therapy
- exercise therapy
- music therapy

Interventions

- cognitive stimulation
- pet therapy
- reminiscence therapy
- therapeutic conversation
- progressive muscle relaxation
- occupational therapy
- psychomotor therapy
- validation therapy

Caregiver training

- dementia special care units
- nursing staff education
- comprehensive interventions

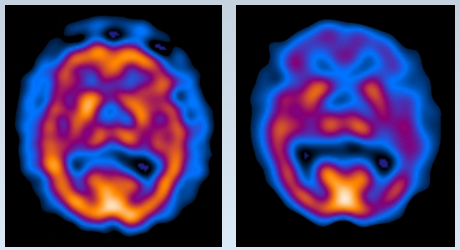
Non-pharmacological interventions for apathy

- systematic review of 9 systematic reviews
- evidence relatively robust
  - ✓ multisensory stimulation
  - ✓ music therapy
  - ✓ cognitive stimulation
  - ✓ pet therapy
- ○ need to be validated further
  - ○ reminiscence therapy, therapeutic conversation, progressive muscle relaxation, art therapy, exercise therapy, occupational therapy, dementia special care units, nursing staff education, and comprehensive interventions
- x not supported by current research
  - x psychomotor therapy and validation therapy
- x Few trials target apathy specifically

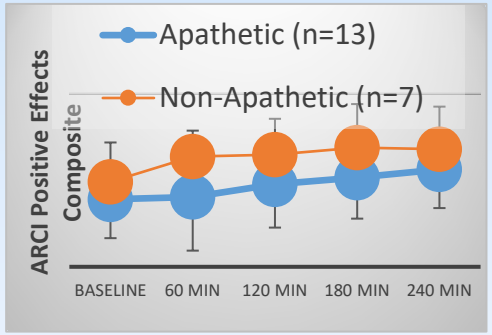
Cai et al 2020

Dopamine and apathy in Alzheimer's disease

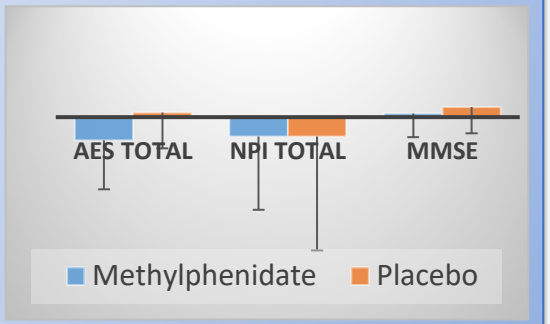
SPECT shows patients with apathy have alterations in rCBF in areas crucial to brain reward system



Pharmacologic challenge suggests differences in DAergic system between apathetic and non-apathetic



Pilot data show apathy decreases following methylphenidate



Lanctôt, 2007; Lanctôt, 2008; Herrmann, 2008

ADMET 2

JAMA Neurology | Original Investigation

Effect of Methylphenidate on Apathy in Patients With Alzheimer Disease
The ADMET 2 Randomized Clinical Trial

Jacobo Mintzer, MD, MBA; Krista L. Lanctôt, PhD; Roberta W. Scherer, PhD; Paul B. Rosenberg, MD; Nathan Herrmann, MD; Christopher H. van Dyck, MD; Prasad R. Padala, MD; Olga Brawman-Mintzer, MD; Anton P. Porsteinsson, MD; Alan J. Lerner, MD; Suzanne Craft, PhD; Allan I. Levey, MD, PhD; William Burke, MD; Jamie Perin, PhD; David Shade, JD; for the ADMET 2 Research Group

