Differentiating apathy from depression in neurocognitive disorders: case presentation and discussion

Krista L. Lanctôt PhD

Damien Gallagher MD FRCPC

John Marotta MD FRCPC

Disclosures

- Krista Lanctôt
  - Research funding from the Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Alzheimer Society of Canada, Canadian Institutes for Health Research, and the Weston Brain Institute.
  - Consultant or Advisory Board: Boehringer Ingelheim, Esai, Exciva, H Lundbeck A/S, Novo Nordisk, Otsuka
- Damien Gallagher
  - Research funding from CIHR and Alzheimer's Association, Alzheimer Society of Canada, Weston Brain institute and ADDF.
  - No conflicts to declare.
- John Marotta
  - Research funding from the Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Alzheimer Society of Canada, Canadian Institutes for Health Research, and the Weston Brain Institute.
  - Lilly payment for presentation 2024; LMC/Centricity consultant to develop community-based cognitive trials site phase 1,2,3 treatments 2022-2024; Last 25 years- PI for cognitive trials sponsored by Elan, Pfizer, Lilly, Novartis, Merck, Roche, Winterlight, Vielight, InmuneBio; Sunnybrook Research Institute phase 3 clinical trials but no ownership/royalties for compounds or diagnostics

Learning Objectives

- Understand overlap between depression and apathy in neurocognitive disorders
- Understand clinical features of each and how to differentiate
- Understand common approaches to clinical care

A typical case*

- 71 yr old female
- Widowed 20 years
- Lives alone
- Presents with daughter
- Reason for referral: ”low mood & forgetfulness”

- Diminished motivation & interest (more withdrawn)
- Initial & middle insomnia
- Reduced appetite & weight loss
- C/o more about back pain/non-specific abdominal pain
- Sad….tearful on daily basis
- Negative ruminations about self and future
- No suicidal thoughts but admits to passive death wish “What’s the point?”

*Based on composite of a commonly seen referral to geriatric psychiatry services

A typical case

Collateral History

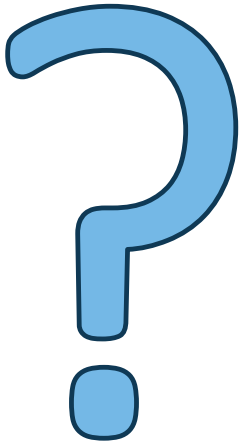
- More forgetful & repetitive over last two years
- Remained independent in BADLs, daughter provided some support with IADLs (daughter took over paying bills, reminders for appointments & medications in blister pack)
- More accelerated decline over last 6 months with increased withdrawal, sadness & weight loss

Past History

- Complicated grief/depression following death of husband
- Took mirtazapine for 6 months and stopped, remained well
- Hypertension/OA/dyslipidemia
- Amlodipine, rosuvastatin, acetaminophen prn

Daughter has questions….

- Is my mother developing dementia/Alzheimer’s?
- Does she have depression or apathy secondary to dementia?
- Is it reversible, what can you do?



Therapeutic approach

Damien Gallagher

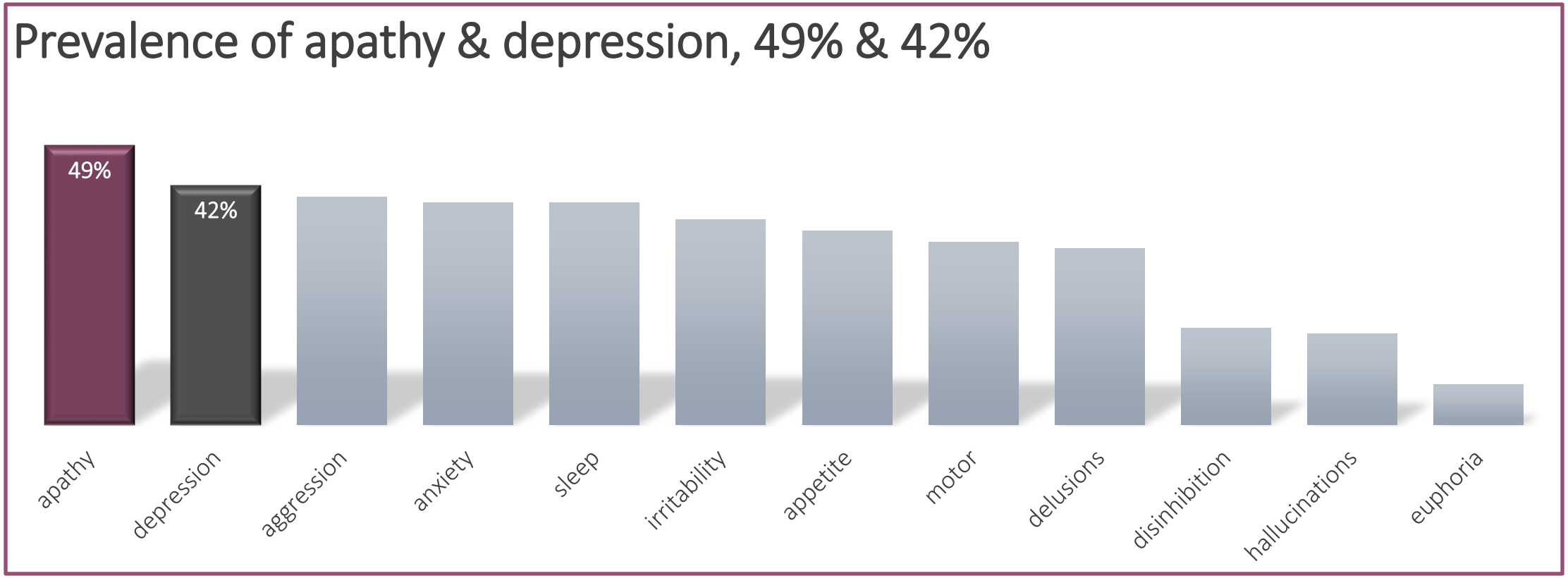
Late life depression

- Common & troubling…
- Point prevalence of approximately 10-15% ”clinically significant depression” in community dwelling populations
- Point prevalence of approximately 1 – 2% for Major Depression in community.
- Depression is not an inevitable part of aging itself
- …but there is a far higher prevalence among those living in long term care and in the context of disability & neurocognitive disorders.

Haigh et al. 2018

Apathy & depression are common NPS in Alzheimer's Disease

- Meta-analysis of 48 studies in AD (NPI scale)



