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THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ISCTM Apathy Workgroup Meeting

February 23rd, 2024

Dr. Krista Lanctôt, Dr. David Miller
Kritleen Bawa, Krushnaa Sankhe

Disclosures

- Krista L. Lanctôt – Consultant or Advisory Board
  - BioXcel Therapeutics
  - Boehringer Ingelheim
  - Bright Minds
  - Bristol Meyers Squibb
  - Cerevel Therapeutics
  - Eisai Co., Ltd.
  - Exciva
  - Ironshore Pharmaceuticals
  - Kondor Pharma
  - H Lundbeck A/S
  - Novo Nordisk
  - Otsuka
  - Praxis Therapeutics
  - Sumitomo Pharmaceuticals

- David Miller
  - Clinical Vice President · Signant Health

Agenda (7:30am-9:15am EST)

Time	Topic
7:30am-7:45am	Welcome and introduction
7:45am-8:30am	Literature review Timeline
8:30am-8:45am	Site updates
8:45am-9:15am	• Discussion/questions

Vision Statement

Apathy as a behavioural and psychological symptom in dementia (BPSD) has increasingly been the focus of research over the last 10 years.

This interest has led to the publication of provisional diagnostic criteria and stimulated interest in this syndrome as a treatment target for both Alzheimer's disease and related dementias.

Apathy can both precede and emerge concurrently with cognitive impairment and other BPSD.

The Apathy Working Group brings together industry, academic and drug regulatory experts.

This expertise will be used to define the relevance of apathy and to better understand, recognize and manage apathy within BPSD and provide a basis for further research.

Literature Update

- Since the last WG meeting in September 2023, these have been the trends in apathy research in neurocognitive disorders:

1. Understanding Mechanisms underlying Apathy:

- *Fronto-striatal alterations correlate with apathy severity in behavioral variant **frontotemporal dementia**.*
- *Establishing the link between motivational disturbances and behavioral rigidity in **frontotemporal dementia**.*

2. Apathy in Prodromal Stages of Cognitive Decline:

- *Pre-stroke and early post-stroke apathy is associated with increased risk of dementia 3 months after stroke.*
- *Apathy and depression in mild cognitive impairment: distinct longitudinal trajectories and clinical outcomes.*
- *Different trajectories of apathy and depression among subjective cognitive impairment individuals with or without conversion to dementia: results from the Memento Cohort in France.*

3. Non-pharmacological and Pharmacological Therapies:

- ***Doll therapy*** *for improving behavior, psychology and cognition among older nursing home residents with dementia: A systematic review and meta-analysis.*
- *Heterogeneity of Response to Methylphenidate in Apathetic Patients in the* ***ADMET 2 Trial.***
- ***Repetitive transcranial magnetic stimulation*** *for apathy in patients with neurodegenerative conditions, cognitive impairment, stroke, and traumatic brain injury: a systematic review*

4. Apathy Evaluation and Management:

- *The development and feasibility evaluation of a program to identify and manage apathy in people with dementia: the SABA program.*
- *Identifying and managing apathy in people with dementia living in nursing homes: a qualitative study.*
- *Developing a machine learning model for detecting depression, anxiety, and apathy in older adults with mild cognitive impairment using speech and facial expressions: A cross-sectional observational study.*

5. Other

- *Cost consequence analysis of Apathy in Dementia Methylphenidate Trial 2 (ADMET 2).*
- *Alleviating the social, health, and economic costs of apathy in dementia.*

Identifying and managing apathy in people with dementia living in nursing homes: a qualitative study

Johanna M. H. Nijsten[1,2,3,4*], Martin Smalbrugge[5,6], Annette O. A. Plouvier[2,3], Raymond T. C. M. Koopmans[2,3,7], Ruslan Leontjevas[2,3,8] and Debby L. Gerritsen[2,3]

- **Aim:** To identify and manage apathy in patients with dementia and apathy, in a nursing home, by engaging with their family and professional caregivers
- **Intervention:** beginning the formulation of the Shared Action for Breaking through Apathy program (SABA)
- **Methods:** A generic qualitative study design was employed to explore individuals' subjective attitudes, opinions, beliefs, and reflections. In-person interviews were conducted with patients and caregivers under the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.
- **Results:** Three themes and several subthemes emerged:

Theme	Sub-themes
The challenge to appraise signals	• Perceiving loss of emotions and behaviour • The importance of knowing the context • Apathy as part of dementia
The perceived impact on well-being	• Perceived impact of apathy on well-being of a patients with apathy • Perceived impact of apathy on the well-being of Family and professional caregivers
Applied strategies to manage apathy	• Stimulating meaningful contact • Adjusting expectations • Appreciating little successes

- apathy; b) apathy adversely affects patients with dementia, and their caregivers; and c) caregivers can effectively use specific strategies to manage apathy
- Strategies such as fostering meaningful interactions, adapting expectations, and acknowledging small achievements can interrupt apathy, temporarily.
- In trying to address apathy, caregivers should maintain a balance between under and overstimulation patients.