Visual Abstract

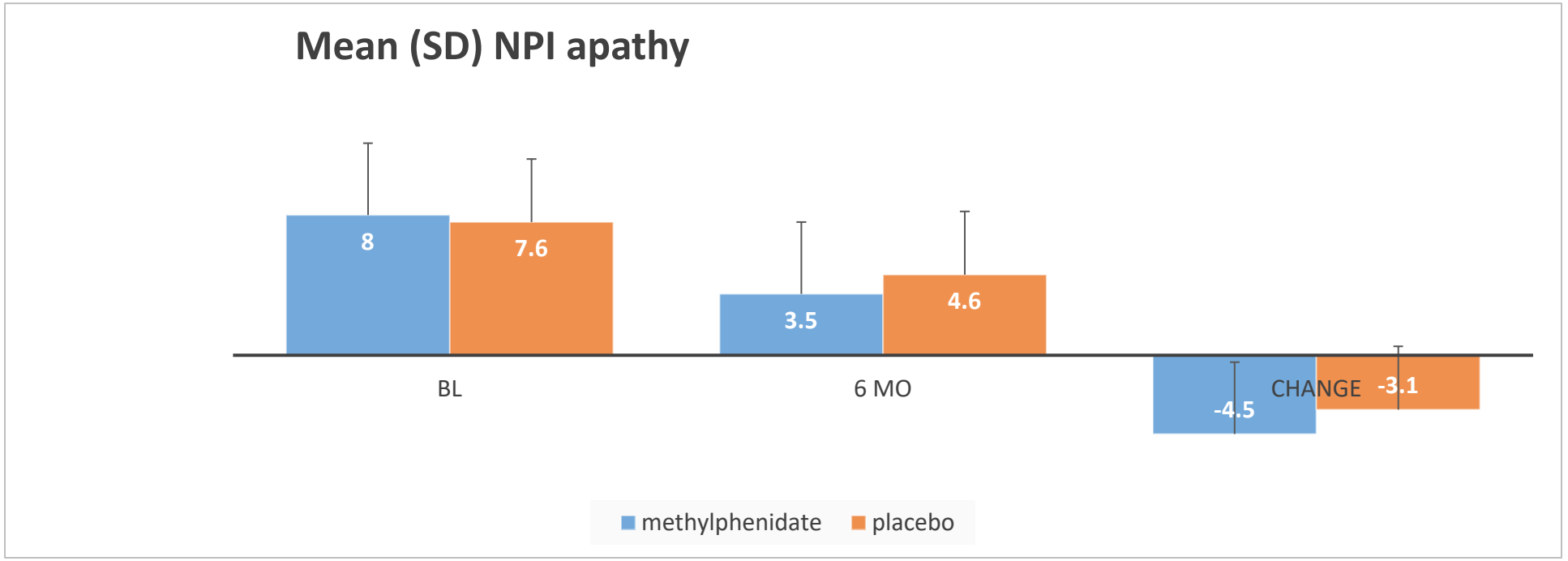
- Apathy in Dementia Methylphenidate Trial 2
  - A phase III randomized multi-centre placebo-controlled trial of 6 months
  - N=200 apathy in AD
  - methylphenidate (20 mg/day) vs placebo (1:1 ratio)
  - psychosocial intervention for both groups
- 9 sites across US and Canada

Mintzer, Lanctôt et al. JAMA Neurol 2021

NIH Aging

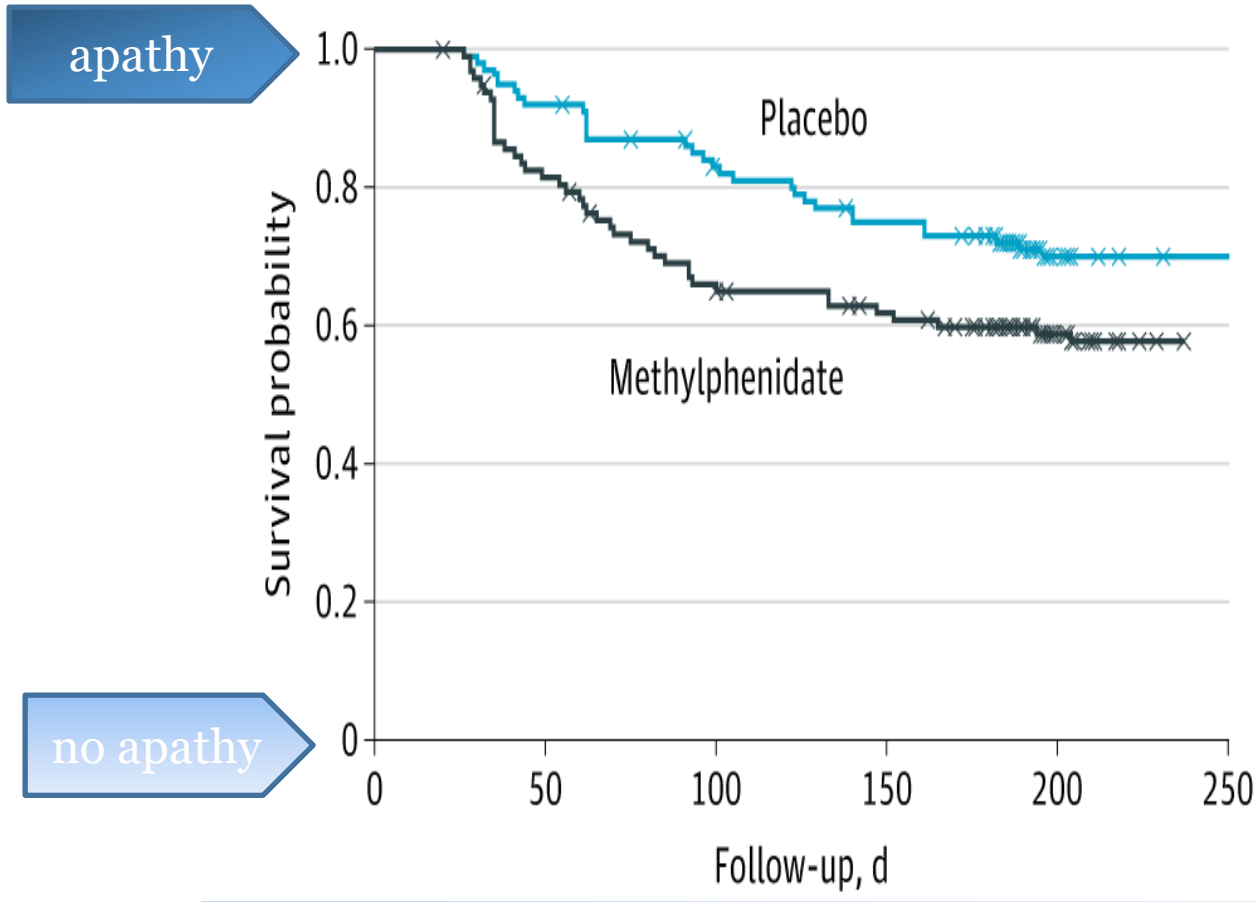
Apathy outcomes

- ✓ NPI apathy score improvement 1.3 points (95% CI 0.5, 2.0) greater in methylphenidate vs. placebo (p=0.002)



Mintzer, Lanctôt et al. JAMA Neurol 2021

Apathy remission



- For the first 100 days, methylphenidate group had >2x increase in remitted compared with placebo group
  - (hazard ratio, 2.16; 95%CI, 1.19-3.91; *P* = .01)
- Over 6 months, 57% more participants in MTP group had NPI apathy score of 0 compared with the placebo group
  - (hazard ratio, 1.57; 95%CI, 0.97-2.53; *P* = .07)
  - model adjusted for age, sex, and presence of diabetes

Mintzer, Lanctôt et al. JAMA Neurol 2021

Tolerability

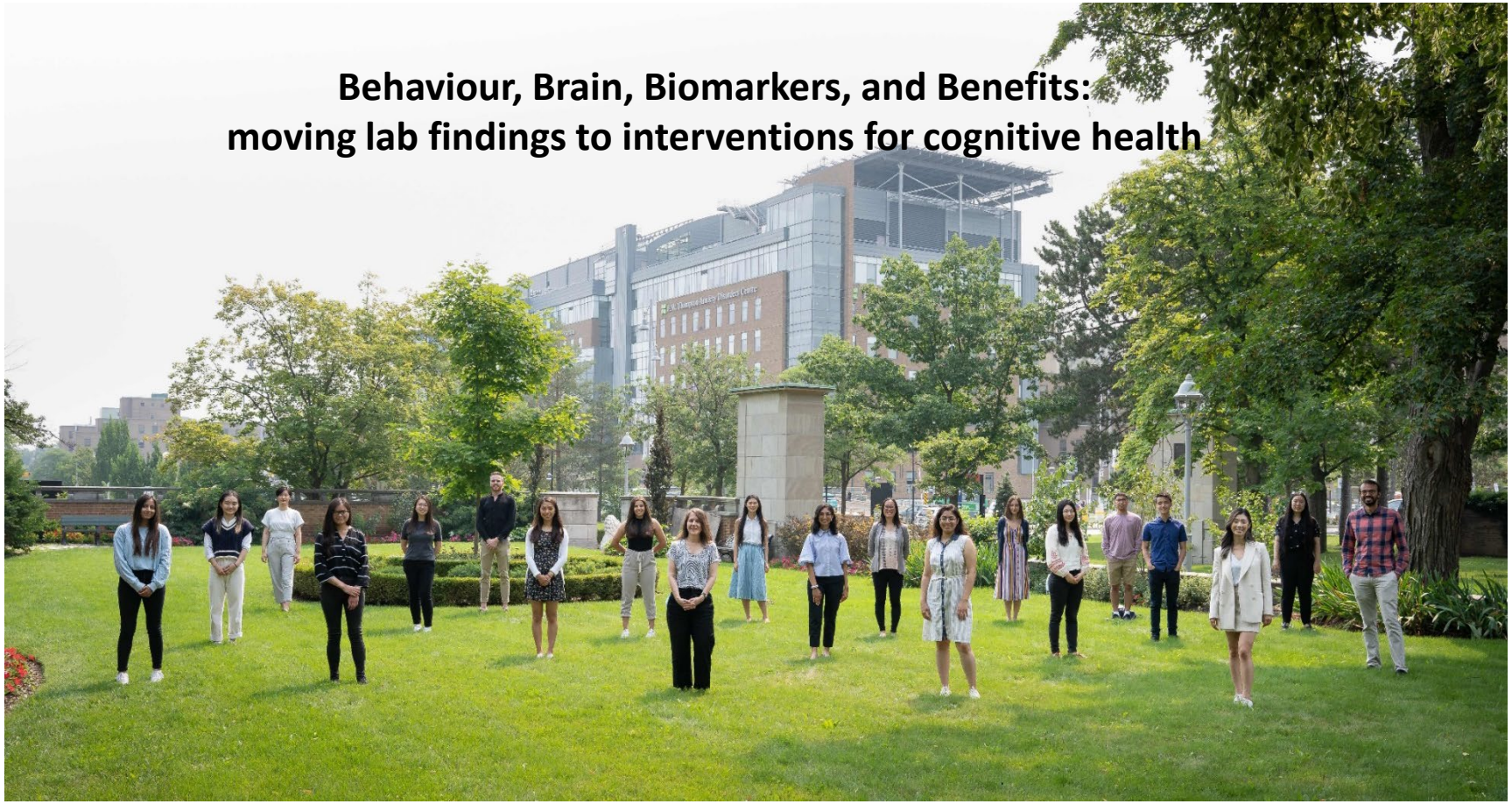
- Serious adverse events: 17 MTP, 12 PLA
  - Of the 17 serious adverse events that occurred with methylphenidate, none were related to the study drug.
- No significant differences in the safety profile were noted between treatment groups.

Mintzer, Lanctôt et al. JAMA Neurol 2021

Summary

- **agitation** common and persistent symptom in those with Alzheimer's disease
- nonpharmacologic interventions can help in mild to moderate AD
  - less effective with severe agitation
- pharmacologic rationale exists for use of cannabinoids
- recent trial of nabilone for agitation shows promise
  - efficacy, but concerns around sedation
  - nabilone and cannabidiol being evaluated for agitation
- in AD, **apathy** is common and also has a negative impact
  - apathy may have a distinct neurobiological profile
- recent diagnostic criteria can define clinically significant apathy
- apathy can be a nonpharmacologic and drug responsive behavior

Thank you! my lab, collaborators, PWD and care partners, funders



Alzheimer's Drug Discovery Foundation

Société Alzheimer Society CANADA

CCNA Canadian Consortium on Neurodegeneration in Aging

CCNV Consortium canadien en neurodégénérescence associée au vieillissement

WESTON BRAIN INSTITUTE

NIH Aging

CIHR IRSC

Resources

Cannabinoids
https://ccsmh.ca/areas-of-focus/cannabis/#modules

Behaviors in dementia tool kit
https://behavioursindementia.ca/

Agitation Diagnostic Criteria

https://pubmed.ncbi.nlm.nih.gov/36880250/

Agitation Treatment Algorithm
https://pubmed.ncbi.nlm.nih.gov/36876335/

Apathy diagnostic criteria
https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12358

Toronto Dementia Research Alliance

- Clinical trials that are running

International Psychogeriatric Association consensus clinical and research definition of agitation in cognitive disorders

- **Criterion A.** meets criteria for a cognitive impairment or dementia syndrome
- **Criterion B.** exhibits at least one of the following behaviors associated with emotional distress
  a) excessive motor activity
  b) verbal aggression
  c) physical aggression
  - persistent or frequently recurrent for a minimum of two weeks
- **Criterion C.** severe and associated with excess distress or excess disability in:
  a) interpersonal relationships
  b) other aspects of social functioning
  c) ability to perform or participate in ADLs
- **Criterion D.** Not attributable solely to another cause
  a) psychiatric disorder
  b) medical condition, including delirium
  c) suboptimal care conditions
  d) the physiological effects of a substance

Sano et al, 2023

CBD and THC

- Cannabidiol (CBD)
  - enhances endocannabinoid signaling
  - interacts with many non-endocannabinoid signaling systems: It is a “multi-target” drug
  - a potent antioxidant
  - anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties [Scuderi et al 2009]
- CBD may potentiate some of THC’s beneficial effects
  - Reduce 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 likely to cause psychotic symptoms compared to low CBD:THC ratios

Devinsky et al 2014

Diagnostic criteria for apathy in neurocognitive disorders

A. Primary diagnoses: any major or mild neurocognitive disorder

B. Characteristic symptoms: diminished initiative, diminished interest, diminished emotional expression/responsiveness

C. Chronology: impairment must be a change from their usual behaviour

D. Duration: 4 weeks

E. Severity: clinically significant impairment in personal, social, occupational, and/or other important areas of functioning.

F. Exclusions: not exclusively explained by psychiatric illnesses, physical disabilities, motor disabilities, change in level of consciousness, or the direct physiological effects of a substance

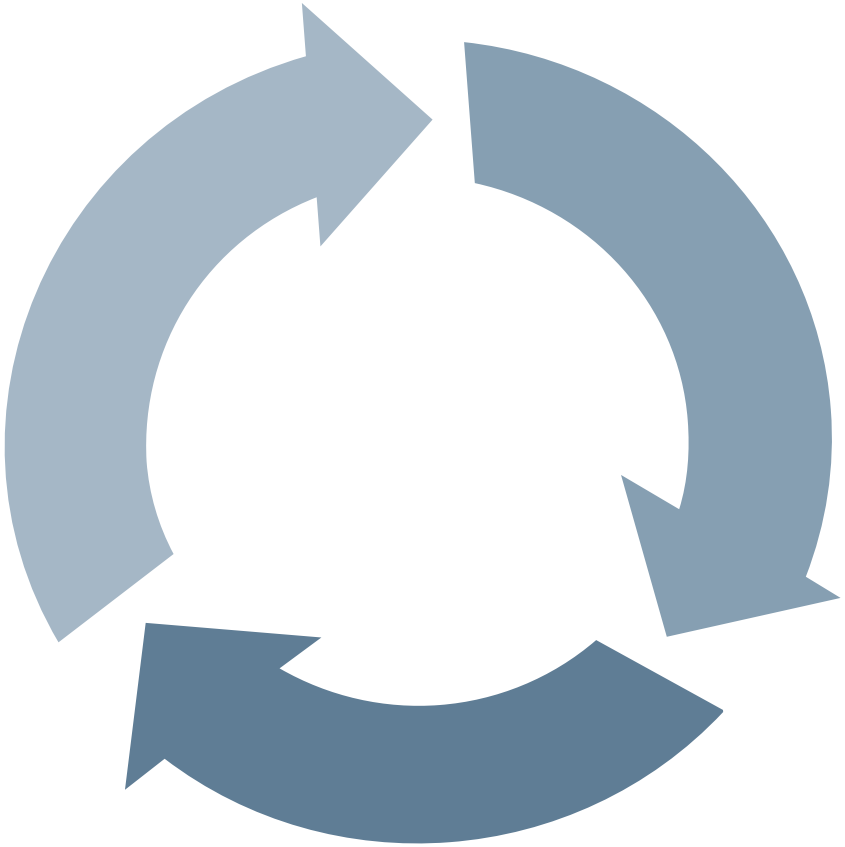
Miller, Robert, Cummings, Sano, Fisher, Baker, Mintzer … Lanctôt, (2021)

Overall Approach – IPA

1 - Investigate

- Review causes and consequences of agitation
- Environmental, interpersonal, psychological circumstances

Builds on IPA definition



2 - Plan

- Well-defined, measurable treatment goals, actions to achieve goals, description of roles and timeline
- Use structured assessment tools (e.g. NPI-NH)

3 - Act

- Interdisciplinary team to execute treatment plan