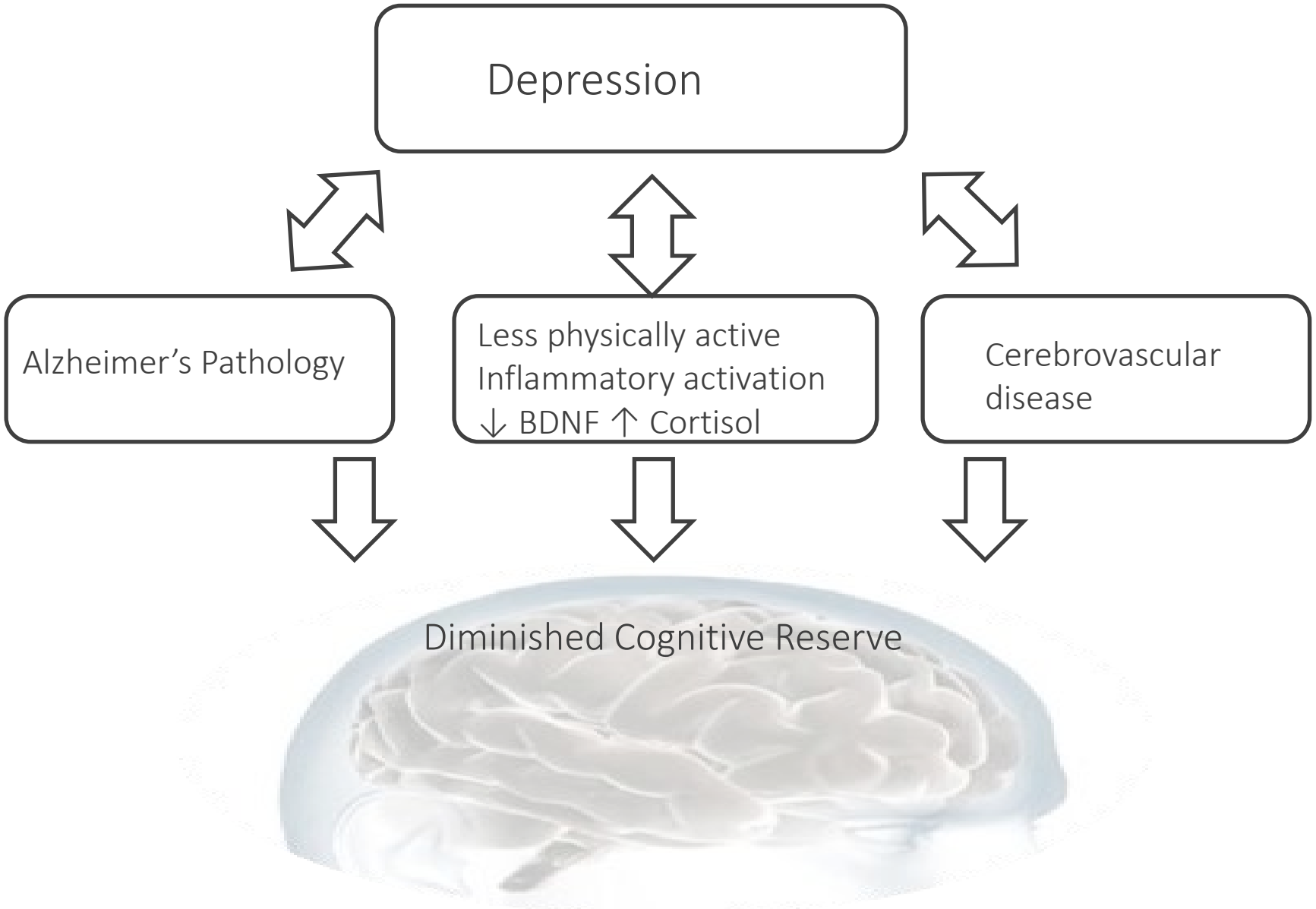
Zhao et al. 2016

Late life depression

- Depression in later life has been associated with an approximate two-fold increased risk of dementia
- Does depression cause cognitive decline ?
- Or do neurocognitive disorders cause depression?

Diniz et al. 2013

…its probably both (bidirectional)



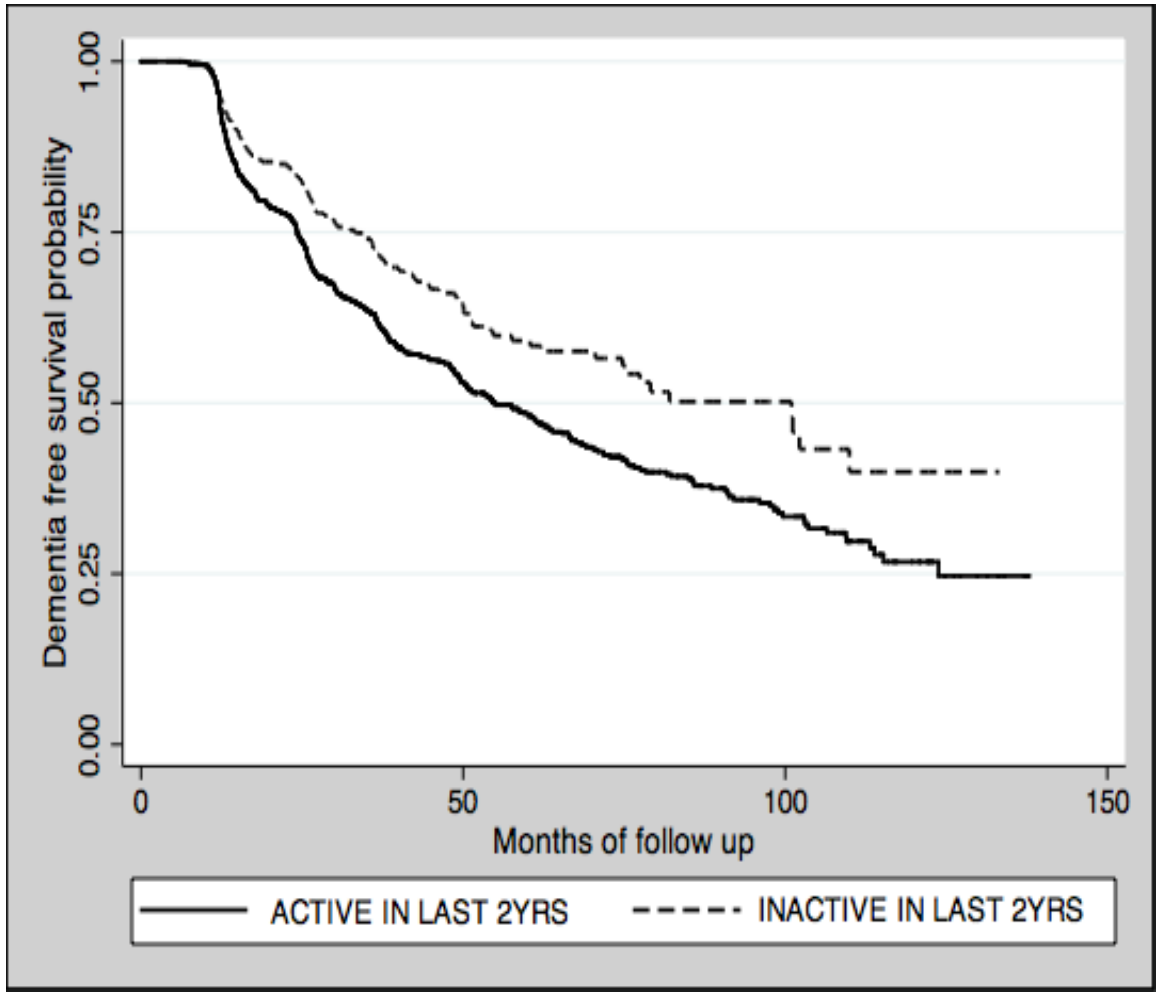
Depression associated with accelerated cognitive decline in MCI

1965 memory clinic patients with MCI followed for median 27 months

656 (41.7%) of those with active depression within the last 2 years developed AD

Compares to 120 (31.6%) of those with a more remote history of depression

($\chi^2 = 13$, $p < 0.001$).



Gallagher et al. Am J Geriatr Psych, 2018

Modifiable risk factors linking depression & dementia

- Canadian Longitudinal Study on Aging,

  n = 14000 followed for mean of 35 months,
- Depression (CESD≥10) associated independently with global cognitive decline
- Several vascular risk factors more prevalent in depression:

  Hypertension,

  DM,

  Sleep apnea,

  Smoking, higher BMI

  Physical & social inactivity.

In mediation analyses, we found that

- *Cerebrovascular disease* ($z = -3.525$, $P < 0.001$)
- *HbA1C* ($z = -4.976$, $P < 0.001$) and
- *Physical inactivity* ($z = -3.998$, $P < 0.001$) each partially mediated the association between depression and cognitive decline.

Screen for & manage vascular risks among older adults with depression.

M Wong, A Kiss, N Herrmann, KL Lanctot, D Gallagher. Modifiable Risk Factors Associated With Cognitive Decline in Late Life Depression: Findings From the Canadian Longitudinal Study on Aging. Can J Psychiatr. 2024

Consequences of depression & apathy

Depression

- Suffering & suicide risk?
- Accelerated cognitive decline
- Physical decline (reduced activity, alcohol/substance/non-adherence to meds?)
- Higher Caregiver burden
- Earlier Institutionalization
- Increased mortality

Apathy

- Accelerated cognitive decline

(some studies that have measured both apathy & depression have reported higher risk of dementia with apathy compared to depression)

- Physical decline (reduced activity/non-adherence to meds?)
- Higher caregiver burden
- Earlier Institutionalization
- Increased mortality

…where to start, a diagnostic approach?

- Some nuances when diagnosing depression in older adults
- May be less likely to report low mood ?
- …but will manifest other typical symptoms of depression (sleep disturbance, poor appetite, weight loss, fatigue, reduced motivation, reduced pleasure in usual activities, more withdrawn, psychomotor agitation/retardation, negative ruminations (guilt, self recrimination, hopelessness, “what’s the point” and/or suicidal thoughts)
- May somatize more? More physical complaints & preoccupation with health concerns (bowel complaints, joint pain, other non-specific symptoms)
- In AD may have more fatigue, psychomotor slowing & apathy vs more mood symptoms, suicidality, anxiety, sleep/appetite disturbance in depression without AD.

