WHY FOCUS ON APATHY?

DIAGNOSIS, SYMPTOMS ASSESSMENT, METHODOLOGY FRAMEWORK

David S. Miller, MD, MA

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ISCTM

ALTERNATE TITLE: WHO'LL STOP THE TRAIN?

David S. Miller, MD, MA

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Disclosure

- I am a full-time employee of Bracket

Addressing this Issue

- In the context of both the NPS-PIA and ISCTM BPSD Working Group

Estimated Prevalence of Apathy

- 2-5% in Cognitively Normal Persons
- 15-43% in MCI
- 36-51% in Mild AD
- 36 – 72% in AD (mild – severe)

Mild Behavioral Impairment (MBI)

- Construct developed by the NPS-PIA
- Acquired in late life
- Sustained
- Impactful
- Can present in advance of any cognitive impairment or along with MCI
- APATHY is one of these symptoms

Apathy's Impact

- Leads to impairment in both ADLs and iADLs
- Causes increased caregiver burden
- Is associated with poorer prognosis
- Can result in increased mortality

IMAGINE…

- Subway
- Commuter train/Acela
- TGV, Frecciarossa, Shinkansen
- You have a symptom that
  - Heralds pending cognitive impairment
  - Speeds the progression from NL cognition -> MCI -> Dementia diagnosis
  - Results in significant caregiver distress
- Would you try to address it/treat it/slow or stop the train?

“A” Distinction

- **A**pathy
- **A**nhedonia
- **A**motivation

As the field has evolved

- Definition of apathy operationalized
- Scales developed to assess apathy (and other NPS) in dementia
- Diagnostic criteria for apathy established
- Improved understanding of the etiology and subtypes

Diagnostic Criteria for apathy in AD

A. Core feature of apathy, diminished motivation, present x ≥4 weeks
B. 2/3 dimensions of apathy, reduced
   - ✓ goal-directed behavior,
   - ✓ goal-directed cognitive activity
   - ✓ emotions
C. functional impairments attributable to apathy
D. exclusion criteria are specified to exclude symptoms and states that mimic apathy

- Inter-rater reliability high (kappa 0.93, p=.0001)

Robert et al 2009, Mulin et al 2011

So, why the apathy re apathy?

- At the time of abstract submission – a search of "apathy and dementia" on clinical trials.gov revealed only 11 studies

- And, how many were pharma initiated?

How many???

- NONE

And, they varied a great deal

- Essentially, all were run by academic investigators
- Interventions included stimulants (modafinil and methylphenidate,) dextromethorphan, rivastigmine, rTMS, *computerized training*
- MMSEs as low as 10
- Varying apathy severity
- Varying apathy criteria (NPI, AES, AES-C, FrSBe)
- Varying outcome measures (NPI, AES, AES-C, CGIC, FrSBe, Apathy Inventory, TUG, LARS, Reaction time on computerized cognitive testing, Motricity)

Can Pharma Trials be Done?

- **YES**
  - Use Established Diagnostic Criteria
  - Acknowledge the subtypes
  - Carefully select outcome measure(s)
  - Evaluate apathy alone or in combo with other NPS (eg – depression)?
  - Incorporate Neuroimaging and Biomarkers
  - Consider pharmacologic challenge
  - Address issues around placebo response
  - Standardize Non-Pharmacologic Interventions
  - Appreciate the source for determining ratings

Psychosocial interventions

- What were they and how often?
- How are those delivering the psychosocial therapies trained and vetted?
- Is the intervention standardized? Is the delivery of the intervention monitored?
- Are the therapies monitored for uptake, quality of implementation, and effect? If so, how?
- Is there any difference if the "caregiver" lives with the subject or not? Any impact on how they utilize and/or report on the outcome of the intervention(s)?

Data Quality Programs

- Identify and significantly reduce rater errors over the course of the trial
- eCOA improves standardization & further reduces errors
- Addition of audio reviews enhances ability to identify and remediate administration &/or scoring errors

ALL ABOARD???

- The train is leaving the station…

Apathy: Diagnostic Criteria

Robert, P et al. Eur Psychiatry 2009. 24 (2): 98-194

Diagnosis requires fulfillment of criteria A, B, C and D		
A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others		
A. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time		
Domain B1 – Behavior	Domain B2 – Cognition	Domain B3 – Emotion
Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:	Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:	Loss of, or diminished, emotion as evidenced by at least one of the following:
Loss of self-initiated behavior (e.g., in starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)	Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).	Loss of spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
Loss of environment-stimulated behavior (e.g., in responding to conversation, participating in social activities)	Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighborhood or community).	Loss of emotional responsiveness to positive or negative stimuli or events (e.g., observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)

Apathy: Diagnostic Criteria cont'd

A. These symptoms (A & B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning

A. The symptoms (A & B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication)