The Interface between Primary Psychiatric Disorders, Aging and Dementia – A Primer for the Busy Clinician

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1

Disclosures

My family and I have no relevant disclosures

2

Agenda

- Epidemiology
- Psychosis in Older Adults
- Bipolar Disorder in Older Adults
- Depression in Older Adults
- The Neurocognitive Disorders
- Neuropsychiatric Symptoms in the NCD
- Dangerousness in the NCD
- Cases
- Questions

3

The USA is Aging Rapidly!

- 16% of adults in the country are aged 65 and above – typically referred to as "older", "elderly" or "geriatric".
- The "oldest-old" aged 85 and over are the most rapidly growing demographic subgroup
  - their numbers will increase from 10% of older adults in 1994 to almost 25% of older adults, and 5% of all Americans, by 2050
- 10% of people age 65 and older have AD dementia
- 32% percent of people age 85 and older have AD dementia
- Approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's dementia

United States Census Bureau data from July 1, 2018;
Herbert et al., 2013; Alzheimer's disease early-onset dementia, 2006

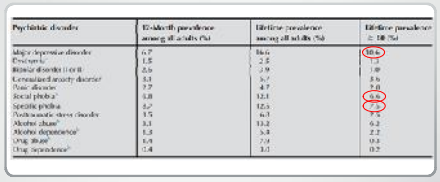
4

Psychiatric Disorders in Older Adults – Study Limitations

- Comorbidity is common - the occurrence of two or more disorders in one individual
  - multiple psychiatric disorders (e.g., comorbid depression and anxiety) or
  - the overlap between mental and physical health disorders (e.g., comorbid depression and diabetes)
- Sampling bias in the older population
  - differential mortality – the relative risk of mortality is 2.22-fold greater for those with mental disorders than those without
  - reluctance to participate
  - The oldest-old population is seldom included in large epidemiological studies

From Renn et al., 2020 *In* Handbook of Mental Health and Aging

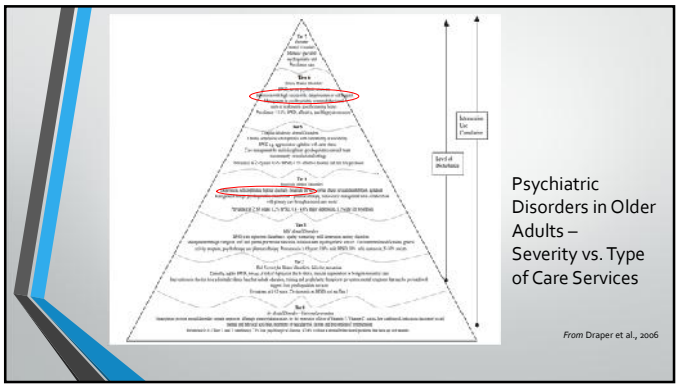
5



Data from the National Comorbidity Study—Replication (NCS-R)
– used DSM-IV-TR criteria for disorders
Kessler et al., 2005; Kessler, Chiu, et al., 2005

Psychiatric Disorders in Community-dwelling Older Adults

6



7

Late-onset Psychosis – Symptoms vs. Disorders

1-year prevalence of psychotic symptoms in community-dwelling non-demented older adults has been shown to be

- 1% in those aged 70 years (DSM-IV; Sigstrom et al., 2009)
- 10% in 85 year olds (DSM-IV; Ostling and Skoog, 2002)
- 7.5% in 95 year olds (DSM-III; Ostling et al., 2007)

In a population-based study of adults aged 60 and above without cognitive deficits or overt psychotic disease

- 20% reported one or more psychotic symptoms
- Among them, 13% reported one or more "minor" psychotic phenomena (illusions, feeling of presence and passage hallucinations)
- None had gustatory hallucinations, auditory verbal hallucinations or delusions
- The prevalence of minor phenomena increased with age

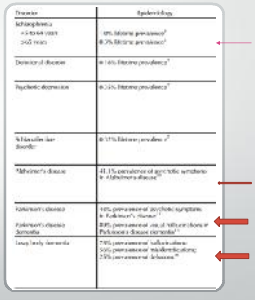
However, higher rates for delusions have been reported elsewhere in the nondemented population

- 1-3% for severe
- 5-6% for delusions of mild intensity

Soulas et al., 2016; Ravina et al., 2007; Freeman, 2006

8

Late-onset Psychotic Disorders - Epidemiology



From Colijn et al., 2015

9

Late-onset Schizophrenia

- Little less than a fourth of all patients with schizophrenia have onset after age 40
- The age cut-off for diagnosis was completely done away with from DSM-IV onward
- The International Late-Onset Schizophrenia Group defined
  - Late-onset schizophrenia (LOS) – onset between age 40-60
  - Very-late-onset schizophrenia-like psychosis (VLOSLP) – onset age >60
- Female sex is associated with late-onset schizophrenia
- There is a lower prevalence of formal thought disorder and affective blunting with a higher prevalence of visual hallucinations
- Patients with VLOSLP, especially men, have higher mortality rates than adults in whom early-onset schizophrenia has continued into late-life

Harris and Jeste, 1988; Tandon, Gaebel et al. 2013
Howard et al. 2000; Talaslahti et al. 2015

10

Does Late-onset Psychosis Increase the Risk of Dementia?

- Nationwide hospital register study from Denmark of first-contact patients with late-onset (N=12,616) and very-late onset (N=7,712) schizophrenia v. OA and general population
  - 2x higher risk of subsequently getting a diagnosis of dementia vis-à-vis general population
  - 3x higher risk of subsequently getting a diagnosis of dementia vis-à-vis osteoarthritis patients
  - Dementia type was unspecified
- Nationwide hospital register study from Denmark of first-contact patients with late-onset (>60 yrs) acute and transient psychosis (N=8,062)
  - 8x higher risk compared to the general population
  - 11x higher risk compared to patients with osteoarthritis
  - Unspecified dementia was again the most common diagnosis

Korner et al., 2009; Korner et al., 2009

11

Late-onset Psychosis and Dementia – Cont'd

In the largest study to date, 37,770 dementia-free men aged 65-85 years with late-onset psychosis were prospectively followed for almost 18 years

- The risk ratio of incident dementia was more than 2x as high among those who had received a diagnosis of psychotic disorder at first evaluation or were diagnosed with a psychotic disorder during follow-up
- The risk was the highest in those with the least number of years lived with psychosis, i.e. shorter duration of illness
- The association could not be attributed to concurrent medical morbidities, hearing loss, depressive and bipolar disorders, and alcohol use disorder

Almeida, Ford et al. 2019

12

Late-onset Psychosis and Dementia – Cont'd

- BUT others have found no difference between older adults with early-onset schizophrenia versus those with LOS
- An influential review of the topic concluded
  - 70-80% of older adults with schizophrenia manifest cognitive deficits
  - Interpatient heterogeneity exists in the level and pattern of cognitive impairment
  - Average deficit is approximately 1 SD below the normative mean of demographic-matched peers in the general population
  - Cognitive deficits are common in immediate recall, processing speed, attention/working memory, and executive functions

Palmer et al., 2010

13

When Should a Dementia Work-up be Considered in Schizophrenia?