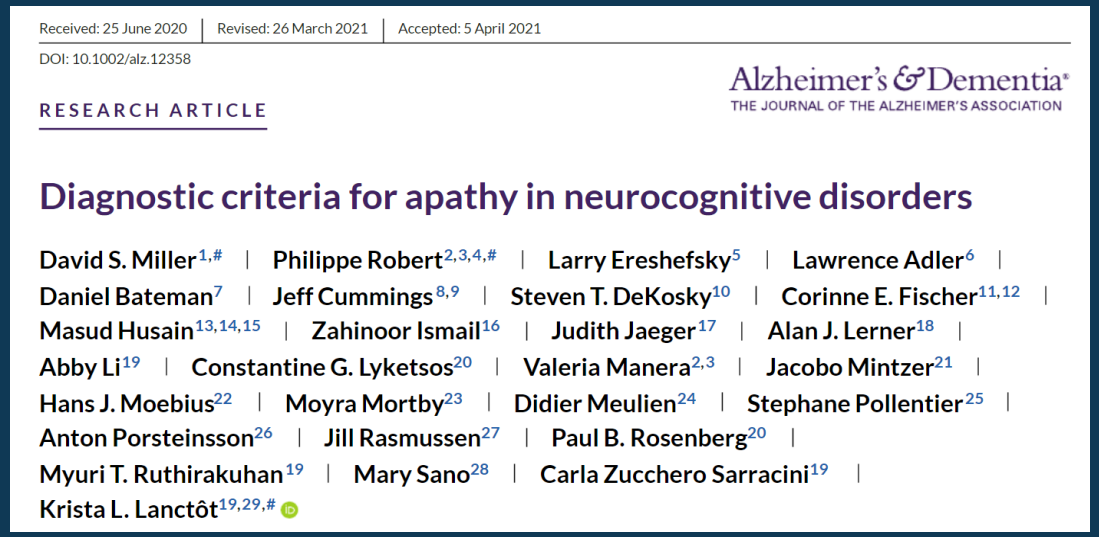
Haigh et al. 2018 Teng et al. 2008

How does a pure apathy syndrome differ?

- Patient unmotivated and flat but does not appear concerned
- Absence of suffering….
- Long, subacute history of decline
- Content to do less & often resent caregiver interventions to activate…
- Deny low mood/sadness
- Not observed to be tearful or sad
- Appetite may be the same (or increased in frontal lobe syndrome)
- Sleep usually preserved (or increased)
- Absence of negative cognitions about self, world and future
- Self care is worse but indifferent to this
- No death wish or suicidal thoughts

Diagnostic criteria for apathy in NCD

Consensus paper 2021



Received: 25 June 2020 | Revised: 26 March 2021 | Accepted: 5 April 2021

DOI: 10.1002/alz.12358

Alzheimer's & Dementia®
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RESEARCH ARTICLE

Diagnostic criteria for apathy in neurocognitive disorders

David S. Miller[1,#] | Philippe Robert[2,3,4,#] | Larry Ereshefsky[5] | Lawrence Adler[6] | Daniel Bateman[7] | Jeff Cummings[8,9] | Steven T. DeKosky[10] | Corinne E. Fischer[11,12] | Masud Husain[13,14,15] | Zahinoor Ismail[16] | Judith Jaeger[17] | Alan J. Lerner[18] | Abby Li[19] | Constantine G. Lyketsos[20] | Valeria Manera[2,3] | Jacobo Mintzer[21] | Hans J. Moebius[22] | Moyra Mortby[23] | Didier Meulien[24] | Stephane Pollentier[25] | Anton Porsteinsson[26] | Jill Rasmussen[27] | Paul B. Rosenberg[20] | Myuri T. Ruthirakuhan[19] | Mary Sano[28] | Carla Zucchero Sarracini[19] | Krista L. Lanctôt[19,29,#]

- Meets criteria for neurocognitive disorder
- Symptoms persistent for 4 weeks at least, change from baseline & associated functional impairment
- Not explained by psychiatric, medical illness or medications/substances.
- At least 1 symptom from 2/3 dimensions below

Initiative	Interest	Emotional Expression

• Less spontaneous and/or active than usual self
• Less likely to initiate usual or novel activities
	• Less enthusiastic about activities
	  • Reduced participation
	  • Less persistence
	  • Less interested in friends and family
		• Less spontaneous emotions
		  • less response to positive or negative events
		  • less affectionate
		  • less empathy

Miller et al… Lanctôt 2021

How to distinguish apathy from depression

	Apathy	Depression
Emotions	Diminished emotion	Dysphoric, sad, tearful
Thoughts and beliefs	Generalized indifference	Hopeless, helpless, worthless
Vegetative symptoms (sleep/appetite)	May be absent	Often present including changes in sleep, appetite, weight
Suicidality	Absent	May be present
Anxiety	Not usually anxious	May be anxious
Counter-transference	No sadness or despair	Clinician feels sadness and despair
Time course	More gradual onset and tends to increase over time	May fluctuate or even decrease with increasing cognitive impairment

Brodaty and Connors 2020
Lanctôt et al. 2023

Assessment

Why now?

- Relevant stressors & unmet needs?
- The first occurrence of any neuropsychiatric syndrome in later life should raise concern….
- Depression with first onset in later life is less likely to be associated with a family history and more likely to be associated with cognitive impairment (Krishnan et al., 2004) (Gallagher et al., 2011).
- Behavioral symptoms are often an early manifestation of a neurocognitive disorder.

Collateral History

- Careful history of cognitive, mood and functional trajectory
- If patient is very amnestic can only really account for how they feel in this moment..
- In case presented, collateral indicates 2 yr hx gradual cognitive decline with superimposed depression during last 6 months.
- Can use validated tools to help that incorporate collateral history (e.g. Cornell scale, NIMHdAD, AES)
- If mild cognitive impairment (non amnestic) may be able to use other tools (e.g PHQ9 or GDS)

Assessment

Mental State Exam

- Exam starts in the waiting room…
- Observe gait(unsteady/parkinsonism/pain?)
- Self care?
- Affect, downcast/flat/distressed/tearful?
- Mood/thought content
- Negative ruminations, delusions?
- Perceptual abnormalities?
- Cognitive assessment (MoCA +/- other neuropsych tests, longitudinal assessment)

Investigations

- To exclude secondary causes or any factors that might exacerbate depression, apathy & cognitive decline
- Physical examination
- Bloodwork
- Neuroimaging

A therapeutic approach (to depression)

- Stepped care approach

- Optimize non pharmacologic strategies initially (consider exacerbating factors, unmet medical needs, pain, social isolation, physical inactivity, situational stressors/boredom)

- Milder depressive symptoms may respond to physical/social/cognitive stimulation and antidepressants ordinarily not indicated at this point. Behavioral or Problem-Solving Therapy/PATH may be helpful.

- In circumstances of moderate to severe depression, antidepressant medication may be indicated (e.g. Sertraline/Duloxetine avoid anticholinergic antidepressants)

- NB: ***Antidepressants not proven to be effective for apathy alone***...can only expect some improvement in motivation if this is secondary to depression.

Hatch et al. 2025

Back to the case, some months later….

- Depression treated, sleep/appetite revert to baseline, patient no longer distressed, able to enjoy certain activities once engaged (goes to day program twice weekly, Sertraline and other meds in blister pack)
- Cognition reassessed (MoCA a little improved but still has marked short term memory loss & needs help with appointments/meds/money management)
- Investigations consistent with early Alzheimer's dementia (MRI, hippocampal atrophy, mild microangiopathic changes, bloodwork non-contributory), vascular risks managed/BP good.
- BUT…..patient remains apathetic, sitting a lot & needs ++encouragement to activate.
- Has lost some muscle mass…one recent fall.
- Daughter concerned about independence/living alone/falls risk
- What to do next ??