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The development and feasibility evaluation of a program to identify and manage apathy in people with dementia: the SABA program

Johanna M. H. Nijsten, Annette O. A. Plouvier, Martin Smalbrugge, Raymond T. C. M. Koopmans, Ruslan Leontjevas & Debby L. Gerritsen

- **Aim:** To develop and evaluate the feasibility of a **theory and practice based intervention** to assist family and professional caregivers to identify and address apathy in patients with dementia living in nursing homes.
- **Intervention:** the Shared Action for Breaking through Apathy program (SABA)
- **Methods:** Development phase- Intervention mapping (IM) method comprising of six steps; Feasibility phase- checking feasibility in terms of demand, acceptability, implementation, practicality, integration and limited efficacy
- **Results:** 10 persons with dementia and apathy participated in the intervention, along with 7 family and 4 professional caregivers; 11 professional caregivers were included in a focus group:
  - Phase I- **needs assessment** with stakeholders gave rise to three themes to be addressed: identifying signs of apathy, perceived effects of apathy, and ability to deal with apathy.
  - Next, behavioral aspects of caregivers that needed change identified
  - feasibility study designed and implemented in Phase II.
- SABA program demonstrated feasibility in identifying and addressing apathy in dementia in NH.
- Caregivers highlighted that materials and procedures were tailored to their needs
- Factors including deprioritization of apathy, staff turnover, and the impact of the Covid-19 pandemic recognized as obstacles.
- Program offered tools and strategies to address knowledge gaps, raise awareness, manage expectations, and bolster caregiver skills.

Apathy and depression in mild cognitive impairment: distinct longitudinal trajectories and clinical outcomes

Michael H. Connors, Armando Teixeira-Pinto, David Ames, Michael Woodward, and Henry Brodaty

Aim: examine apathy and depression longitudinally in a sample of patients with MCI over a 3-year period

Measures: Apathy and depression on NPI; function, cognition, caregiver burden, dementia severity, and other neuropsychiatric symptoms (NPS)

Methods: assess longitudinal trajectories over time, separate linear mixed models with apathy as outcomes, time since diagnosis, age, sex, depression, antidepressant use, antipsychotic use, total number of medications and incident dementia as predictors.

Similar analysis on NPI- depression and clinical correlates also conducted.

Results:

- prevalence of apathy gradually increased over study, with depression remaining stable.
- Apathy associated with worse function, cognition, dementia severity and other NPS over time.
- Depression associated with worse function, to lesser degree than apathy, and NPS over time, not cognition or dementia severity

Conclusions: Apathy increases in MCI and is associated with worse clinical outcomes.

Due to distinct trajectories and clinical correlates, need to distinguish apathy and depression.

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Measuring clinically relevant change in apathy symptoms in ADMET and ADMET2

Tumati, S, Herrmann, N, Perin, J, Rosenberg PB, Lerner, AJ, Mintzer J, Padala PR, Brawman-Mintzer O, van Dyck CH, Porsteinsson, AP, Craft S, S9, Levey AI, Shade, D, Lanctôt KL

Are the change scores on apathy scales **clinically meaningful**?

FDA
PATIENT-FOCUSED DRUG DEVELOPMENT GUIDANCE PUBLIC WORKSHOP, 2019

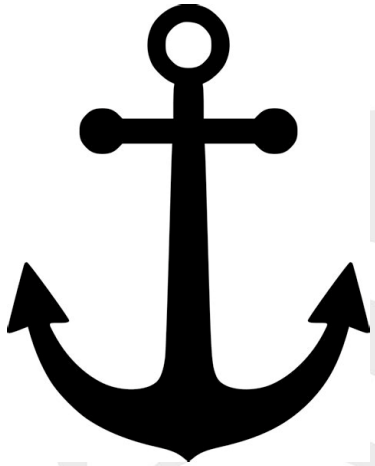
III. MEANINGFUL WITHIN-PATIENT CHANGE

Section Summary

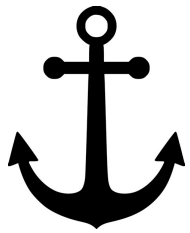
To aid in the interpretation of study results, FDA is interested in what constitutes a meaningful within-patient change (i.e., improvement and deterioration from the patients' perspective) in the concepts assessed by COAs. Statistical significance can be achieved for small differences between comparator groups, but this finding does not indicate whether individual patients have experienced meaningful clinical benefit.

Technical Summary: Key Messages in This Section

- What constitutes, from a patient perspective, a meaningful within-patient change in the concepts evaluated by COAs.
- FDA recommends the use of anchor-based methods to establish meaningful within-patient changes, although there are other methods that can be used.
- Anchors selected for the trial should be plainly understood in context, easier to interpret than the clinical outcome itself, and sufficiently associated with the target COA and/or endpoint.
- Anchor-based methods should be supplemented by the use of empirical cumulative distribution function (eCDF) curves and probability density function (PDF) curves.



- **Within-person** change
- Reported by the **individual or a proxy**



Anchor measure

Clinical Global Impression of Change in Apathy (CGIC-A)

Rated by independent clinician (blinded) following interview with participant and care partner

7-level ordinal scale

Improved (1-3):
Marked – Moderate – Minimal

No change (4)

Worsened (5-7):
Minimal – Moderate – Marked

Target scales

Administered to care partner by clinician (blinded)

- **Neuropsychiatric Inventory – Apathy (NPI-A)**
  Range: 0-12; frequency x severity
  ≥ 4 was an inclusion criteria for both trials
  Change at Wk 6 (ADMET) and each month (ADMET 2)

- **Apathy Evaluation Scale – Informant rated (AES-I)**
  Range: 18-72; 18-item questionnaire, rated 0-4
  Change at Wk 2, 4 and 6 in ADMET

- **Dementia Apathy Interview and Rating Scale (DAIR)**
  Range: 0-3; 16-item questionnaire, rated 0-3
  Change at each month in ADMET 2

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Apathy in Dementia Methylphenidate Trials

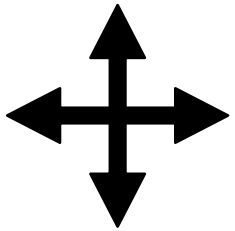
Methylphenidate (MPH - 20mg/day) vs Placebo

- ADMET : Phase II, 6-week, multi-site, randomized, double blind trial; Assessment visits at **weeks 2, 4 and 6**
- ADMET 2 : Phase III, 6-month, multi-site, randomized, double blind trial; Assessment visits at **each month (1 to 6)**

Both (MPH and placebo) groups also received an effective psychosocial intervention.

