ADRC Spring Meeting, Clinical Core session

*Psychiatric disorders vs. early neuropsychiatric symptoms of a neurodegenerative disease: What’s a clinician, or a clinical core, to do?*

Jennifer R. Gatchel MD PhD
Associate Professor, Baylor-MEDVAMC; Assistant Psychiatrist Mass General Hospital
Outline

• I. Late life neuropsychiatric symptoms and mild behavioral impairment

• II. Clinical overlap with primary psychiatric disorders

• III. Neuropsychiatric features of a neurodegenerative disease (emerging, related to underlying degenerative disease) vs. pre-existing or co-morbid psychiatric disorder
  • Principles of Assessment
  • Emerging Biomarkers

• IV. Future Directions
Neuropsychiatric Symptoms: multi-dimensional, ranging from mild to severe, across the dementia clinical spectrum

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>• Geriatric Depression Scale</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>• Apathy Evaluation Scale</td>
</tr>
<tr>
<td>Agitation</td>
<td>• Hospital Depression and Anxiety Scale</td>
</tr>
<tr>
<td>Depression</td>
<td>• Cohen Mansfield Agitation Inventory</td>
</tr>
<tr>
<td>Elation</td>
<td>• Beck's Depression Inventory</td>
</tr>
<tr>
<td>Anxiety</td>
<td>• Beck's Anxiety Inventory</td>
</tr>
<tr>
<td>Loss of empathy</td>
<td>• Neuropsychiatric Inventory</td>
</tr>
<tr>
<td></td>
<td>- Apathy</td>
</tr>
<tr>
<td></td>
<td>- Disinhibition</td>
</tr>
<tr>
<td></td>
<td>- Irritability</td>
</tr>
<tr>
<td></td>
<td>- Sleep</td>
</tr>
<tr>
<td></td>
<td>- Appetite changes</td>
</tr>
<tr>
<td></td>
<td>- Aberrant motor behavior</td>
</tr>
<tr>
<td></td>
<td>- Obsessions/compulsions</td>
</tr>
</tbody>
</table>

Adapted from ISTAART NPS PIA 2022 Year in Review
Neuropsychiatric Symptoms have Widespread Impact

- **Prevalence**
  - Cognitively normal
  - Mild Cognitive Impairment
  - Dementia

- **Associations with disease pathology**
  - AB, tau, phospho-tau, NfL, other disease markers

- **Negative Implications**
  - ↓ decline in IADL/ADL
  - ↓ quality of life
  - ↑ disease progression; mortality
  - ↑ care partner burden
  - ↑ institutionalization
  - ↑ burden on healthcare system

*Adapted from ISTAART NPS PIA 2022 Year in Review*
Neuropsychiatric Symptoms have Widespread Impact

Prevalence

Incomplete understanding of biological mechanisms

Associations with Alzheimer’s disease

Lack of treatment options: repurposed agents; potential adverse side effects

Negative Implications

Missed opportunities: early recognition of dementia syndromes
Mild Behavioral Impairment

Emergence of NPS in late life (age 50 or later); **persistence** for 6 months or longer (normal cognition, subjective cognitive impairment, mild cognitive impairment)

<table>
<thead>
<tr>
<th>MBI domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased motivation</td>
</tr>
<tr>
<td>• Emotional dysregulation</td>
</tr>
<tr>
<td>• Impulse dyscontrol</td>
</tr>
<tr>
<td>• Social inappropriateness</td>
</tr>
<tr>
<td>• Psychosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>• MBI checklist (MBI-C)</td>
</tr>
<tr>
<td>• Neuropsychiatric Inventory</td>
</tr>
</tbody>
</table>

Adapted from ISTAART NPS PIA 2022 Year in Review
Sample: N=50 cognitively unimpaired Aβ+ from BioFINDER2

Biomarkers tau-PET ([^18F]RO948 retention in entorhinal cortex/hippocampus) and cerebrospinal fluid (CSF) P-tau$_{181}$

- higher tau-PET signal + CSF P-tau$_{181}$ levels: higher MBI-C scores
- MBI ~ tau association: independent of memory deficits