A therapeutic approach to apathy

John Marotta

Impact of Apathy

- Faster cognitive and functional decline [Starkstein et al 2006]
- Among NPS, apathy strongest predictor of faster functional decline [Zhu et al 2024]
  - agitation, delusions and hallucinations correlated with functional decline, but magnitudes smaller
  - depression not associated
- Greater caregiver burden [Dauphinot et al 2015]
- Reduced quality of life [Hongisto et al 2018]
- Institutionalization and decreased survival [Garcia-Martin et al 2025, Nijsten et al 2017]

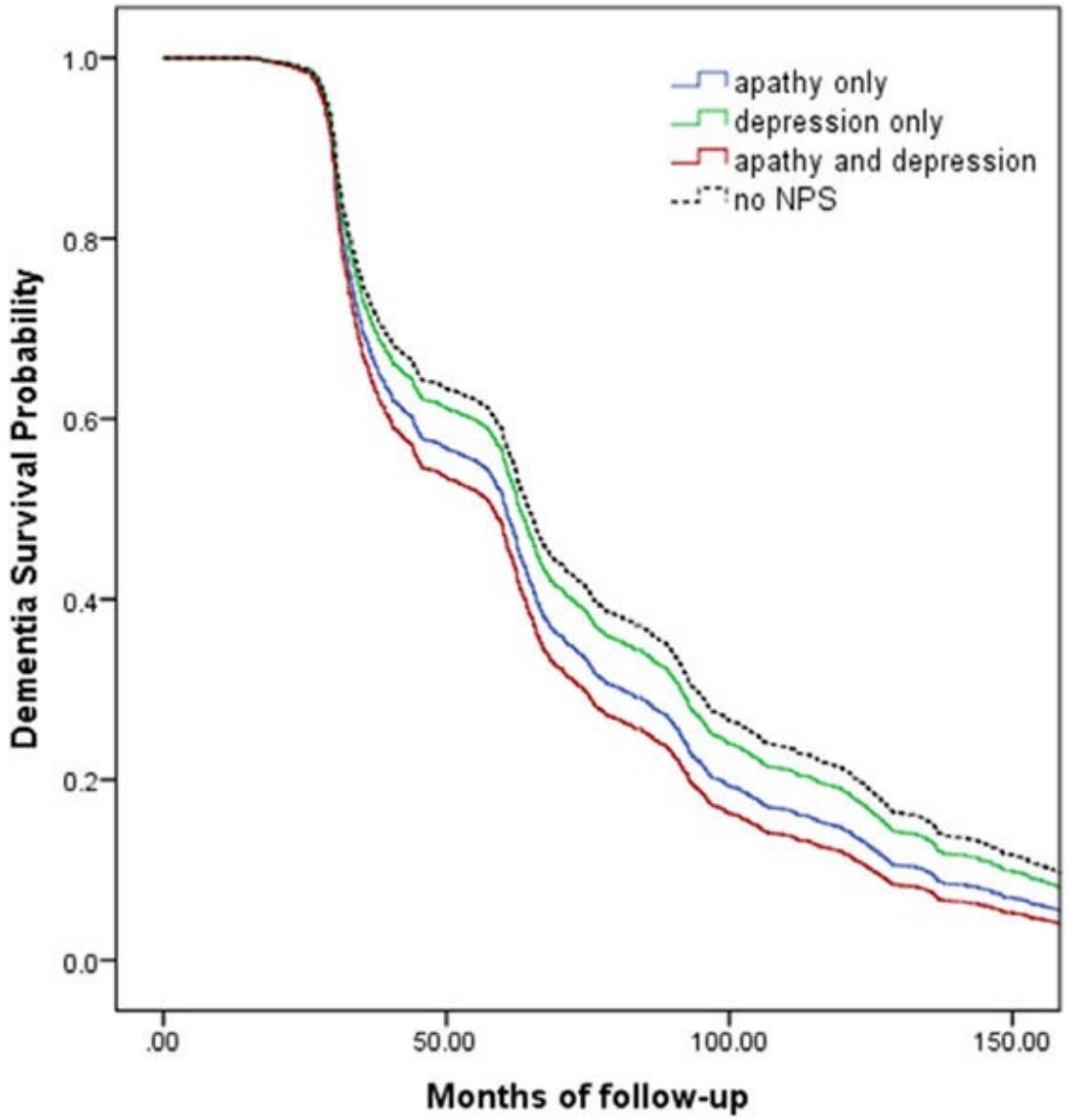
Apathy vs. depression: risk of AD

NACC UDS participants with MCI at baseline (n=4,932)

Followed till onset of AD or loss to follow-up

Risks of developing AD

Apathy alone or both apathy and depression are at a greater risk of developing AD compared to those with no NPS or depression alone



Ruthirakuhan et al. 2019

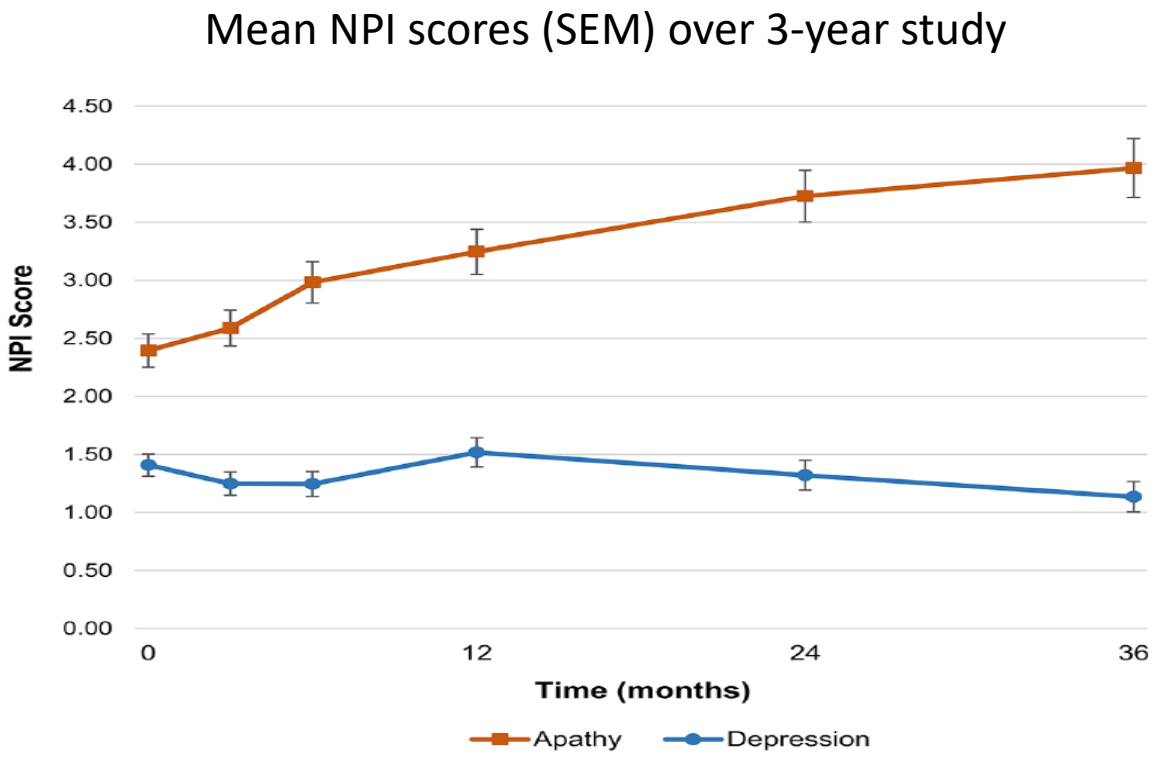
Apathy vs. depression over time

Patients with dementia at baseline (n=779) from memory clinics in Australia, followed 3 years

Baseline: 52% apathy, 50% depression, 32% both

Connors et al. 2023

- Apathy scores increase over time, depression scores did not



- Apathy, but not depression, associated with greater dementia severity, poorer cognition and function, driving cessation and mortality
- Both apathy and depression associated with greater neuropsychiatric symptoms, psychosis, caregiver burden and institutionalization

Psychosocial interventions

- recent review of psychosocial intervention in AD [Oba et al 2022]
  - 4 controlled studies measured apathy Sx (2 with depression)
  - PSI effective in all 4
    - biographically oriented mobilization [Treusch et al 2015], art therapy [Hattori et al 2011], reminiscence group therapy [Hsieh et al 2010] and robot-assisted intervention [Valenti Soler et al 2015]
  - apathy severity low, participants not selected for apathy (except Treusch, where apathy stabilized)
- expert consensus [Manera et al 2020]
  - 20 experts (researchers and healthcare professionals) from 8 countries
  - tailored to deficits, clinical objectives, and preferences
  - technology may help improve treatment and delivery
- structured research, targeting apathy, needed

Recent RCTs with psychosocial interventions for apathy

- Yang et al (2022) –horticultural therapy in n=32 nursing home residents with AD and apathy
  - reduced apathy (AES-I)
- D'Cunha et al (2021) – virtual group cycling experience vs. seated physical activity session in n=10 nursing home residents with cognitive impairment
  - no difference in between-group apathy (PEAR), however participants responded positively to the virtual cycling experience
- O'Sullivan et al (2022) – tablet-based intervention vs. standard activity sessions with n=162 nursing home residents with dementia
  - both decreased apathy (AES-I) slightly
- Pereira et al (2025) – immersive virtual reality (VR) reminiscence intervention vs. non-immersive VR experience in n=20 dementia patients
  - immersive VR reduced apathy (measured by PEAR scale) more

Cognitive enhancers

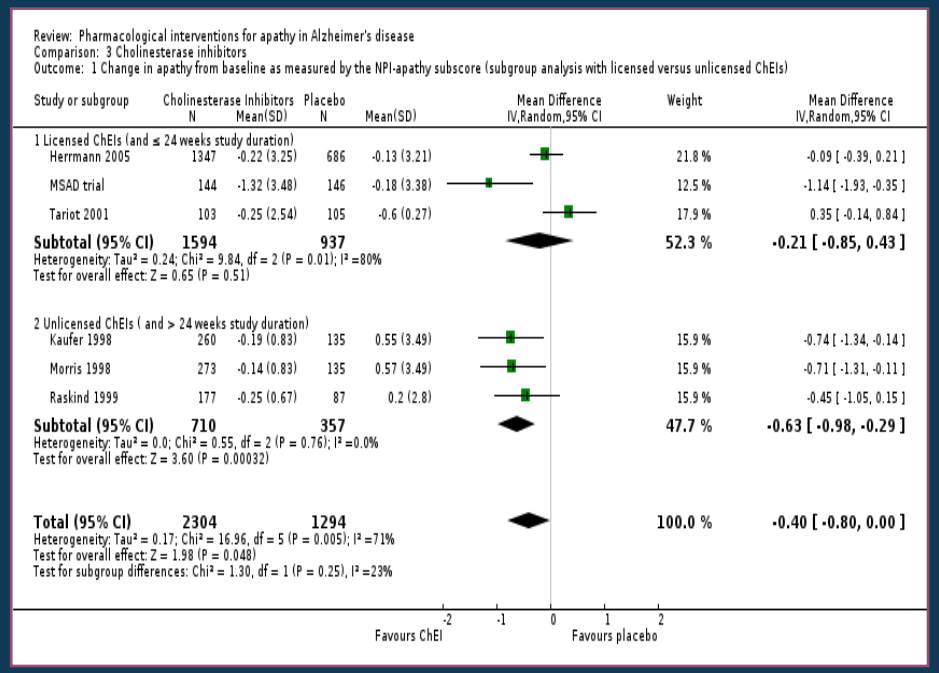
Cholinesterase Inhibitors

- ✓ ChEIs slightly improve apathy compared to placebo (MD -0.40 [95% CI -0.8 to -0.0], P =.05, I^2= 71%)

Memantine

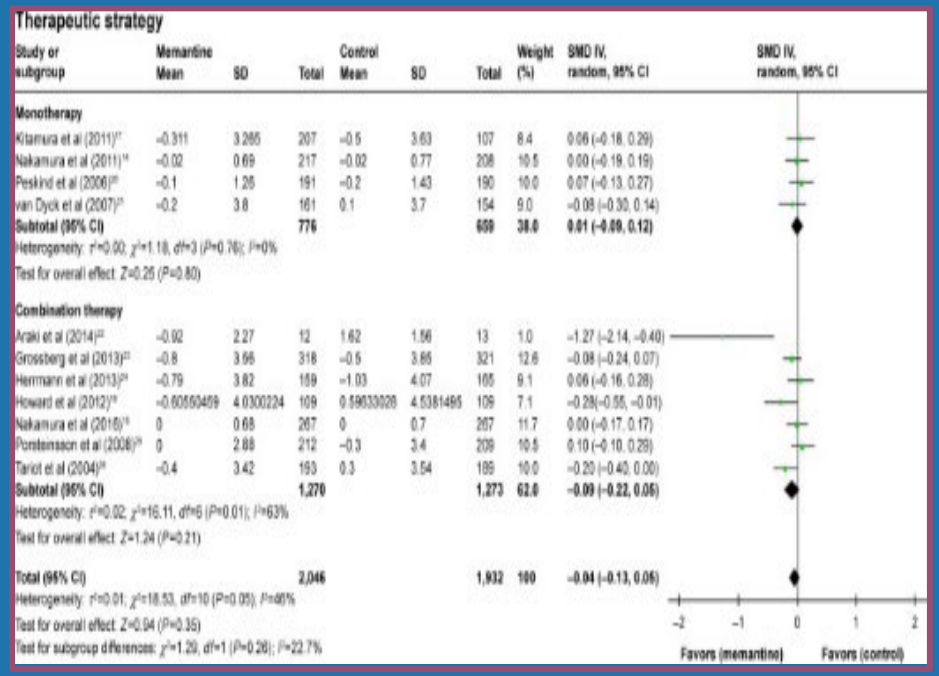
- Memantine alone showed no improvement in apathy

6 studies (n = 3598) of ChEIs with apathy as a secondary outcome (NPI-apathy)



Ruthirakuhan et al. 2018

4 studies (n=1500) memantine vs placebo



Kishi et al. 2017

ADMET 2

Apathy in Dementia Methylphenidate Trial 2

Investigators:

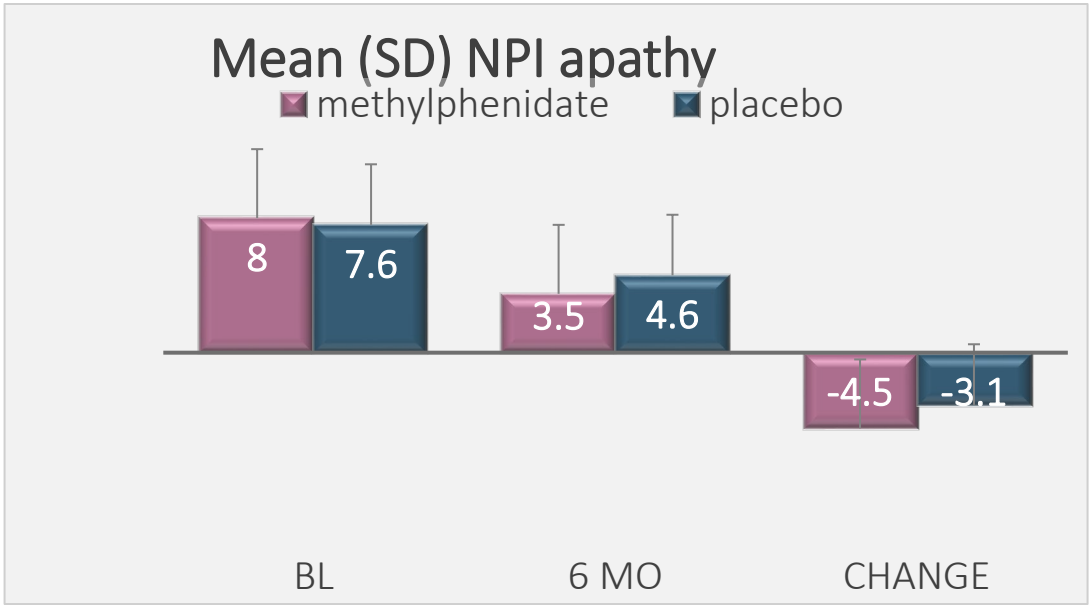
- Jacobo Mintzer
- Krista Lanctôt
- Paul Rosenberg
- Roberta Scherer
- Nathan Herrmann
- Christopher van Dyck
- Prasad Padala
- Olga Brawman-Mintzer
- Anton Porsteinsson
- Alan Lerner
- Suzanne Craft
- Allan Levey
- William Burke
- Jamie Perrin
- David Shade

*Supported by the National Institute for Aging (*R01 AG046543)

Apathy in Dementia Methylphenidate Trial 2

- phase 3 RCT of 6 months, N=200 apathy in AD
- methylphenidate (20 mg/day) vs placebo, psychosocial intervention for both groups
- 9 sites across US and Canada
- 169/180 (93.9%) met diagnostic criteria for apathy [Lanctôt et al 2022]

NPI apathy score improvement 1.3 points (95% CI 0.5, 2.0) greater in methylphenidate vs. placebo (p=.002)

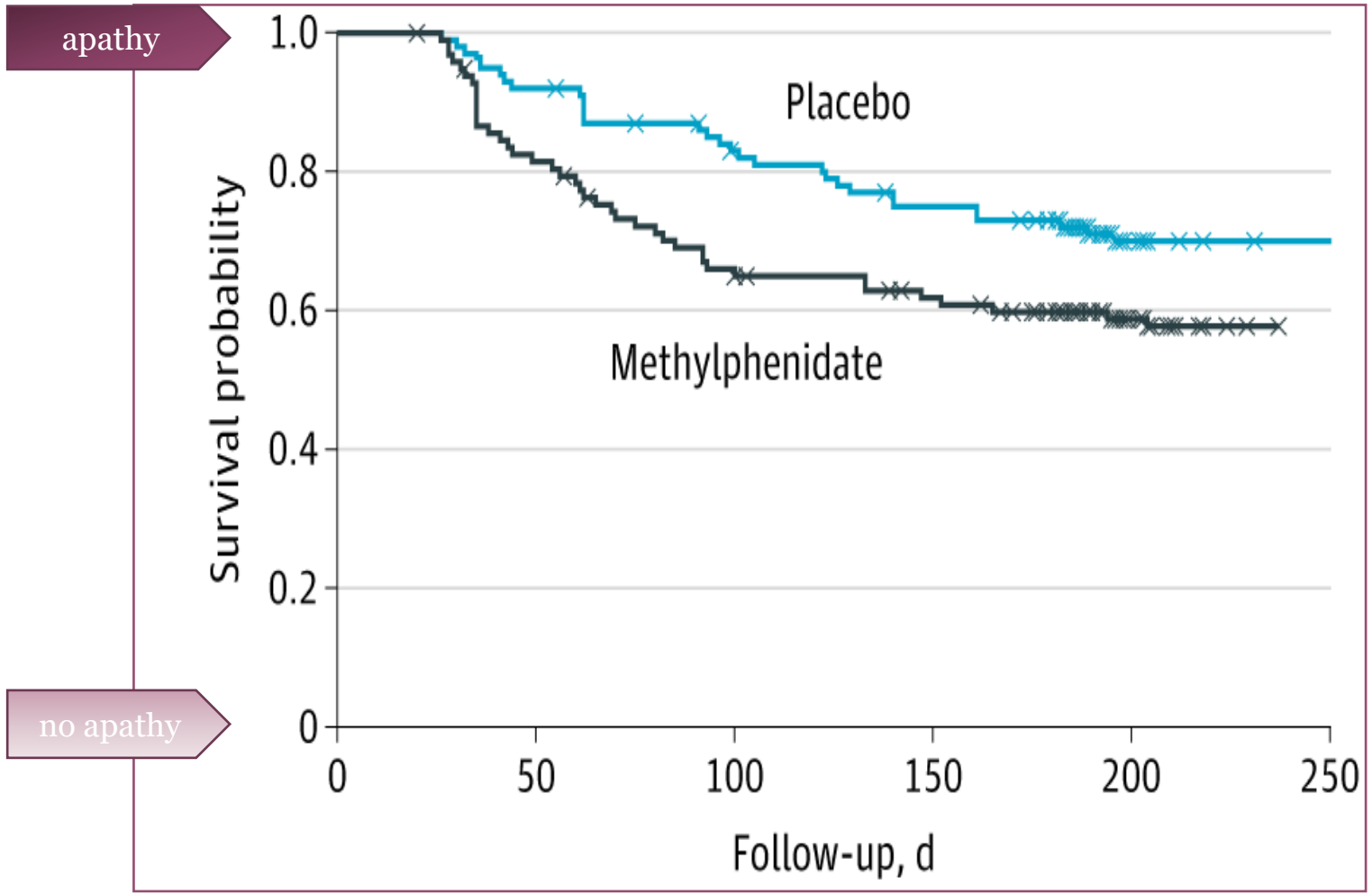


Apathy remission

For the first 100 days, methylphenidate group had >2x increase in remitted compared with placebo group (hazard ratio, 2.2; 95%CI, 1.2-3.9; *P* = .01)

Over 6 months, groups similar (HR 1.6; 95%CI, 0.97-2.5; *P* = .07)

- models adjusted for age, sex, and presence of diabetes



Mintzer, Lanctôt et al. JAMA Neurol 2021

Tolerability

- Completed
  - 89.8% (89/99) MTP, 91.1% (92/101) placebo
- No difference in other NPS, except increased NPI aberrant motor behavior in methylphenidate (mean difference 0.7; 95% CI, 0.1-1.3; P = .03)
- Serious adverse events
  - 17% (17/99) MTP vs 12% (12/101) placebo
  - Unrelated
- Deaths
  - None

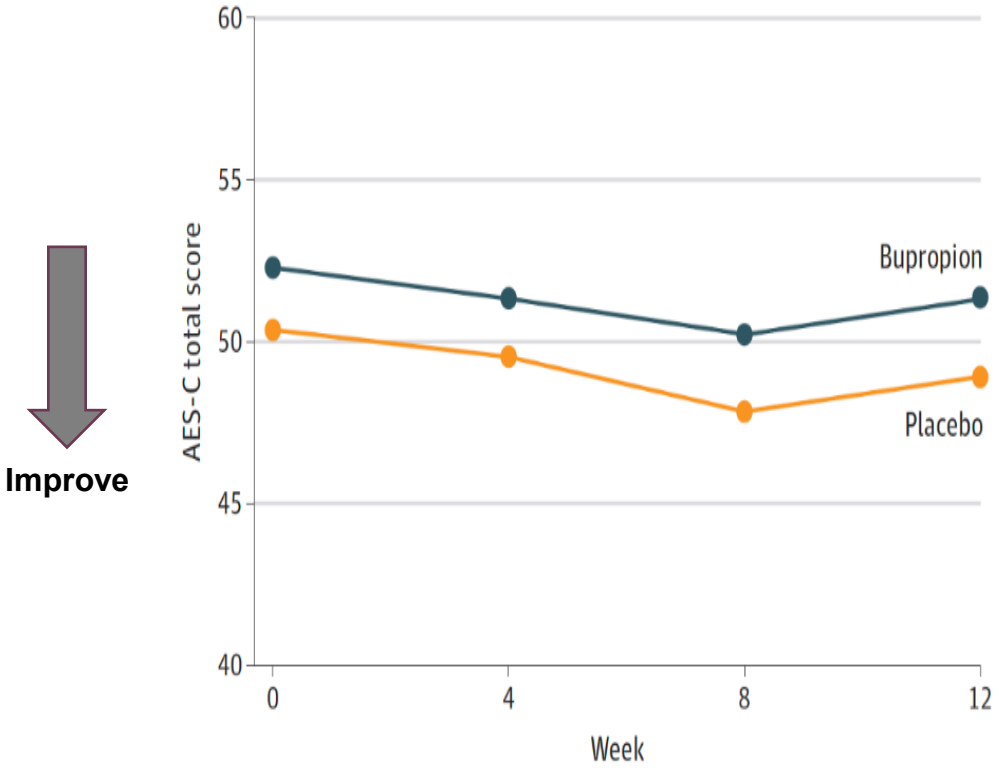
Mintzer, Lanctôt et al. 2021

- > MPH group
  - greater weight loss over 6-month follow-up, with between group difference of 2.8 lb (95% confidence interval, CI: 0.7, 4.9 lb)
  - More falls during follow-up, 10 versus 6 in MPH and placebo groups, respectively
- No differences
  - systolic and diastolic blood pressure
  - post-baseline insomnia
  - no myocardial infarction, congestive heart failure, arrhythmia, stroke, or cardiomyopathy throughout study

Zeng et al. 2024

Unsuccessful treatment of apathy with bupropion in AD

Apathy Evaluation Scale over 12 weeks

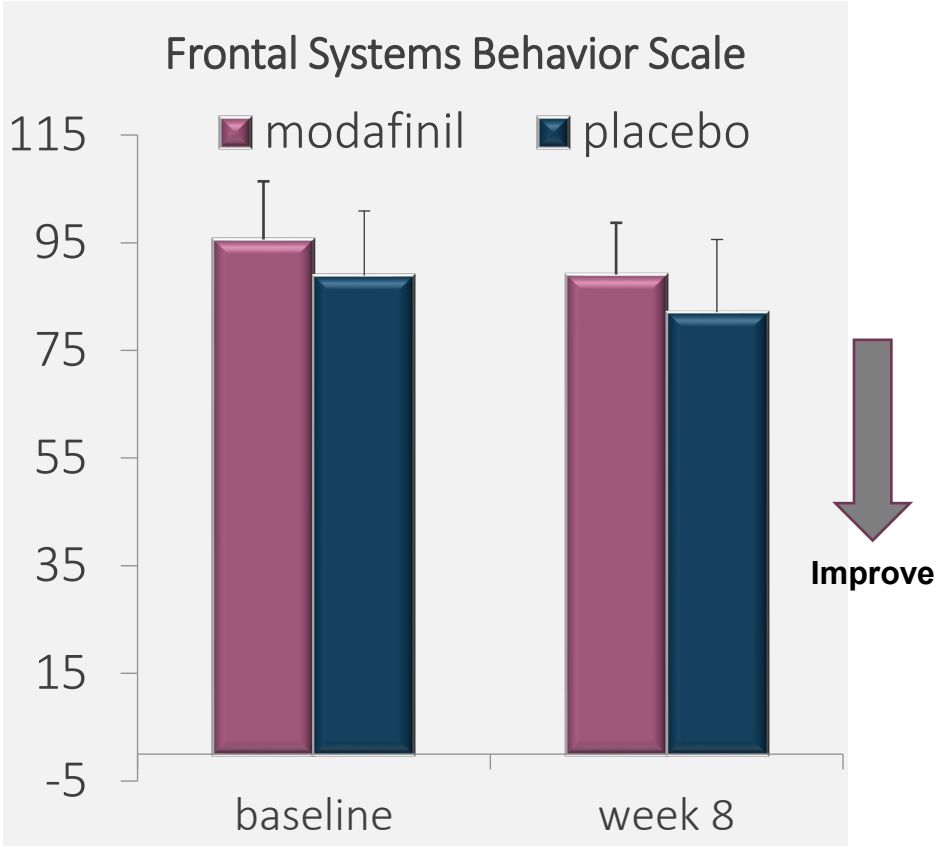


- Multicentre, double-blind, placebo-controlled, randomized trial on apathy in DAT (MMSE 10-25) (n=108)
- bupropion x 12 weeks (150mg x 4 wks, 300mg x 8 wks)
  - inhibits norepinephrine and dopamine reuptake and antagonizes nicotinic acetylcholine receptors
- No significant effect of bupropion compared with placebo
  - trend of worsening in bupropion (adjusted mean difference [95%CI] = 2.2 [–0.5, 4.9]; P = .11)
- Proportions of adverse events similar across groups
  - 39/54 (72%) bupropion, 33/54 (61%) placebo
- Negative effects of bupropion
  - AES-C (emotional subscale)
  - NPI total
  - NPI Caregiver Distress
  - MADRS (depression severity)
  - Quality of Life in Alzheimer Disease Scale

Maier et al. 2020

Unsuccessful treatment of apathy with modafinil

- n = 23 mild-to-moderate probable AD randomized to placebo or modafinil (200 mg daily)
- both groups significant ↓ in apathy (Frontal Systems Behavior Scale)
  - No significant group x time interaction over 8 wks
- MOA distinct from amphetamines (? Inhibit DAT and NE transporters, and ↑ DA, 5-HT, glutamate, and histamine release)



Frakey et al. 2012

Successful treatment of apathy with rTMS

Apathy Evaluation Scale change at 12 weeks

- 20 subjects (N = 9 rTMS and n = 11 sham) with apathy [Padala et al 2020]
  - **Apathy** (AES-C) favouring rTMS vs. sham [–10.1 (–15.9 to –4.3); t (16) = –3.69; p = 0.002]
  - Cognition (3MS) favouring rTMS [6.9 (1.7 to 12.0); t (15) = 2.85; p = 0.012]
  - Instrumental ADL favouring rTMS [3.4 (1.0 to 5.9); χ21 = 7.72; p = 0.006]
  - CGI-S favouring rTMS [1.4 (0.5 to 2.3), t (16) =3.29; p = 0.005]

- Meta-analysis of 4 RCTs involving 89 patients with apathy in AD or MCI [Jin et al 2024]
  - improvement in apathy with high-frequency rTMS at 120% RMT compared to sham (SMD = 1.36, [95% CI = 0.61–2.12]; P = 0.0004)
  - but not with rTMS at 80% RMT

Padala et al. 2020

Approach

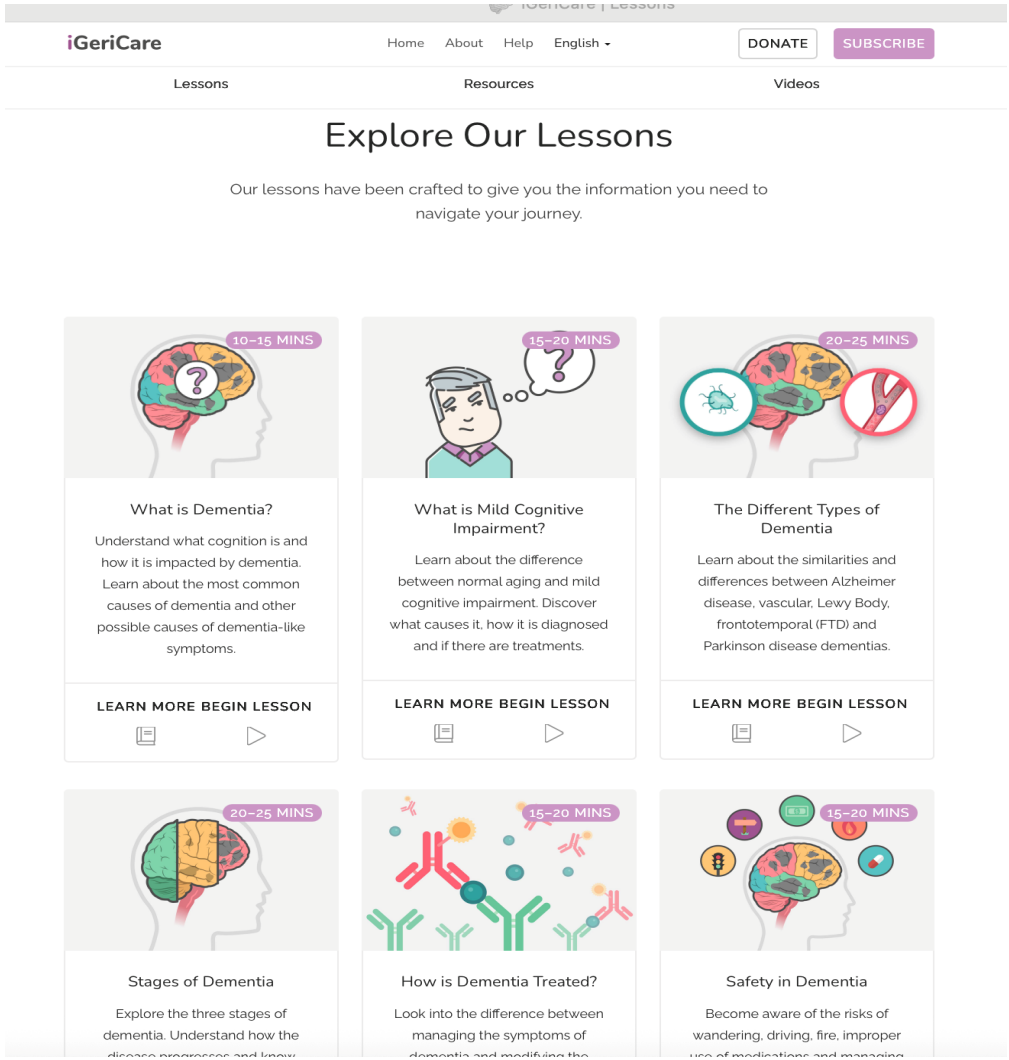
depression

- Psychosocial/patient centred care
- Antidepressant when needed

apathy

- Psychosocial interventions
- Cholinesterase inhibitors
- Other pharmacologic
- (neurostimulation?)