	ADMET (N=60)	**ADMET 2** (N=200)
Treatment (MPH)	29 (48.3%)	99 (49.5%)
Age (median)	78	76
Sex (male)	23 (38.3%)	131 (65.5%)
Education		
HS or less	24 (40.0%)	49 (24.5%)
Some College	13 (21.7%)	40 (20.0%)
Bachelor's degree	13 (21.7%)	58 (29.0%)
Grad/Professional	9 (15.0%)	52 (26.0%)
MMSE	20.1 (6.0)	18.9 (4.8)
Alzheimer's Medications		
None	-	42 (21.0%)
ChEI-Yes	43 (71.7%)	145 (72.5%)
Memantine-Yes	37 (61.7%)	75 (37.5%)
Others-Yes	-	3 (1.5%)
NPI-total	16.5 (7.9)	16.4 (9.8)
NPI-Apathy (NPI-A)	7.5 (2.3)	7.8 (2.4)
NPI-A Severity		
Mild	8 (13.3%)	24 (12.0%)
Moderate	43 (71.7%)	132 (66.3%)
Severe	9 (15.0%)	43 (21.6%)
AES-I/DAIR	49.7 (11.7)	1.92 (0.50)

Score range on scales can limit assessment of symptom severity



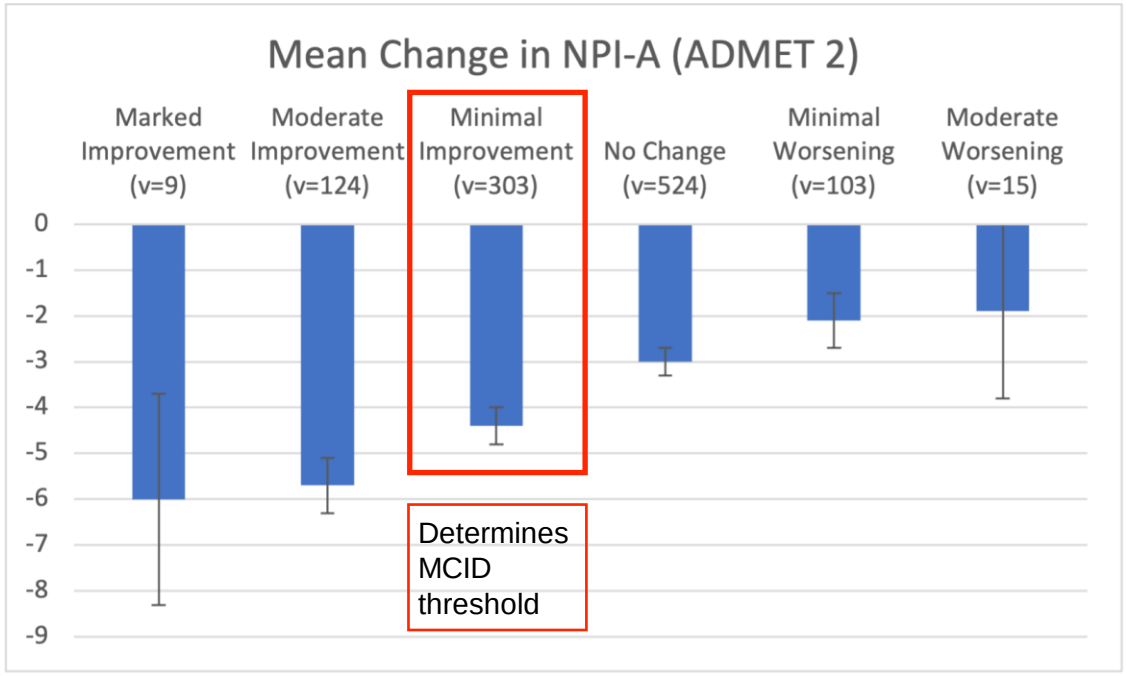
	ADMET (visits=240)		ADMET 2 (visits=1294)	
	NPI-A	**AES-I**	**NPI-A**	**DAIR**
Mean (SD)	5.79 (3.28)	49.7 (11.7)	4.75 (3.34)	1.52 (0.70)
Floor (%)	10 (4.2%)	0 (0%)	198 (14.9%)	35 (2.7%)
Ceiling (%)	11 (4.6%)	0 (0%)	73 (5.6%)	0 (0%)

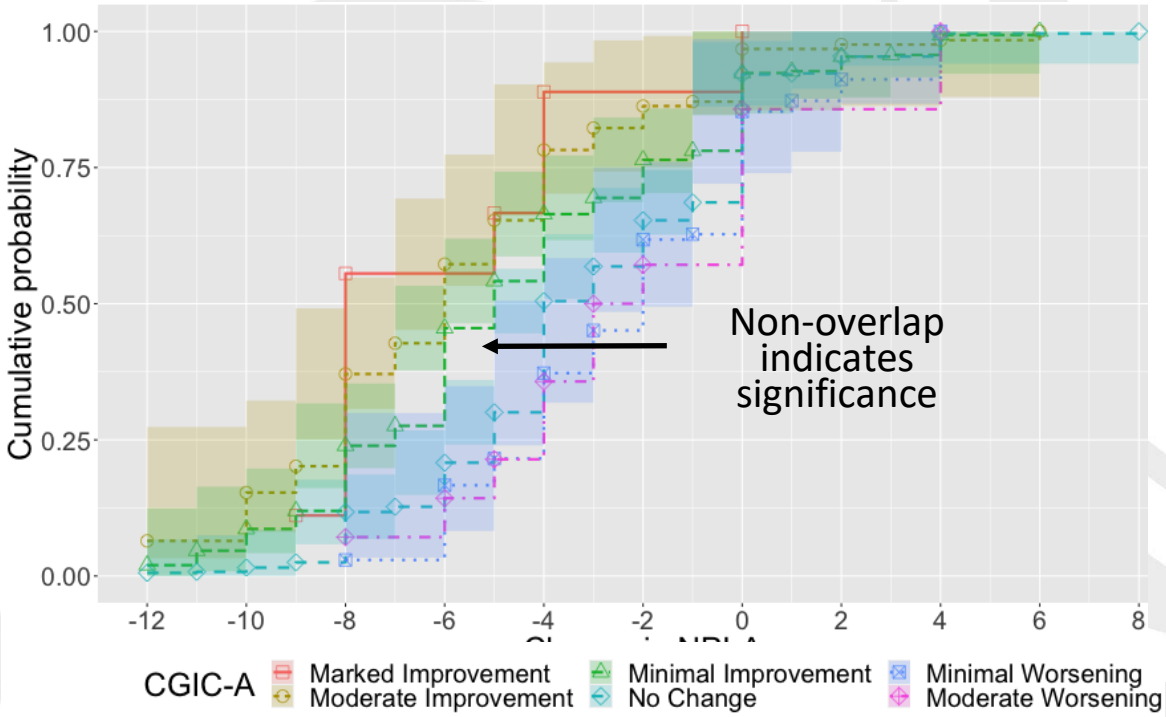
Includes those with remitted apathy

Do change scores "move" relative to CGIC ratings?

	Correlation r(CI) with CGIC-A	**Test-retest** r(CI) CGIC-A: No change
NPI-A (ADMET)	0.2 (0.0-0.5)	0.3 (0.0-0.6)
AES-I	0.4 (0.2-0.6)	0.9 (0.7-0.9)
NPI-A (ADMET 2)	0.4 (0.3-0.5)	0.3 (0.1-0.5)
DAIR	0.4 (0.2-0.5)	0.5 (0.3-0.6)

Spearman correlations





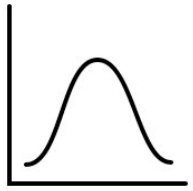
CDF: Cumulative Distribution Frequency

Estimated thresholds indicating MCID:

NPI-A : 4 points

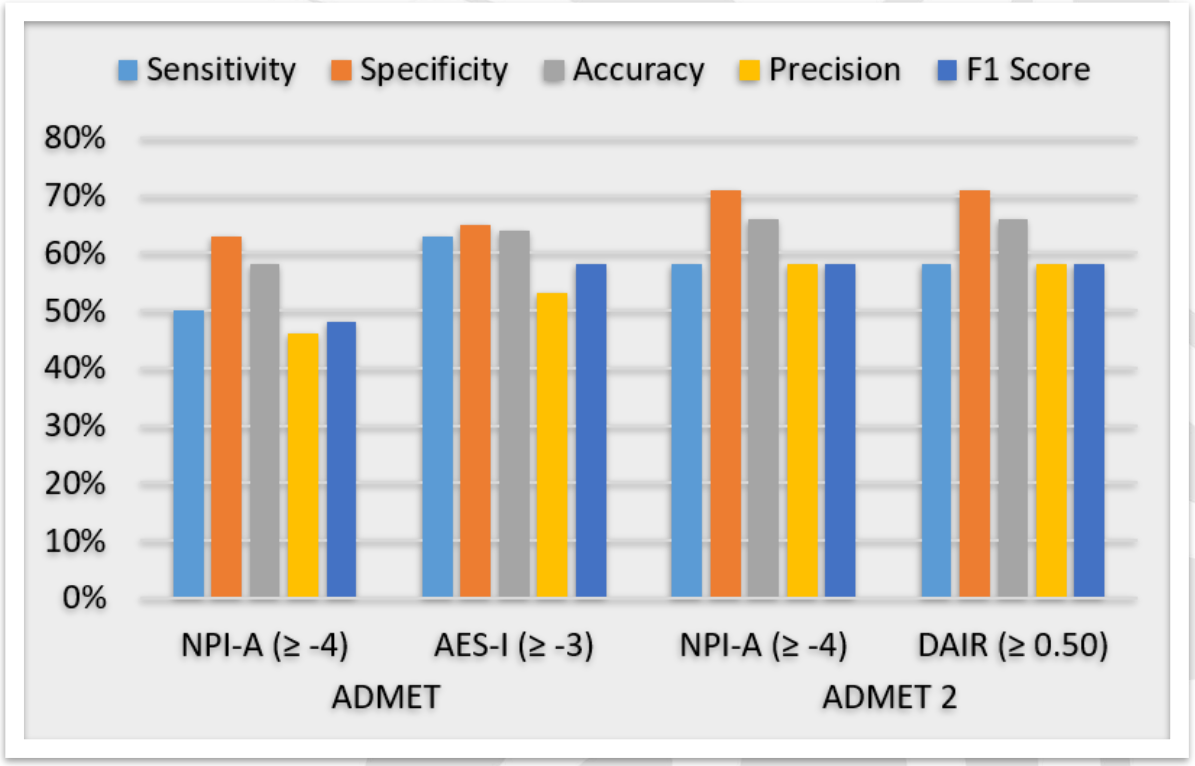
DAIR : 0.50 points

~~AES-I : 3 points~~



Reliability Change Index (95% confidence)			
ADMET		ADMET 2	
NPI-A	**AES-I**	**NPI-A**	**DAIR**
3.5	11.6	3.6	0.50

Performance is modest (~60%) on all metrics: specificity and accuracy highest on the NPI-A



- **Need to consider alternative scales that**
  Can measure symptoms of apathy better

  Map onto the Diagnostic Criteria for Apathy

- **Blood-based biomarkers**

  Neural damage: Neurofilament light (NFL)
  S100B

  Inflammation: Interleukin (IL)-6, IL-10,
  Tumor Necrosis Factor (TNF)

  Oxidative stress: 4-hydroxynonenal (4-HNE)
  Lipid hydroperoxides (LPO)
  8-isoprostanes (8-ISO)
  Ratio of 8-ISO to LPO (8-ISO/LPO)

- **Outcomes** at 6 months

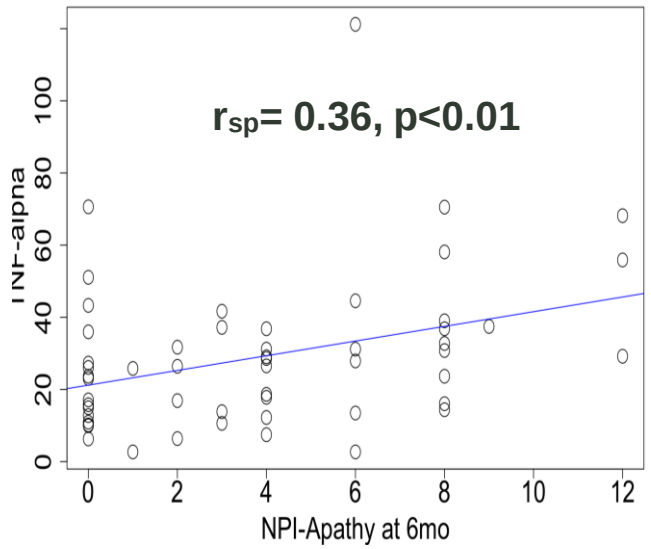
(1) Change in NPI-A

(2) Remitters: (NPI-A = 0)

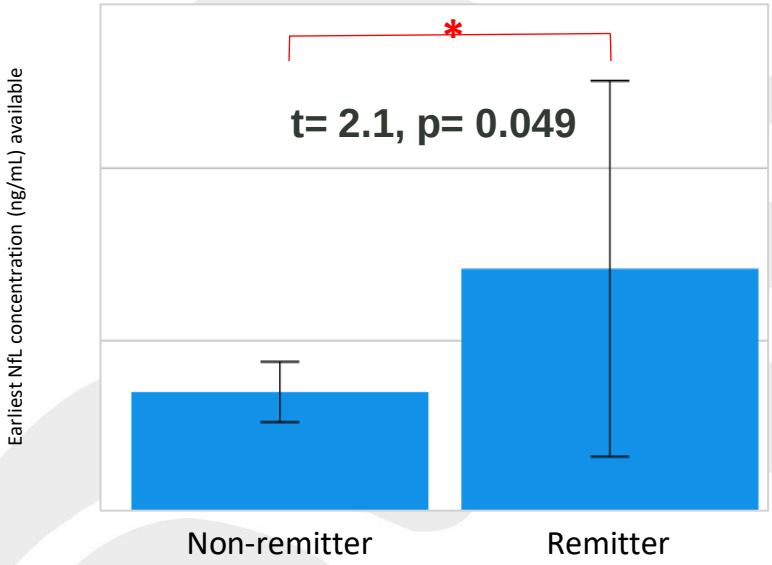
ADMET 2 subset: baseline characteristics

	n=49
Age (median, IQR)	75 (71-81) y
Sex (Female, %)	42.6%
Education (%)	
Up to High school diploma or GED	19.1%
Some college or associate degree	25.5%
College degree	27.6%
Graduate/Professional degree	27.6%
Alzheimer's medications (%)	68.1%
Diastolic, mean (SD)	78 (69.5 - 82.5)
Systolic, mean (SD)	137 (125 - 151.5)
MMSE, mean (SD)	19.8 (4.7)
Digit span, mean (SD)	8.3 (2.8)
NPI-Total, mean (SD)	16.7 (8.8)
NPI-apathy, mean (SD)	8.5 (1.9)

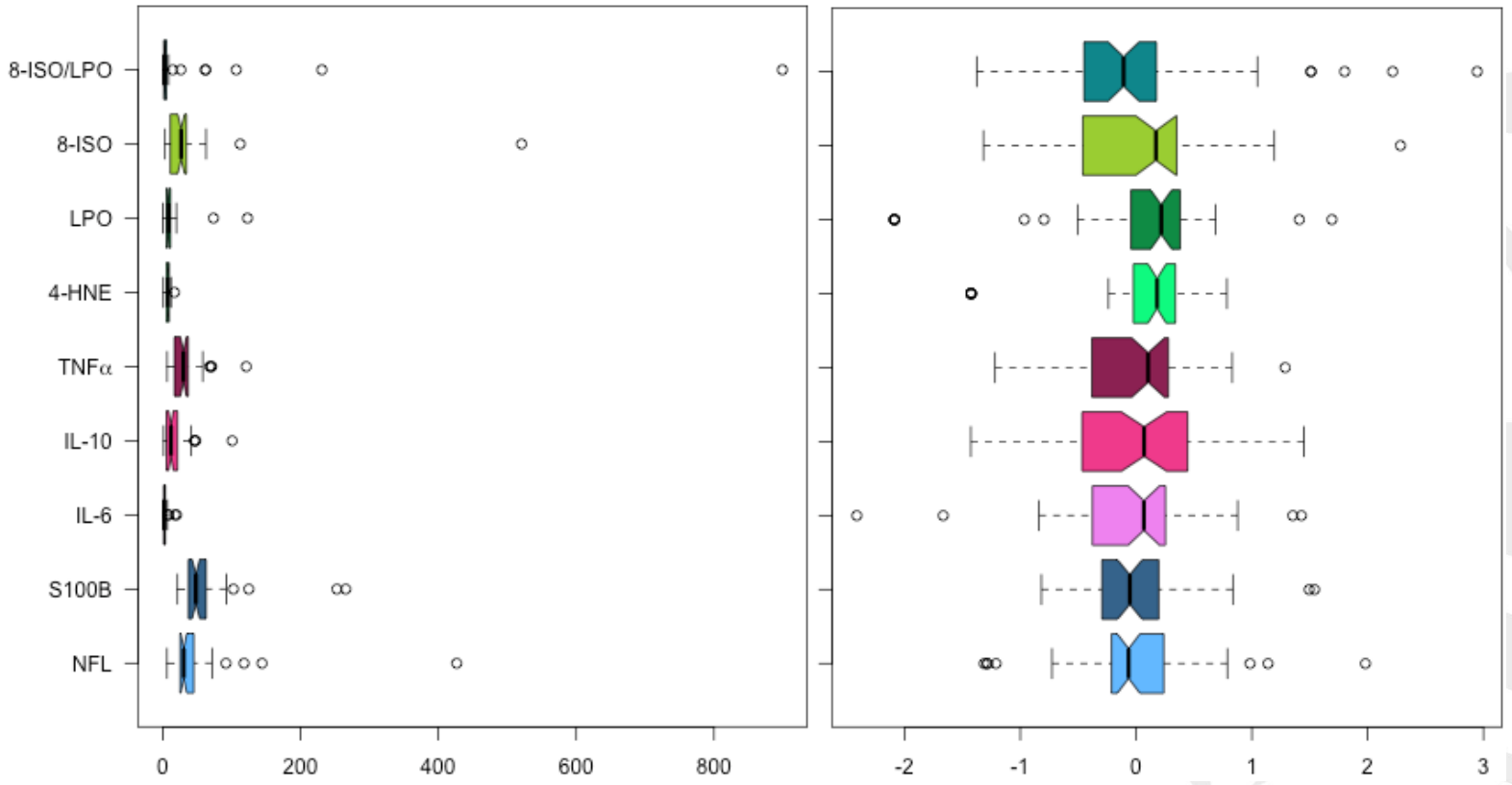
Biomarkers	
NFL, ng/ml, mean (SD)	45.1 (61.4)
S100B, pg/ml, mean (SD)	59.3 (46.8)
IL-6, pg/ml, mean (SD)	3.6 (3.8)
IL-10, ng/ml, mean (SD)	17.4 (18.9)
TNFα, pg/ml, mean (SD)	31.5 (21.0)
LPO, uM, mean (SD)	12.6 (20.4)
5-HNE, pmol/ug, mean (SD)	8.1 (2.4)
8-ISO, pg/ml, mean (SD)	34.3 (74.1)
8-ISO/LPH	0.94 (0.24)



Higher baseline TNF associated with higher apathy after 6 months



Nf-L	n	Mean	SD
Remitter	16	70.9	102.2
Non-remitter	39	35.1	27.0



Biomarker distribution before & after normalization (log_{10} + pareto scaling)

Normalization facilitates biomarker analysis by reducing large absolute differences in concentration between biomarkers[2]

Pareto scaling

$$\frac{x - mean(x)}{sqrt(sd(x))}$$

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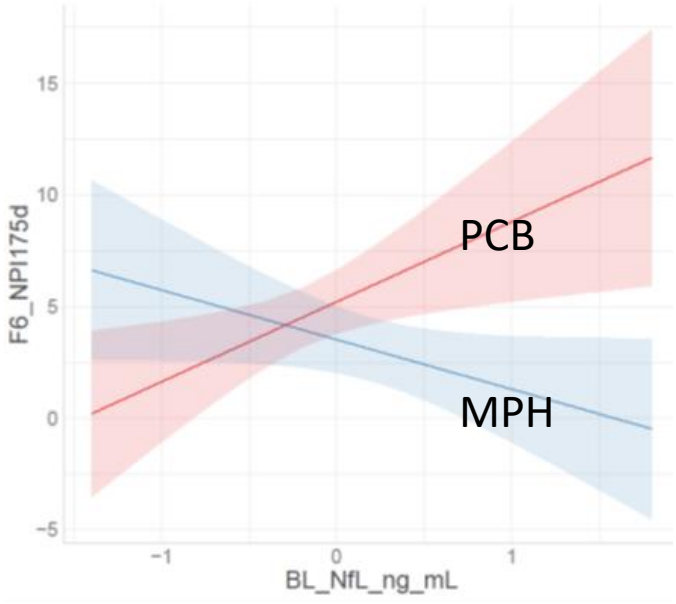
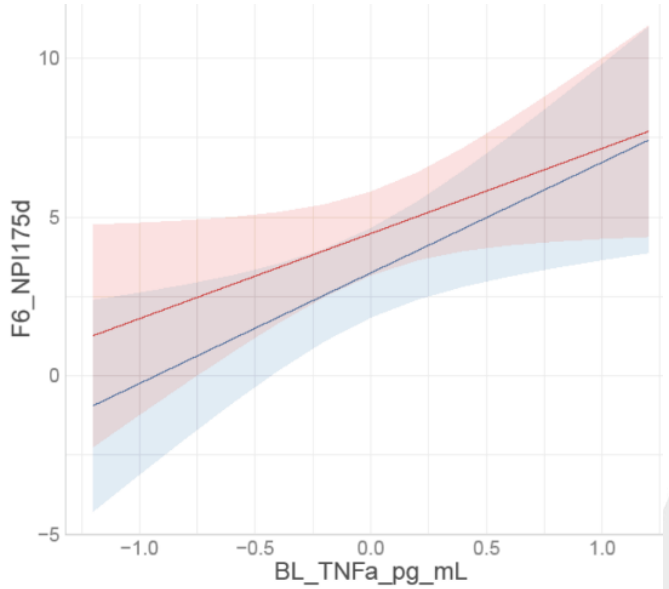
NFL



TNF



Change in NPI-Apathy from Baseline

Biomarker	No. of Patients	Estimate (95% CI	P Value
Overall	49	-1.294 (-3.64, 1.052)	0.285
NFL			
Placebo	26	3.649 (0.927, 6.372)	0.015
Methylphenidate	23	-2.933 (-4.946, -0.92)	0.005
S100B			
Placebo	26	-0.907 (-3.709, 1.894)	0.532
Methylphenidate	23	-2.632 (-7.006, 1.742)	0.252
IL-6			
Placebo	26	-0.249 (-2.524, 2.027)	0.832
Methylphenidate	23	0.58 (-3.179, 4.34)	0.765
IL-10			
Placebo	26	-0.523 (-2.63, 1.584)	0.631
Methylphenidate	23	0.156 (-2.58, 2.891)	0.912
TNF			
Placebo	26	2.845 (0.099, 5.591)	0.054
Methylphenidate	23	3.539 (0.936, 6.141)	0.015
4-HNE			
Placebo	26	1.685 (-0.759, 4.128)	0.190
Methylphenidate	23	-0.223 (-6.507, 6.062)	0.945
LPO			
Placebo	26	-0.785 (-2.469, 1.333)	0.370
Methylphenidate	23	1.22 (-0.89, 2.117)	0.271
8-ISO			
Placebo	26	-1.282 (-3.898, 18.333)	0.347
Methylphenidate	23	-0.356 (-2.829, 19.117)	0.781
8-ISO/LPO			
Placebo	26	-0.099 (-0.207, 0.009)	0.085
Methylphenidate	23	0.007 (-0.098, 0.112)	0.900

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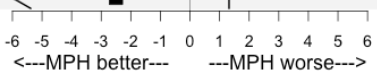
Those with higher NFL responded better

Those with lower TNF responded better

Those with lower 8-ISO responded better

Change in NPI-Apathy from Baseline

Biomarker	No. of Patients (%)	Estimate (95% CI)	n Placebo	n Methylphenidate	LRT(df), p^
Overall	49 (100)	-1.29 (-3.64, 1.05)	26	23	
Nf-L					6.43(2), 0.04
Low	17 (35)	-1.02 (-5.68, 3.64)	13	4	
Medium	16 (33)	1.05 (-2.95, 5.05)	7	9	
High	16 (33)	-5.77 (-9.32, -2.22)	6	10	
S100B					0.16(2), 0.922
Low	17 (35)	-1.19 (-4.89, 2.5)	8	9	
Medium	16 (33)	-0.97 (-5.38, 3.45)	9	7	
High	16 (33)	-2.02 (-5.95, 1.92)	9	7	
IL6					0.16(2), 0.921
Low	17 (35)	-1.77 (-6.54, 3.01)	13	4	
Medium	16 (33)	-0.7 (-5.17, 3.77)	6	10	
High	16 (33)	-0.62 (-4.9, 3.67)	7	9	
IL10					0.3(2), 0.859
Low	17 (35)	-0.75 (-5.9, 4.4)	13	4	
Medium	16 (33)	-1.63 (-5.21, 1.96)	8	8	
High	16 (33)	-0.02 (-4.68, 4.65)	5	11	
TNFa					2.58(2), 0.275
Low	18 (37)	-3.44 (-6.65, -0.23)	9	9	
Medium	15 (31)	-0.55 (-5.02, 3.92)	8	7	
High	16 (33)	0.78 (-3.7, 5.25)	9	7	
4-HNE					2.49(2), 0.287
Low	17 (35)	-0.63 (-3.82, 2.56)	10	7	
Medium	16 (33)	0.38 (-4.12, 4.87)	8	8	
High	16 (33)	-3.88 (-8.41, 0.66)	8	8	
LPO					0.19(2), 0.91
Low	17 (35)	-1.27 (-5.71, 3.16)	11	6	
Medium	16 (33)	-1.53 (-5.61, 2.54)	6	7	
High	16 (33)	-0.33 (-4.69, 4.02)	9	7	
8-ISO					4.41(2), 0.11
Low	17 (35)	-4.36 (-8.19, -0.53)	9	8	
Medium	16 (33)	1.1 (-3.38, 5.58)	10	6	
High	16 (33)	0.13 (-3.77, 4.02)	7	9	
8-ISO/LPO					2.14(2), 0.344
Low	17 (35)	-2.49 (-6.11, 1.13)	8	9	
Medium	16 (33)	1.17 (-3.86, 6.19)	10	6	
High	16 (33)	-2.5 (-6.32, 1.32)	8	8	