MBI may be an important early clinical manifestation related to tau pathology in preclinical AD
Study of multimodal biomarkers of NPS/MBI: Take home points

• Preclinical and prodromal populations: NPS/MBI associated with:
  • Abeta 42, t-tau/Abeta 42 and p-tau (CSF)
  • p-tau-181, markers of AD, neurofilament light (NfL) (plasma)
• Neuroimaging markers (amyloid PET, regional tau-PET, atrophy)

• Depressive symptoms, apathy, anxiety: associated with AD pathology (Aβ + tau) +
  accelerated cognitive decline (Gatchel et al. 2019; Johansson et al., 2020;
  Johansson et al. 2021; Donovan et al. 2018; Gatchel et al. unpublished data)
But wait…

MBI/NPS, map onto symptoms that may be related to primary psychiatric disorders.

What’s a clinician, or a clinical core, to do?

<table>
<thead>
<tr>
<th>This domain describes interest, motivation, and drive</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person lack curiosity in topics that would usually have attracted her/his interest?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person lost the motivation to act on their obligations or interests?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does she/he no longer care about anything?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This domain describes mood or anxiety symptoms</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less able to experience pleasure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become discouraged about their future or feel that she/he is a failure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person view herself/himself as a burden to family?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>
Major depressive disorder (MDE)
Diagnostic criteria (summarized from DSM-5-TR)

• 5 of 9 criteria
  • Depressed mood
  • Anhedonia (loss of pleasure)
  • Weight loss (or gain)
  • Insomnia (or hypersomnia)
  • Psychomotor agitation or retardation
  • Fatigue
  • Feeling worthless
  • Problems concentrating, thinking, or making decisions
  • Suicidal ideation

• Symptoms present most of the day, nearly every day, for > 2 weeks
• Symptoms cause functional impairment (change in activities)
• Not better explained by medications, medical illness or bereavement

<table>
<thead>
<tr>
<th>This domain describes interest, motivation, and drive</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person lack curiosity in topics that would usually have attracted her/his interest?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person lost the motivation to act on their obligations or interests?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does she/he no longer care about anything?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This domain describes mood or anxiety symptoms</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed sadness or appear to be in low spirits? Does she/he have episodes of tearfulness?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less able to experience pleasure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become discouraged about their future or feel that she/he is a failure?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person view herself/himself as a burden to family?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>
Major depressive disorder (MDE)

Diagnostic criteria (summarized from DSM-5-TR)

- 5 of 9 criteria
- Depressed mood
- Anhedonia (loss of pleasure)
- Weight loss (or gain)
- Insomnia (or hypersomnia)
- Psychomotor agitation or retardation
- Fatigue
- Feeling worthless
- Problems concentrating, thinking, or making decisions
- Suicidal ideation

- Symptoms present most of the day, nearly every day, for > 2 weeks
- Symptoms cause functional impairment (change in activities)
- Not better explained by medications, medical illness or bereavement

Bipolar depression in Older Adults:

- Disturbances in sleep, appetite and activity level
- Cognitive impairment
- Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy

<table>
<thead>
<tr>
<th>This domain describes interest, motivation, and drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
</tr>
<tr>
<td>Has the person lost curiosity in topics that would usually have attracted her/his interest?</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
</tr>
<tr>
<td>Does the person lose the motivation to act on their obligations or interests?</td>
</tr>
<tr>
<td>Has the person lost affectionate and/or lacking in emotions when compared to her/his usual self?</td>
</tr>
<tr>
<td>Does she/he no longer care about anything?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>This domain describes mood or anxiety symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed sadness or appear to be in low spirits? Does she/he have episodes of tearfulness?</td>
</tr>
<tr>
<td>Has the person become less able to experience pleasure?</td>
</tr>
<tr>
<td>Has the person become discouraged about their future or feel that she/he is a failure?</td>
</tr>
<tr>
<td>Does the person view herself/himself as a burden to family?</td>
</tr>
<tr>
<td>Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?</td>
</tr>
<tr>
<td>Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?</td>
</tr>
</tbody>
</table>

Ismail et al.
J Alzheimer Dis 2017
• Frontotemporal dementia (FTD): changes in socioemotional behavior

• bvFTD: clinical symptom overlap with major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, autism spectrum disorders and personality disorders.

• NPS in ADRD may resemble major depressive disorder, generalized anxiety disorder, panic disorder, bipolar disorder, schizophrenia
Important dichotomy?

Adapted from Jack et al. 2011
NPS: symptom of dementia syndrome or comorbidity

• Manifestation of neurodegenerative disease (NDD) (mechanisms may be shared or distinct from those underlying cognitive decline); +/- comorbid psychiatric illness, superimposed on character traits => distinct symptom constellation

• Clinical case: patient with probable AD dementia, no past psychiatric illness, develops apathy, anxiety, and paranoia: manifestations of neurodegenerative disease (NDD) superimposed on character traits (dependent + avoidant personality traits)

• Implications for management: response to conventional psychotropics or DMT (future directions: develop more targeted treatments for NPS in dementia syndrome)
NPS in late life: preclinical or prodromal stages of a dementia syndrome?

• manifestation of a neurodegenerative disease (NDD) (mechanisms may be shared or distinct from those underlying cognitive decline +/- psychological reaction superimposed on character traits) NDD

• primary psychiatric disorder (variable underlying neurobiology, predominantly non-neurodegenerative; risk for subsequent dementia syndrome ↓ “neuropsychiatric reserve”) psychiatric

• Both phenomena (manifestation of NDD + primary psychiatric disorder comorbidity or prodrome) NDD + psychiatric

⇒ Implications for early detection, accurate diagnosis, management and prognosis (i.e. bvFTD vs. bipolar disorder or MDD); patient and care partner counselling; quality of life
Clinical features: atypical presentations

• Obsessions that are non-ego-dystonic (not disturbing to the patient, as is typically observed in OCD); compulsions without obsessions

• Depression with marked apathy or anxious distress; lack of anhedonia
Clinical features: atypical presentations...

- Newly emergent; change from baseline
- Late age of onset; (anxiety, mania, OCD, psychosis outside of mood episode)
- Loss of empathy; emotional detachment, lack of distress
- Sustained manic state without grandiosity or euphoria; absence of depressive symptoms
- Schizophrenia without complex delusions or hallucinations
- Progressive cognitive dysfunction; progressive impairment
- Lack of treatment response
- Any signs of motor neuron disease or parkinsonism on exam
- Family history of FTD or another dementia; strong family history of psychiatric disease, and/or neurodegenerative disease in a patient whose symptoms develop later in life
False dichotomy...

• In some cases, psychiatric symptoms are more “typical”

• Patients with neurodegenerative disease will present with syndromes that do meet ‘typical’ DSM-5-TR criteria for psychiatric disorders (co-morbidity or prodome); age of onset may be the only outlier
  • C9orf72 mutations in FTD, most common presentations: bvFTD and ALS, prodromal psychiatric syndromes
Principles of Assessment

• History: medical and neuropsychiatric (informant(s)) report; onset and persistence
• Current medications, overt and covert substance use, vascular risk factors.
• Family history (in FTD--what constitutes a positive family history; Goldman score)
• Physical and Neurological exam
• Clinical assessment: all sections of the standard medical and neuropsychiatric assessment; mental status exam
• Consideration of impaired insight (almost always present in bvFTD, but also in other dementia syndromes in preclinical/prodromal stages):
  • a care-partner-based history is essential +/- independent relative or friend (given potential bias in care-partner or relational tensions in the dyad)
  • Objective assessments of emotional-behavioral function (emotion recognition paradigms)
Harvard Aging Brain Study: Elevated Aβ, ER Tau and IT Tau associated with greater study-partner reported apathy

\[ \beta = -3.6, p = 0.005 \]
\[ \beta = -3.9, p = 0.025 \]
\[ \beta = -4.9, p = 0.027 \]
Consider underlying somatic illness or medication (example: late onset mania)

• Neurologic
  • Dementia
  • Traumatic Head injury
  • CNS tumor
  • Multiple sclerosis
  • CVA
  • Epilepsy
  • Huntington’s; Wilson’s disease

• Sleep apnea
• Vitamin B12/niacin deficiency

• Endocrine
  • Hypo- or hyperthyroidism
  • Hypercortisolemia

• Infectious
  • HIV encephalopathy
  • Neurosyphilis
  • Lyme disease
  • Viral encephalitis

• Toxic
  • Substances
  • Medications
Consider underlying somatic illness or medication (example for late onset mania)

- Neurologic
  - Dementia
  - Traumatic Head injury
  - CNS tumor
  - Multiple sclerosis
  - CVA
  - Epilepsy
  - Huntington’s; Wilson’s disease

- Sleep apnea

- Vitamin B12/niacin deficiency

- Endocrine
  - Hypo- or hyperthyroidism
  - Hypercortisolemia

- Infectious
  - HIV encephalopathy
  - Neurosyphilis
  - Lyme disease
  - Viral encephalitis

- Toxic
  - Substances
  - Medications

- Consider neuropsychological testing
- Laboratory evaluation:
  - CMP, Creatinine, GFR, CBC
  - TSH; free T3/T4 if TSH abnormal; liver function tests
  - Urinalysis and Urine drug screen
  - B12, folic acid
  - Serum blood levels of current medications
  - Infectious serologies if indicated
- MRI or CT consider functional imaging or EEG
Principles of assessment...

• Neuroimaging: standard in neurodegenerative disease assessment, no clear guidelines in psychiatric patients—routine imaging not part of standard work-up
  • Atypical features
  • provide clinical details to the radiologist; neurology + neuroradiological consultation
    • Quantification of structure and function
• Genetic analysis?
  • Screening all psychiatric patients for FTLD-related mutations—not practical
  • Autosomal dominant pattern of inheritance; genetic testing for C9orf72 if at least one first degree relative with FTD, ALS or other early onset neurodegenerative disease
Consensus recommendations?

The Neuropsychiatric International Consortium for Frontotemporal Dementia: consensus recommendations to distinguish behavioral variant frontotemporal dementia from psychiatric disorders (Ducharme et al. BRAIN 2020)

• Clinical assessment: full neuropsychological battery + at least one formal social cognition test
• 3D-T1 brain MRI with standardized review: validated visual atrophy rating scales, volumetric analyses
• 18F-fluorodeoxyglucose PET for the exclusion of bvFTD when normal; “non-specific regional metabolism abnormalities should not be over-interpreted”
• potential role of CSF or plasma neurofilament light chain to differentiate bvFTD
• Screening for C9orf72 mutation: in all possible/probable bvFTD cases or suspected cases with strong psychiatric features; if at least one first degree relative with FTD, ALS or other early onset neurodegenerative disease
Role of biomarkers

• For AD: CSF amyloid-β (Aβ42), total tau (T-tau), phosphorylated tau (p-tau); amyloid and tau PET imaging

• plasma Aβ42/Aβ40 and p-tau immunoassays: high specificity for AD.

But... no similar biomarkers for other common or rarer neurodegenerative disorders

• CSF analysis: exclude Alzheimer’s disease pathology; isolated increase of CSF tau without CSF amyloid-b42: favor a bvFTD diagnosis

• Plasma NfL: high correlation with CSF NfL

Role of Biomarkers

Ashton et al. NATURE COMMUNICATIONS (2021)
Conclusions and future investigation of NPS in ADRD

• MBI/NPS: early clinical features of a NDD related to underlying disease pathology

• Common: differential diagnosis: NPS of a neurodegenerative disease vs. a primary psychiatric disorder
  • NPS in dementia: symptom of NDD +/- psychiatric comorbidity + baseline
  • Preclinical or prodromal dementia: consider these etiologies: *neurodegenerative disease (NDD); psychiatric* or *‘NDD + psychiatric’*
  • Atypical features, study partner(s) report, objective assessments
  • Role of biomarkers (neuroimaging, genetic, fluid, multimodal)
Conclusions and future investigation of NPS in ADRD...

• Do NPS travel with “core” AD pathology or have distinct neurobiology
  • Measurement properties; subjective + objective assessments

• Formal NPS diagnostic criteria—apathy, psychosis; also needed for other NPS: depression, anxiety, irritability

• Longitudinal study design; well characterized samples; consensus NPS diagnostic criteria + biomarkers + clinical outcomes