Resources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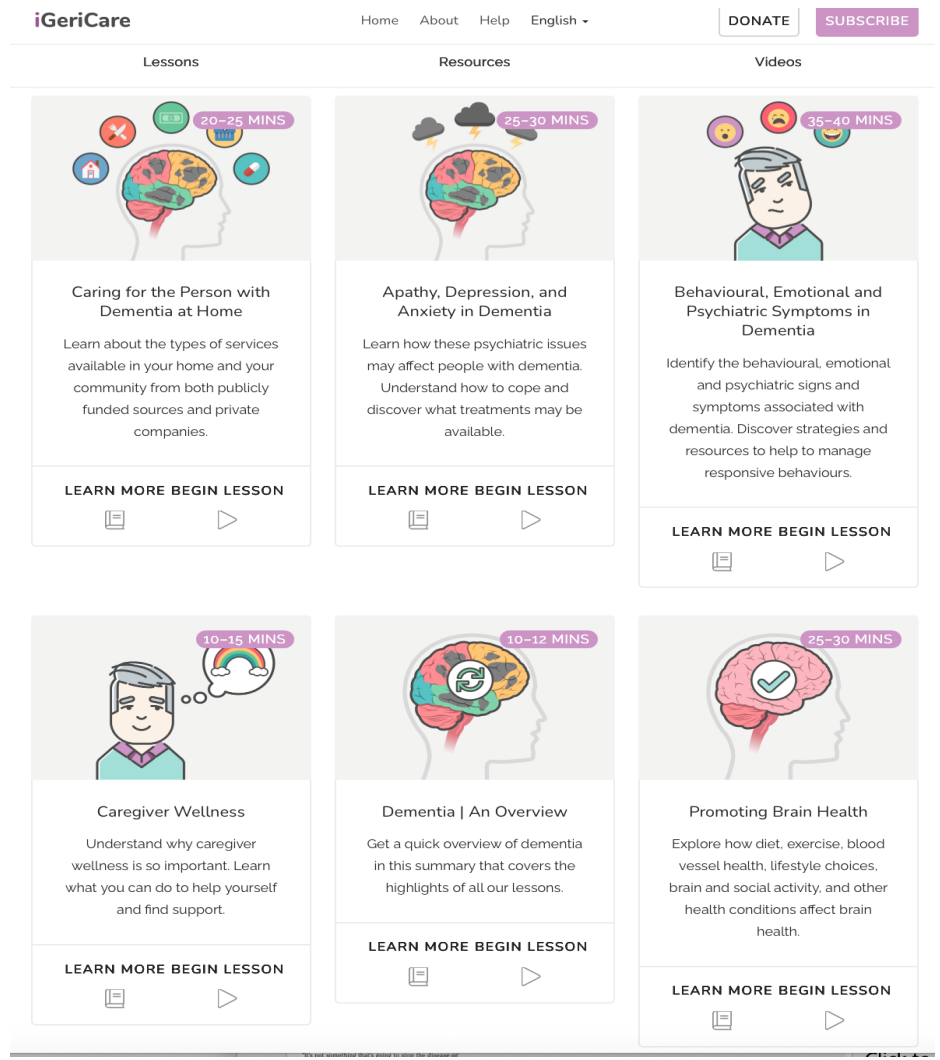
What is Dementia?
Understand what cognition is and how it is impacted by dementia. Learn about the most common causes of dementia and other possible causes of dementia-like symptoms.
LEARN MORE BEGIN LESSON
15–20 MINS
What is Mild Cognitive Impairment?
Learn about the difference between normal aging and mild cognitive impairment. Discover what causes it, how it is diagnosed and if there are treatments.
LEARN MORE BEGIN LESSON
20–25 MINS
The Different Types of Dementia
Learn about the similarities and differences between Alzheimer disease, vascular, Lewy Body, frontotemporal (FTD) and Parkinson disease dementias.
LEARN MORE BEGIN LESSON
20–25 MINS
Stages of Dementia
Explore the three stages of dementia. Understand how the
15–20 MINS
How is Dementia Treated?
Look into the difference between managing the symptoms of
15–20 MINS
Safety in Dementia
Become aware of the risks of wandering, driving, fire, improper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Apathy, Depression, and Anxiety in Dementia
Learn how these psychiatric issues may affect people with dementia. Understand how to cope and discover what treatments may be available.
LEARN MORE BEGIN LESSON
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Behavioural, Emotional and Psychiatric Symptoms in Dementia
Identify the behavioural, emotional and psychiatric signs and symptoms associated with dementia. Discover strategies and resources to help to manage responsive behaviours.
LEARN MORE BEGIN LESSON
10–15 MINS
Caregiver Wellness
Understand why caregiver wellness is so important. Learn what you can do to help yourself and find support.
LEARN MORE BEGIN LESSON
10–12 MINS
Dementia | An Overview
Get a quick overview of dementia in this summary that covers the highlights of all our lessons.
LEARN MORE BEGIN LESSON
25–30 MINS
Promoting Brain Health
Explore how diet, exercise, blood vessel health, lifestyle choices, brain and social activity, and other health conditions affect brain health.
LEARN MORE BEGIN LESSON

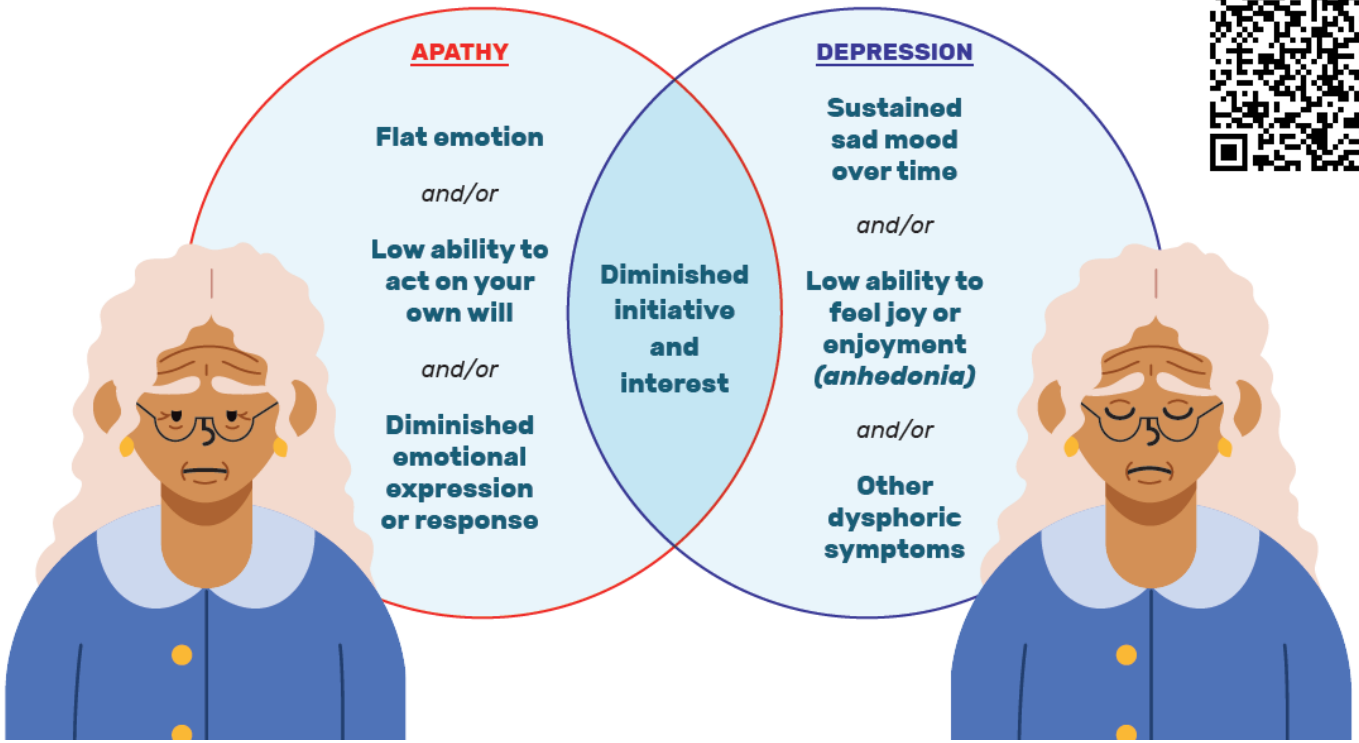
Resources

Distinguishing APATHY from DEPRESSION in neurocognitive disorders

English

Français

- Both APATHY and DEPRESSION are common across neurocognitive disorders. It can be difficult to differentiate them.
- These syndromes often occur simultaneously and have overlapping symptoms.
- Recognizing APATHY as a dementia-related syndrome is critical for people living with neurocognitive disorders, their families and care partners.



CCNA·CCNV

Lanctôt et al. Am J Ger Psychiatr. 2023

Summary

Depression and apathy co-occur in neurocognitive disorders

While clinical features can overlap, these syndromes can be differentiated

A stepped approach to care is recommended

Resources

- ✓ iGeriCare
- ✓ CCNA distinguishing apathy from depression

Discussion

Geriatric Psychopharmacology Research Program

Brain, Behaviour, Biomarkers, and Benefits:
moving lab findings to interventions for cognitive health

Alzheimer's Drug Discovery Foundation

CIHR IRSC
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WESTON BRAIN INSTITUTE

alzheimer's association

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