- "Rapid forgetting" – a hallmark of AD dementia
- Decline in "crystallized" verbal knowledge i.e. long-term verbal knowledge
- Decline in IADLs and BADLs (vs. increase in negative symptoms with age)
- Aphasia (vs. disorganized and idiosyncratic pattern of speech in psychosis)

Collateral information from a reliable historian regarding baseline is essential to make the diagnosis

Palmer et al., 2010

14

Clinical Practice Points

- About a fifth of non-demented older adults develop new-onset psychotic symptoms
- New-onset psychosis in older adults often (not always) heralds the onset of dementia
- Onset of dementia can take up to 10 years from onset of psychosis (mean interval 5±4.7 years)
- Hazard ratio is the highest for new-onset hallucinations and the lowest for non-delusional paranoid ideations
- The risk is higher in those with recent-onset/ shorter duration of the psychotic illness
- Is late-onset psychosis a risk factor for dementia or does dementia present with prodromal psychosis?

Ostling et al., 2007; Taragano et al., 2018; Almeida et al., 2019

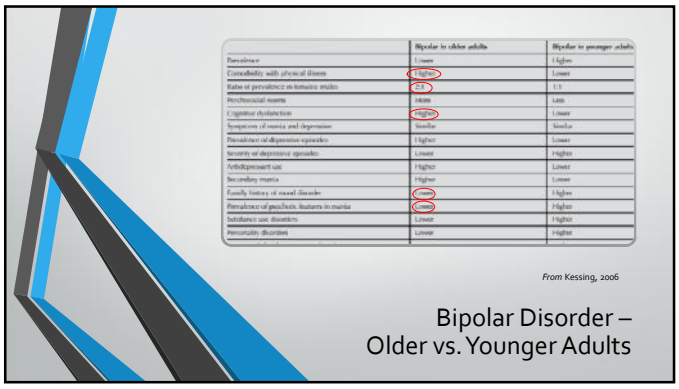
15

Late-onset Bipolar Disorder

- The Older-Age Bipolar Disorder Task Force recommends the definition to include those aged 40 and above
- The estimate of the 12-month prevalence of bipolar I or II disorder among all US adults is 2.6%
- Among adults aged 65 and older, 12-month estimates are lower
  - 0.4%-0.5% for bipolar I disorder
  - 0.2% for bipolar II disorder
- About a quarter of all patients with bipolar disorder are 60 or older
  - Includes early-onset, late-onset and "converters"
- There are no specifiers for the bipolar disorders in DSM-5 pertinent to older adults

Sajatovic et al., 2015 ; Kessler, Chiu, et al., 2005; Blanco et al., 2017; Lin et al., 2014; Sajatovic et al. 2005, Dols et al. 2016

16



From Kessing, 2006

Bipolar Disorder – Older vs. Younger Adults

17

Late-onset BD and Risk of Dementia

- Meta-analysis of 6 studies found that BD greatly increased the risk of incident dementia
- Cross-sectionally, impairments in adult euthymic patients with BD are seen in
  - Attention/processing speed, verbal memory, verbal fluency and executive function
- Longitudinally, only worsening of executive function has been found
- Bipolar disorder as a dementia prodrome?
  - Unlikely, as euphoria is the least common neuropsychiatric symptom in AD dementia with a prevalence of ~5%

Diniz et al., 2017; Robinson et al., 2006; Torres et al., 2007; Torrent et al., 2012; Nunes et al., 2007; Cipriani et al., 2017; Zhao et al., 2015

18

Clinical Practice Points

- BD in older adults is more common in females
- It presents with more physical comorbidities and less severity of psychiatric symptoms
- Psychiatric phenomenology is essentially no different from that in younger adults
- An increased risk of dementia in BD over time is reported by many but not all studies
- The dementia that occurs is not AD dementia
  - Older BD patients with cognitive impairment have not been found to have the typical CSF AD biomarkers
- Comorbid cannabis use in BD has been associated with cognitive decline
- Medication effects – lithium lowers, VPA increases risk? Still speculative

Depp et al., 2008; Gildengers et al., 2009; Kvitland et al., 2015; Almeida et al., 2016; Forlenza et al., 2016

19

Late-life Depression

- 12-month prevalence of Major Depressive Disorder (MDD) is adults 50 and above is around 4.8%
- About 8-16% of community-dwelling older adults have clinically significant depressive symptoms
- Subsyndromal depression in community-dwelling older adults is much more common with a point prevalence of 4-23%
- Point prevalence of subsyndromal depression can be as high as 50% in long-term care settings
- The longitudinal risk of developing syndromal depression in patients with subsyndromal depression is around 8-10% annually

NSDUH, 2016; CBHSQ, 2017; Blazer, 2003; Meeks et al. 2011

20

Late-life Depression – Cont'd

- LLD is a heterogenous category that includes
  - Major Depressive Disorder and subsyndromal depression
  - Late-onset depression and Recurrent MDD persisting into old age
- Clear phenomenological differences between the clinical presentation of MDD in older and younger adults have not been consistently found
- DSM-5 uses the same diagnostic criteria for major depressive disorder, regardless of age at onset
- LLD has poorer response rates to antidepressant treatment in the acute phase and higher rates of recurrence and relapse

Thomas, 2013; APA, 2013; Haighes et al., 2018

21

Cognitive Impairment and Late-life Depression

- 30-40% older adults with depression without dementia have evidence of executive dysfunction on cognitive assessment
- Depression-executive dysfunction syndrome (DEDS) is
  - a predictor of poor treatment response
  - a risk-factor for progression to a dementia
- Cognitive symptoms can be severe enough to reach the severity of a dementia, which is typically reversible
  - "depressive pseudodementia" or dementia syndrome of depression
- Depressed patients with a reversible dementia at baseline have been shown to be almost 5x times more likely to develop irreversible dementia over a follow up period compared to the group with no dementia at baseline