Apathy diagnostic criteria

Diagnostic criteria for apathy (DCA)	• Diagnostic criteria for apathy (DCA) in neurocognitive disorders developed in 2021.
Delphi panel	• Next, assessed whether apathy scales (NPI-C and AES) map onto the DCA.
Inter-rater reliability	• NPI-C apathy showed substantial agreement.
Apathy checklist	• panel members suggested creation of a condensed scale based on NPI-C apathy (2 questions per dimension from NPI-C)
Site Recruitment	• Collecting data on NPI-C apathy domain and DCA in a clinic setting from patients with NCD with and without apathy
Current sites	• Sunnybrook, Johns Hopkins, Mount Sinai, Centre Hospitalier Universitaire de Nice

Feedback from the experts meeting

- Important to collect caregiver feedback and obtain caregiver validation as part of the study

Caregiver questionnaire

- **Purpose:** To obtain qualitative and quantitative information on the impact of apathy on the caregiver

- **3 sections:**
  - 1st section: To collect brief information on overall neuropsychiatric symptom presence
  - 2nd section: To understand the impact of individual apathy dimensions to caregiver
  - 3rd section: Questions on the overall impact of apathy

Proposed DCA checklist based on NPI-C apathy domain

Sample DCA Checklist	Yes	No
Diminished initiative: Less spontaneous and/or active than usual self		
1. Does the patient seem less spontaneous and active than usual?		
2. Is the patient less likely to initiate a conversation?		
Dimension describes diminished interest: less enthusiastic about usual activities		
1. Is the subject less enthusiastic about his/her usual interests?		
2. Is the subject less interested in or curious about routines or new events in his/her environment?		
Dimension describes diminished emotional expression/responsiveness		
1. Does the subject express less emotion in response to positive or negative events?		
2. Is the subject less affectionate or lacking in emotions when compared to his/her usual self?		

Proposed DCA checklist: performance

Patients (n=9)	Met Diagnostic criteria	NPI-C total (clinical impression column)	Questions on DCA checklist*	Domains on the DCA checklist**
1	Yes	29	6/6	3/3
2	Yes	31	6/6	3/3
3	Yes	17	5/6	3/3
4	No	8	3/6	2/3
5	No	3	1/6	1/3
6	No	3	1/6	1/3
7	No	2	2/6	2/3
8	No	0	0/6	0/3
9	No	0	0/6	0/3

*scored out of 6 for 6 questions on the DCA checklist
**Met 1 symptom in at least 2 domains on checklist; scored out of 3 for 3 domains on DCA checklist

Current status and next steps

- Paper in progress: *"Mapping of validated apathy scales onto diagnostic criteria for apathy in neurocognitive disorders"*
- Collect data on the DCA, NPI-C apathy subscale, from patients with neurocognitive disorders in clinics over this year
- Received REB approval from Sunnybrook Research Institute site
- Currently recruited 3 sites
- Compare checklist and NPI-C to formal DCA
- Translating DCA into other languages
  - Dr. Alonso Morales (Spanish)
  - Dr. Phillipe Robert and Dr. Adrian Noriega (French)

Discussion

Current sites recruited

Collaborating sites	Collaborating scientists	Study design	Ethics/Legal submission	Updates
Sunnybrook Hospital, Toronto, Canada	Dr. Krista Lanctot Dr. David Miller	Prospective	✓	• Currently going to geriatric clinic to recruit participants • Looking to collaborate across clinics in Sunnybrook
Icahn School of Medicine at Mount Sinai , New York, USA	Dr. Laili Soleimani	Prospective	✓	• Waiting for REB approval
Johns Hopkins, Baltimore, Maryland, USA.	Dr. Paul Rosenberg	Mix of prospective and retrospective	✓	• Received approval • Recruiting patients
Centre Hospitalier Universitaire de Nice, Nice, France	Dr. Philippe Robert	Prospective	• In progress	• Translated the DCA checklist into French • Will start using the checklist in clinic
Université de Toulouse, Toulouse France	Dr. Maria Soto	Retrospective (chart review)	• In progress	• Gathering documents to send over NPI-C chart data

Prospective study design:

Goals: To create and validate the DCA checklist that can be used to identify apathy in NCD within a clinical setting

Sample Size: As this is a pilot study, a convenience sample of 100 patients (20 participants per site) will be included in this study.

Study Design:

We will approach individuals from geriatric clinics at their regular clinic appointments. Each participant must meet all of the following inclusion criteria to participate in this study:

1) Subjects who meet DSM-5 criteria for mild or major NCD

2) Apathy score on the NPI-C apathy domain

3) Complete diagnostic criteria for apathy in NCD (positive or negative)

4) Stable (>4 weeks) dose of any medication that affects cognition or behaviour

5) Written informed consent by the subject and/or care partner

6) The subject and care partner are sufficiently fluent in spoken and written English to complete all study assessments.

****Open to collaborating with sites with retrospective data on NPI-C apathy domain/chart review****