Lockwood et al. 2002; Dzierzewski et al. 2015; Alexopoulos et al. 1993; Alexopoulos, Kiosses et al. 2002

22

LLD vs. LOD and Risk of Dementia

- LLD is not synonymous with LOD and the distinction therefore has clinical implications
- One of the largest studies followed the trajectories of depressive symptoms prior to the onset of dementia over 28 years
  - only depressive symptoms in the decade preceding the dementia diagnosis were associated with an increased incidence of dementia
  - chronic recurring midlife depressive symptoms did not increase the incidence
- Consistent with the hypothesis that LOD is either a dementia prodrome or the two share a common etiology and are not a risk factor for dementia

Singh-Manoux et al. 2017

23

Does Treatment Impact Progression to Dementia?

- Antidepressant use does not appear to protect against the development of MCI and dementia (meta-analysis of 18 longitudinal studies, mean age in the trials ranged from 55-81 years)
  - did not look at the differential impact of antidepressants in those with and without dementia syndrome of depression
- Ongoing long-term SSRI treatment (>4 years) in patients with MCI and a history of depression with onset at any age but without active depressive symptoms for at least one year (i.e. responders) *can delay progression* to AD dementia (~3 years) compared to shorter-term treatment, treatment with other antidepressants or no treatment at all
- Global cognitive benefit of vortioxetine does not appear to be secondary to improvement in depressive symptoms, but rather a direct treatment effect (network meta-analysis, mean age range 36.6 to 79.6 years)

Chan et al. 2019; Bartels et al. 2018; Mahableshwarkar et al. 2015

24

Impact of Treatment on Progression to Dementia – Cont'd

- Escitalopram-memantine vs. escitalopram-placebo double-blind RCT in depressed older adults (average age 71.9 years) with subjective memory complaints over a 6-month study period, followed by a 60-month naturalistic follow-up
  - depression significantly improved in both groups
  - escitalopram-memantine group also showed a significantly greater improvement in delayed recall, executive functioning and global performance at 12 months
- Adding a cholinesterase inhibitor to antidepressant treatment in older adults with depression and cognitive impairment has yielded mixed results

Lavretsky et al., 2019; Pelton et al., 2008; Reynolds, Butters et al. 2011

25

Clinical Practice Points

- Late-life MDD is less common than in younger adults; subsyndromal depressive symptoms are more common
- LLD and LOD have different clinical implications
- The phenomenology of late-onset depression is mostly similar to that in early-onset depression
- Family history of depression is less common in LOD
- Dysexecutive symptoms are common in LLD
- "Depressive pseudodementia" may have a good short-term prognosis but increases the risk of eventual dementia

Haigh et al., 2018; Grayson & Thomas, 2013;

26

The Neurocognitive Disorders

- DSM-5 criteria require
  - Concern about cognition by patient/informant/clinician; and
  - Objective evidence of cognitive decline from expected level from testing or clinical assessment
- DSM-5 also distinguishes between Major and Mild NCD (previously Cognitive Disorder NOS)
  - Major NCD – cognitive deficits interfere with independent functioning
  - Mild NCD – cognitive deficits do not interfere with independent functioning as individuals are able to compensate
- Big change - A substantial decline in a single non-memory domain can still receive a diagnosis of NCD in DSM-5

APA, 2013

27

The 3x3 Model of the NCD

NCD can be conceptualized along two axes

Three symptom clusters
(cognitive symptoms should become prominent *eventually*)

- Cognitive (several domains)
- Neuropsychiatric (several domains)
- Motor

Three thresholds –

- Subjective cognitive decline (SCD)
- Objective without functional (IADL) decline (Mild NCD)
- Objective with functional decline (Major NCD)

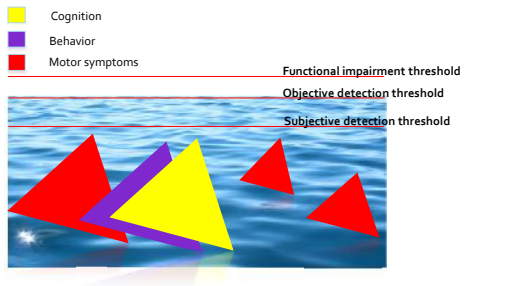
28

The 3x3 Model – Cont'd

	Cognitive	Behavior	Motor symptoms
Subjective	Subjective cognitive decline (SCD)	Mild behavior impairment (MBI) – Prodromal	
Objective w/o functional decline	Mild cognitive impairment (MCI)	Mild behavior impairment (MBI) – Preclinical	PD, ALS, PSP, CBD, MSA
Objective w/ functional decline	Dementia	Psychiatric disorders	PD, ALS, PSP, CBD, MSA

29

The NCD Iceberg



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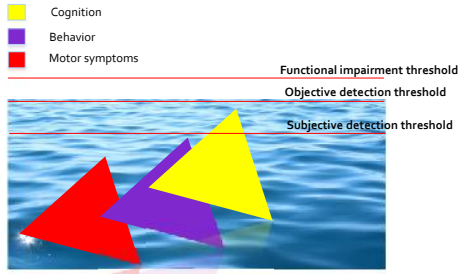
30

Subjective Cognitive Decline



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31

Subjective Cognitive Decline

- Self-experienced persistent decline in cognitive capacity from baseline and unrelated to an acute event
- Normal age-, gender-, and education-adjusted performance on standardized cognitive tests
- Must not be due to mild or major NCD, psychiatric or another neurologic disease, medical disorder, medication, or substance use
- SCD is not a DSM-5 diagnosis

Jessen et al., 2014

32

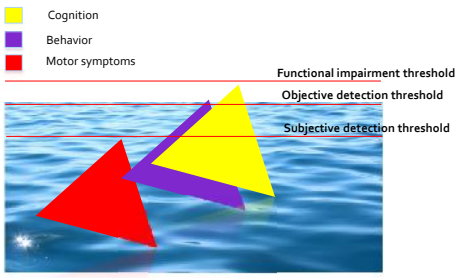
SCD – Outcome

- Meta-analysis of SCD studies largely conducted in primary care settings found annual conversion rate
  - 6.6% to MCI
  - 2% to dementia
  - Vis-à-vis 1% conversion to dementia for healthy controls
- Not all SCD progresses to dementia or even MCI
- Different rates of progression of SCD domains to MCI or dementia
  - Executive function deficits → 7 years
  - Amnestic deficits → 5 years
  - Multidomain deficits → 2 years

Mitchell et al., 2014; Toledo et al., 2015

33

Mild Neurocognitive Disorder



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Mild NCD/ Mild Cognitive Impairment

- Mild Cognitive Impairment (MCI) is defined as per NIA-AA (2011) as:
  - Change in cognition reported by patient or informant or clinician
  - Objective evidence of impairment in one or more cognitive domains
  - Preservation of independence in functional abilities
  - Not demented
- DSM-5 Mild (minor) Neurocognitive Disorder encompasses "a more diverse group of entities, including mild impairments in younger individuals and impairments that may be transient or static or reversible"
- MCI can be subdivided into (not in DSM-5)
  - single-domain amnestic MCI → AD or depression
  - single-domain nonamnestic MCI → FTD
  - multiple-domain amnestic MCI → AD, VaD or depression
  - multiple-domain nonamnestic MCI → DLB or VaD

Albert et al., 2011; Ganguli et al., 2011; Tuokko et al., 2003; Tschanz et al., 2006; Peterson, 2004; Winblad et al., 2004; Petersen and Morris, 2005; APA, 2013; Ferman et al., 2013

35

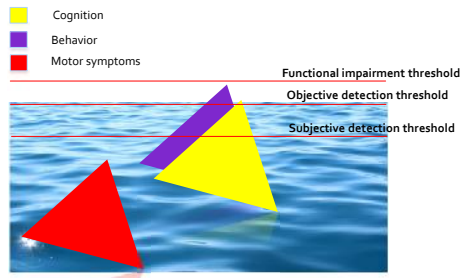
Mild NCD – Cont'd

- MCI to dementia conversion rate is 10-15% annually; BUT
- At the individual level, MCI is an inherently unstable diagnosis
- 18% reversion rate from MCI to normal cognition, may be as high as 26% (2016 meta-analysis)
- Reversion ≠ no future risk:
  - Reverters from amnestic (single or multiple domain) MCI normalize their risk of progression to dementia
  - Reverters from nonamnestic subtypes of MCI continue to have a risk as high as nonreverters of developing dementia

Canevelli et al., 2016; Aerts et al., 2017

36

Mild Behavioral Impairment



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37

Mild Behavioral Impairment

- Mild Behavioral Impairment (MBI) is the behavioral counterpart of Mild Cognitive Impairment (MCI)
- A concurrent diagnosis of MCI is neither necessary to diagnose MBI nor does its presence rule out MBI
- First recognized in 2003, it was finally defined in 2016 -
  - Late-onset (age 50 or above) psychiatric symptoms
  - that must persist or present intermittently for at least 6 months (thereby excluding adjustment disorder precipitated by life stressors)
  - must result in at least minimal impairment in social, occupational, or interpersonal function which must be due to the changes in personality and behavior, and not due to cognitive decline, and without leading to a loss of functional independence
- Additional red-flag for new-onset dementia in those with SMI
  - Change in quality of symptoms or treatment-responsiveness

From The provisional research diagnostic criteria for MBI proposed by the International Society to Advance Alzheimer's Research and Treatment Neuropsychiatric Symptoms Professional Interest Area (ISTAART NPS PIA) ; Ismail et al., 2016

38

MBI – Cont'd

5-year study comparing MBI, amnestic MCI and psychiatry patients

- Rate of conversion to dementia is the highest for MBI
  - MBI (70%) > MCI-MBI (60%) > amnestic MCI (35%) > psychiatric patients (14%)
  - Amnestic MCI patients → AD, none to DLB
  - MBI → FTD > DLB > AD
  - Psychiatric group →DLB > FTD
- MBI patients often receive an erroneous diagnosis of a primary psychiatric disorder early in the course of the disease, especially when behavioral symptoms predominate

Taragano et al., 2018; Woolley et al., 2011

39

MBI – Cont'd

- Five psychiatric domains have been proposed for MBI -
  - Motivation
  - Affective dysregulation
  - Impulse dyscontrol
  - Social inappropriateness
  - Abnormal perception or thought content
- A 34-item MBI checklist (MBI-C) has been developed to operationalize the ISTAART criteria
- A cut-off of 6.5 in SCD patients was found to identify MBI using the ISTAART criteria with a sensitivity of 100% and a specificity of almost 80%

Ismail et al., 2016; Mallo et al., 2018

40

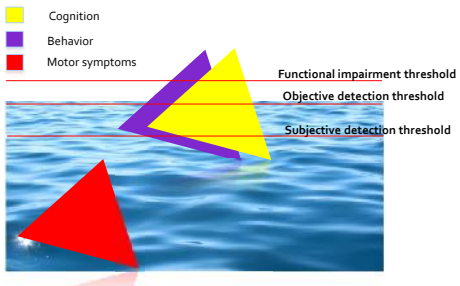
Major Neurocognitive Disorder

4 basic elements -

- Cognitive decline from pre-existing baseline (which needs to be known)
- In someone who is alert and cooperative (i.e. rule out delirium)
- Resulting in functional impairment
- Not better explained by a primary psychiatric disorder

41

Major Neurocognitive Disorder



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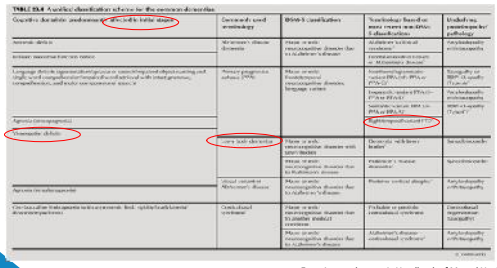
42

Common NCD Subtypes



From Aga et al., 2020 *In* Handbook of Mental Health and Aging

43

Common NCD Subtypes – Cont'd

From Aga et al., 2020 *In* Handbook of Mental Health and Aging

44

Neuropsychiatric Symptoms in the NCD

Can be analyzed by dementia type at three levels –

- At the individual symptom level
- At the subsyndromal level
- At the psychiatric disorder level

45

NPS in Mild NCD

- 35-85% of all MCI patients have NPS – depends on the setting
- DSM-5 allows diagnosis of Mild NCD with or without behavioral disturbance
  - Depression and anxiety are more common in amnestic and non-amnestic MCI
  - Psychotic symptoms are the least common
- Presence of NPS is more strongly associated with conversion to dementia than the presence or severity of cognitive impairment
  - 10-15% in MCI without NPS v 20-25% in MCI with NPS

Monastero et al., 2009; Gallagher et al., 2011; Rosenberg et al., 2013; Rozzini et al., 2008; Taragano et al., 2008

46

NPS in the Major NCD – Symptom Level

- NPS are very common across the dementia types
- Apathy is the most common NPS, with prevalence ranging from 41 to 95% across the dementias
- Depression is the next most common NPS in AD and vascular neurocognitive disorder, while
- Agitation is the second most common NPS in DLB and bvFTD
- Over a 3-yr period
  - delusions, hallucinations, agitation, anxiety, apathy, disinhibition, irritability, and aberrant motor behavior (especially wandering) increase across the dementias, while
  - depression, euphoria, nighttime behavior and appetite problems do not
- Greater baseline NPS are associated with male sex, severity of dementia and a diagnosis of bvFTD

Legesse et al., 2017; Brodaty et al., 2015; Savva et al., 2009

47

NPS in AD Dementia – Symptom Level

- A meta-analysis looked at all published studies of NPS in AD dementia between 1964-2014
- Overall pooled prevalence of NPS –
  - Apathy 49% (95% CI 41–57%)
  - Depression 42% (95% CI 37-46%)
  - Anxiety 39% (95% CI 32–46%).
  - Delusions 31% (95% CI 27-35%)
  - Hallucinations 16% (95% CI 13-18%)
  - Euphoria 7% (95% CI 5-9%)

Zhao et al., 2015

48

NPS in AD Dementia – The Gold Standard

- A large study looked at NPS in patients with autopsy-confirmed pure AD neuropathology (N=455) compared to controls
- Patterns of NPS was found to differ from the clinical studies
  - NPS were noted across all stages
  - Increased odds for agitation, anxiety, depression and sleep disturbances in early stages (Braak stage I/II)
  - Increased odds for agitation continued into the middle stages (Braak stage III/IV)
  - Higher stages (Braak stage V/VI) were associated with a higher odds for delusions (in the absence of synucleinopathy)
  - Apathy was not common

Ehrenberg et al., 2018

49

NPS in the Major NCD – Subsyndromal Level

- Neuropsychiatric subsyndromes are not stable constructs across studies or across time in AD dementia
- A total of 34 different item clusters identified in DSM-IV AD dementia across 15 studies in one review
  - The most consistent symptom cluster found in a third of all studies is an anxious-depression cluster comprised of agitation/aggression+depression/dysphoria+anxiety+irritability
- Their use in clinical practice is best avoided due to their inherent instability, EXCEPT
  - Psychosis (delusions and hallucinations) loaded together on the psychosis cluster in 100% of included studies - stable construct
  - Four CMAI factors appear to be stable across studies of nursing home residents with AD/vascular/mixed dementia
    - aggressive behavior, physically non-aggressive behavior, verbally agitated behavior, and hiding and hoarding

Canevelli et al., 2013; Connors et al., 2018; Rabinowitz et al., 2005

50

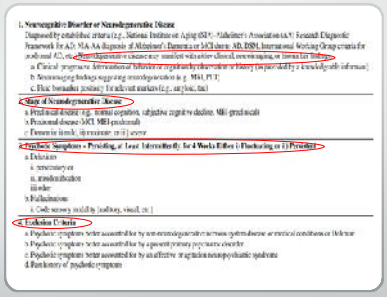
Psychosis in AD Dementia

- Psychosis of AD dementia first defined in 2000
- Two subtypes of psychosis in AD dementia identified on exploratory factor and cluster analysis
  - Simple and delusional misidentifications/ auditory and visual hallucinations
  - Persecutory delusions – less bizarre than in schizophrenia
- In the DSM-5 criteria, "behavioral disturbance" in the NCD includes psychosis
- Allows the diagnosis to be made with either Major or Mild NCD, BUT
  - Psychotic symptoms (delusions vs. hallucinations) are not identified
  - There is no reference to disease biomarkers
  - Measures of frequency, duration or severity are absent

Jeste and Finkel, 2000; Cook et al., 2003; APA, 2013

51

Psychosis in AD Dementia – 2020 Update



From Fischer et al., 2020

52

Psychosis in AD Dementia vs. VLOSLP

- Suggest VLOSLP
  - Auditory hallucinations of human voices OR 3.57 P<0.01
  - Paranoid delusions OR 2.43 NS
  - Partition delusions OR2.24 NS
  - Visual hallucinations of animals OR 1.76 NS
- Suggest AD+P
  - Visual hallucinations of humans OR 0.80 NS

Van Assche et al., 2019

53

Psychosis in AD Dementia – Clinical Practice Points

- Around a third of AD dementia patients in clinic-based and a fourth in community-based cross-sectional studies have psychotic symptoms at any given time
- Delusions are twice as common as hallucinations
- Simple persecutory delusions of theft are the most common delusions
- Visual hallucinations are twice as common as auditory
- Psychosis is less common as a prodrome in AD and is of lesser severity
- In clinic-based (but not in autopsy) studies, delusions decline in severe dementia, but hallucinations do not, which may be due to
  - superimposed delirium in a sizeable number of patients with advanced AD?
  - an artifact of the increasing frequency of mixed pathologies seen with increasing age in dementia?
- Older age has been found to be associated with more delusions but not hallucinations across all study settings
- Familial clustering of psychosis in AD dementia exists

54

Psychosis in Dementia with Lewy Bodies

- Recurrent visual hallucinations - core clinical feature
  - well-formed visual hallucinations are seen in 80% of DLB patients
  - typically complex, often involving people, children or animals
  - may be accompanied by typical "parkinsonian hallucinations" – presence, passage – and illusions
- Pareidolias are a special form of complex visual hallucinations
  - common in DLB patients
  - involve ambiguous stimuli that are perceived as meaningful objects (e.g. seeing a face in a piece of toast)

McKeith et al., 2017; Uchiyama et al., 2012; Christodoulou and Malliara-Loulakaki, 1981; Cipriani et al., 2013; Nagahama et al., 2007

55

Psychosis in DLB – Cont'd

Hallucinations in other modalities, systematized delusions – supportive clinical features

- About 25%-75% of patients have delusions
- Cover the entire spectrum, from persecution and theft to jealousy to hypochondriacal delusions to delusions of pregnancy
- Delusional misidentification and related symptoms are seen in about 55% of DLB patients
  - patient consistently misidentifies places, persons or events, with a central feature being the belief in the existence of the double
  - include Capgras syndrome, Phantom Boarder syndrome and re-duplicative paramnesia
- Misidentification symptoms have been reported in around 23% and delusions of caregivers being impostors in 3% in late-onset AD (≥60 yrs) with high familial loading for AD

McKeith et al., 2017; Uchiyama et al., 2012; Christodoulou and Malliara-Loulakaki, 1981; Cipriani et al., 2013; Nagahama et al., 2007 Sweet et al., 2010

56

Psychosis in DLB vs. VLOSLP

- Suggest DLB
  - Visual hallucinations of humans — OR 0.23 p<0.05
  - Visual hallucinations of animals — OR 0.37 NS
- Suggest VLOSLP
  - Paranoid delusions — OR 9.02 p<0.05
  - Partition delusions — OR 4.60 p<0.01
  - Auditory hallucinations of human voices — OR 2.69 NS

Van Assche et al., 2019

57

Psychosis in DLB – Clinical Practice Points

- DLB patients have the highest prevalence of psychosis
- Complex visual hallucinations are the most common
- Unusual phenomenology more common
- Up to 80% of older Capgras syndrome patients have a neurodegenerative disorder
- A combination of visual hallucinations with Capgras syndrome should prompt the clinician to comprehensively assess for DLB

Josephs, 2007

58

Psychosis in behavioral variant frontotemporal dementia

- The frequency of psychotic symptoms in bvFTD has been consistently shown to be high
  - hallucinations across clinical and pathological studies range from 0-50%
  - delusions reported in about 25%.
  - both auditory and visual hallucinations reported
  - wider range of delusions reported – persecutory, erotomanic, somatic, Cotard's, Fregoli's and referential
- bvFTD patients can resemble primary psychiatric disorders at initial presentation
- In 97 consecutive neuropathologically confirmed FTLD cases
  - Only 15% were initially diagnosed with FTD, while
  - 42% were initially diagnosed with a psychiatric disorder

Hall and Finger, 2015; Landqvist et al., 2015

59

bvFTD vs. Primary Psychiatric Disorders Checklist

Scoring:
- Score 1 point for all the No responses in Part A and Yes responses in Part B
- Score ≥11 strongly indicative of bvFTD (specificity 94%, sensitivity 71%, PPV 89%)
- Scores ≤8 strongly indicative of a PPD (specificity 91%, sensitivity 77%, PPV 93%)
- Scores of 9–10 considered indeterminate

From Ducharme et al., 2019

60

Psychosis in bvFTD – Clinical Practice Points

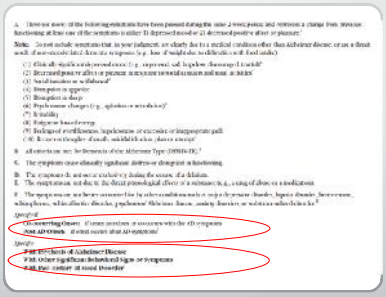
Some "red flags" suggest a diagnosis of bvFTD

- Lack of distress
- Illness that is progressive and refractory to treatment
- Unusual psychiatric presentations
  - sustained manic-like states without grandiosity or euphoria
  - compulsions without obsessions
  - schizophrenia lacking hallucinations or complex delusions
  - profound loss of empathy early on
- Hyperorality or compulsive eating (particularly a predilection for sweets) vs. overeating due to antipsychotics
- New onset of psychiatric disorder in middle-aged and older adults

Wylie et al., 2013; Cooper and Ovsiew, 2013

61

Defining Depression in AD Dementia



The National Institute of Mental Health (NIMH) provisional diagnostic criteria for depression of AD (PDC-dAD)
From Olin et al., 2002

62

Depression in AD Dementia – Cont'd

A meta-analysis and systematic review of prevalence studies that compared the validity of the dAD criteria against DSM-IV and ICD-9 MDD diagnostic criteria found

- The dAD criteria had higher specificity for depression in AD than DSM or ICD
- dAD criteria covered a wider range of depressive symptoms
- An aggregate of 47% overlap found between dAD and DSM-IV MDD criteria based on three studies
- Feelings of worthlessness, hopelessness, excessive or inappropriate guilt, social isolation and irritability were more prevalent in patients diagnosed by the dAD criteria
- Psychomotor changes, suicidality, and appetite disruption were more prevalent in DSM-IV MDD
- Lower frequency of suicidal thoughts were identified in patients diagnosed via dAD (27%) compared to DSM (41%)

Sepehry et al., 2017

63

Depression in DLB

- Depression is listed as one of the supportive clinical features in the DLB diagnostic criteria
- Prevalence rates reported in DLB
  - major depression of around 20%
  - "minor" depression of around 35%
- The frequency of DSM-IV major depression is greater in DLB (almost 20%) than in AD (almost 10%)

McKeith et al., 2017; Aarsland et al. 2001; Chiu et al. 2017; Simard et al. 2000

64

NPS in the Dementias – Psychiatric Disorder Level

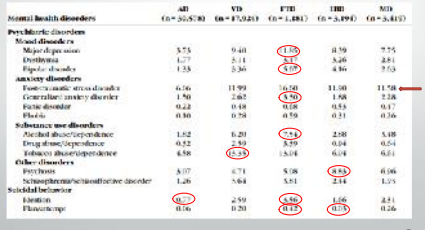
Analysis of 2-year prevalence of ICD-9 CM mental health disorders in 56,296 patients ≥ 50 years across the 5 commonest dementia subtypes using 2 large national databases

- FTD 45%
- Vascular dementia 40%
- Lewy body dementia 33%
- Mixed dementia (any 2 or more co-occurring dementias) 33%
- AD dementia 20%

Lai et al., 2018

65

Psychiatric Disorders – Cont'd



One of the databases was a large VA database

From Lai et al., 2018

66

Dangerousness in the NCD – The 3x3 Model

1. Resulting from the direct actions of the person with dementia
   1. Due to a mismatch between cognitive and functional levels – person with advanced dementia continues to drive/ operate machinery/ managing finances and investments
   2. Due to dementia-related NPS – agitation/aggression- self/others
   3. Due to associated neurological symptoms of dementia – REM-sleep behavior disorder, carbohydrate craving, Kluver-Bucy syndrome (pica, coprophagia)
2. Resulting from the indirect impact of the person with dementia - caregiver stress leading to psychiatric and physical problems, including early mortality
3. Resulting from actions of caregivers/ strangers on the person with dementia - phishing and telemarketing scams, financial and physical abuse

67

NCD and Suicide

- Suicidal behaviors are uncommon in dementia overall, FTD > AD
- Risk factors – white race, new dementia diagnosis, receiving treatment for depression or anxiety, history of recent inpatient psychiatric hospitalization (National VA Data 2001-2005)
- Protective factors – placement, nursing home admission
- Must ask about access to guns - 73% took their lives with a firearm
- Completing suicide may also be a "rational" decision in patients who are not clinically depressed, driven by
  - distaste for a life of dependence
  - non-maleficence (a wish to avoid burdening others)
  - beneficence (preservation of assets to pass on to others)
- Assess capacity for decision making in all such "rational" patients

Kales et al., 2011; Davis, 2013; Yager et al., 2018

68

Case #1

The man who could not find his room

69

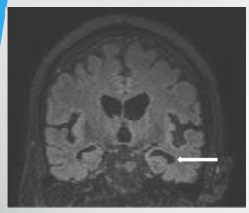
- 65 y o Caucasian male who did not graduate HS, later obtained a GED, never in the service
- Living in a secure facility for 2.5 years
- Been moved because he was wandering into the street in previous facility
- Long-standing diagnosis of schizophrenia with stable auditory hallucinations and persecutory delusions, has always talked quietly to voices
- Has had episodes of catatonia in the past
- Was relatively stable at admission on an olanzapine+lamotrigine combination
- Recently staff have noticed problems with short-term memory, trouble recalling names
- Now also getting lost in the facility and unable to find his room
- New delusions that meds are poisoning him
- Now unable to shower, dress and groom independently
- Medical problems include legal blindness, HTN, possible TBI history, obesity, T2DM and chronic Hep C
- No current substance use, remote history present, details unknown (IVDU?)
- Family history unknown
- Neuropsych testing in Feb 2020 – performed in the impaired range on virtually all cognitive domains, learning of new information was virtually non-existent
- At initial visit, he was not cooperative with office cognitive screening (MoCA-Blind)

70

All the following are consistent with new-onset AD dementia in schizophrenia EXCEPT

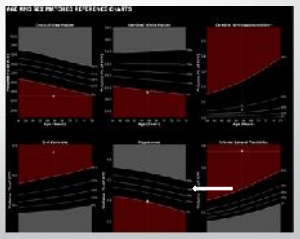
A. New-onset STM impairment
B. Almost non-existent new learning on neuropsych testing
C. New delusions about medications
D. Decline in ADLs
E. History of catatonic episodes

71



MRI brain without contrast in June 2020 read as "generalized cerebral volume loss"

Volumetric analysis using NeuroQuant



72

When Should a Dementia Work-up be Considered in Schizophrenia Flashback

- "Rapid forgetting" – a hallmark of AD dementia
- Decline in "crystallized" verbal knowledge i.e. long-term verbal knowledge
- Decline in IADLs and BADLs (vs. increase in negative symptoms with age)
- Aphasia (vs. disorganized and idiosyncratic pattern of speech in psychosis)

73

Case #2

The lady who sold her home for nothing

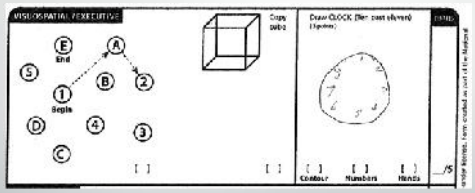
74

- 83 y o widowed Caucasian female with 2 years of college education and never in the service
- Long history of recurrent major depressive disorder, mostly mild-moderate
- Episodes of severe depression in 1997 after a stroke and in 2012 when husband of many years died
- No prior history of psychosis, psychiatric hospitalization or suicide attempt
- Mild problems with short term memory starting around 2018, minimal effect on functioning
- Continued to live independently
- Increasing depression and anxiety starting early 2020 related to sale of house where she had lived x55 years and impending move
- Increasingly unable to make decisions, increasing problems with short-term memory
- Moved in March 2020 to a Catholic retirement community in a new town
- The COVID lockdown began 2 weeks after her move, making her increasingly isolated
- Patient was moved to her sister's, then to her daughter's home
- By that time, was severely depressed and psychotic
- Convinced that she had sold her home for nothing
- And the new owners were going to come after her for some unclear acts of commission or omission during the sale (they were actually very pleased with the home)
- Started to talk about killing herself
- While living at daughter's home, wandered away one morning looking for a creek to jump in while daughter was working from home
- Could not find it, was able to find her way back home and told her daughter what she had done
- Daughter was able to get her psychiatrically hospitalized on an adult psychiatric unit in May 2020

75

- By Jan 2020, patient was already on paroxetine, which had been increased with no benefit
- She was switched to fluoxetine prior to her psychiatric hospitalization, again with no benefit
- In the hospital, lorazepam, risperidone and methylphenidate were added to her regimen
- Discharged after 2 weeks to SNF x1week, then to an ALF near daughter's home
- Depression and cognitive problems continued to increase
- Began to require lots of assistance with ADLs and complete assistance with IADLs
- Medical problems – Sjogren's disease, HTN, stroke in 1997, couple of TIA's, mild hearing loss
- No substance use issues
- Family history of late-onset mild dementia in her mother in her 80s before she died
- When I saw her in the outpatient clinic, she had severe psychotic depression with marked anhedonia, spending much of her time in bed but not sleeping, marked loss of appetite and weight and severe problems with short term and working memory
- Could barely participate in the initial interview
- Scored 15/15 on the GDS-short form and could not even complete a clock on the MoCA

76

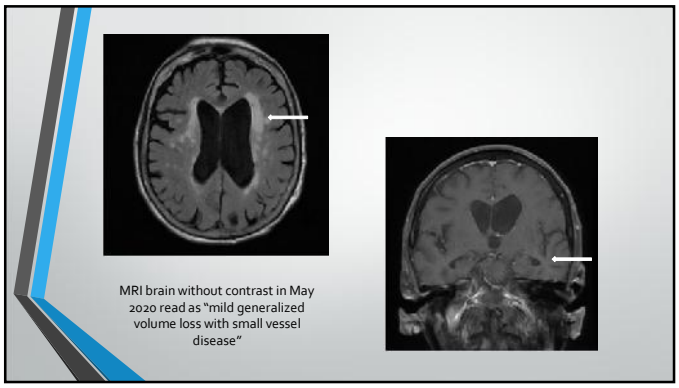


77

All the following are true EXCEPT

A. The patient should first be treated for depressive pseudodementia
B. Further decline in oral intake would indicate need for hospitalization
C. Long history of recurrent depression makes dementia unlikely
D. First-time psychotic symptoms is a red-flag for new-onset dementia
E. Even if her symptoms resolve with treatment, she will need close psychiatric follow-up

78



79

Cognitive Impairment and Late-life Depression Flashback

- 30-40% older adults with depression without dementia have evidence of executive dysfunction on cognitive assessment
- Cognitive symptoms can be severe enough to reach the severity of a dementia, which is typically reversible
  - "depressive pseudodementia" or dementia syndrome of depression
- Depressive patients with a reversible dementia at baseline has been shown to be almost 5x times more likely to develop irreversible dementia over a follow up period compared to the group with no dementia at baseline
- Depression-executive dysfunction syndrome (DEDS) is
  - a predictor of poor treatment response
  - a risk-factor for progression to a dementia

80

Case #3

The lady who was being harassed by shadows

81

- 72 y.o. widowed Caucasian female, a high school graduate and never in the service
- 4-year history of progressively increasing delusions of persecution and visual hallucinations
- She was being followed by a group of people who were also harassing her by "messing" with her yard and shining flashing lights into her bedroom
- Saw lights, shadows of people in her yard but only in dim light
- She had called the police on these people several times and installed security cameras, but neither the caught any "people"
- She never made any move to approach them but threatened to use her BB gun on them if the "harassment" continued
- Progressively increasing word finding problems, minimal short-term memory problems and no visuospatial deficits, started after the psychotic symptoms
- Past history – long history of depression and anxiety, in partial remission
- Relevant medical history - hypertension, hyperlipidemia, history of obstructive sleep apnea (not using CPAP due to paranoia), one TIA in 2009
- Family history – late-onset dementia in maternal grandmother in her 90s, mother alive and relatively cognitively intact at 91

82

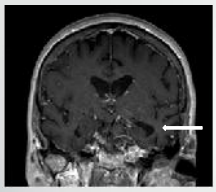
- Parkinsonian features on neuro exam - stooped posture, reduced arm swing on the right
- At initial visit, mild depression (GDS score 6/15)
- Cognitive screening (NCSE/ Cognistat) – prominent problems with confrontation naming and minimal short-term memory impairment
- No single word comprehension problems or impaired object knowledge
- Reading and writing relatively intact with no evidence of surface dyslexia
- Neuropsychological testing - significant impairment in expressive language (naming, verbal fluency), verbal memory, attention and processing speed.
- Most consistent with a primary progressive aphasia (FTD-language variant)

83

All the following are true EXCEPT

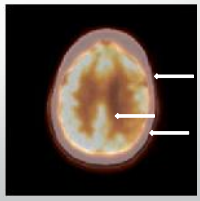
A. VLOSLP, DLB and AD dementia are all in the clinical differential
B. Visual hallucinations of humans suggests DLB but are non-diagnostic
C. Onset of psychotic symptoms before cognitive symptoms is consistent with a VLOSLP diagnosis
D. Patients meets the ISTAART provisional criteria for a diagnosis of MBI
E. Patient is at high risk of shooting someone in self-defense

84



MRI brain with contrast in 2017 read as "generalized cerebral atrophy"

FDG-PET scan of the brain in 2018 shows asymmetric involvement of the dominant hemisphere with bilateral hypometabolism of the posterior cingulate cortex



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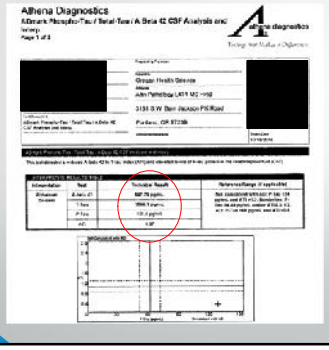


CSF AD Biomarker Testing (ADMARK)

AD dementia versus no dementia

Aβ42<500 pg/ml
sensitivity 0.81 and specificity 0.45

T-Tau>350 pg/ml
sensitivity 0.77 and specificity 0.79

p-Tau>61 pg/ml
sensitivity 0.73 and specificity 0.87

ATI=0.8
sensitivity 0.90 and specificity 0.56

Tariciotti et al., 2018

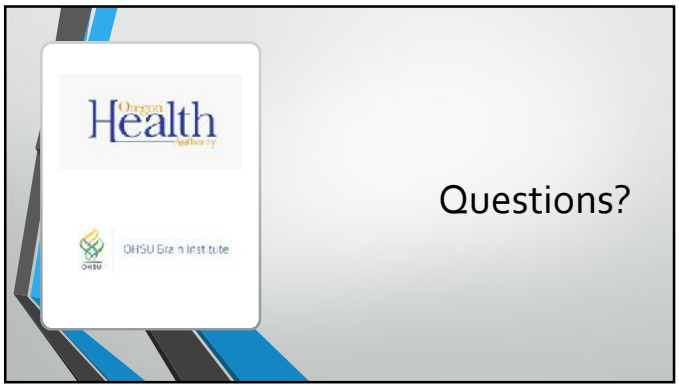
86

- Late-onset (age 50 or above) psychiatric symptoms
- That must persist or present intermittently for at least 6 months (thereby excluding adjustment disorder precipitated by life stressors)
- Must result in at least minimal impairment in social, occupational, or interpersonal function which must be due to the changes in personality and behavior, and not due to cognitive decline, and without leading to a loss of functional independence
- Rate of conversion to dementia is the highest for MBI
  - MBI (70%) > MCI-MBI (60%) > amnestic MCI (35%) > psychiatric patients (14%)
  - Amnestic MCI patients → AD, none to DLB
  - MBI → FTD > DLB > AD
  - Psychiatric group →DLB > FTD

MBI Flashback

87

88



89