Anxiety, Depression, and Dementia/Alzheimer Disease: What are the Links?

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Why talk about these conditions?

• Alzheimer Disease (AD) and other dementias become increasingly common as we grow older.

• Anxiety and depression are common throughout adulthood.
• Early Adulthood

• Middle Adulthood

• Late Adulthood

DEMENTIA

ANXIETY & DEPRESSION
Depression and Anxiety *
Across adulthood

* % seeking help for these conditions

Mackenzie C. et al., Depression and Anxiety, 2012, 29 (3):234-242
Prevalence

Depression

Dementia
Prevalence

Depression

Dementia
Depression
Anxiety

Chicken Or Egg?

Dementia

Causes?
Consequences?
Coincidence?
In basic terms

• People who experience anxiety and depression early in life may have an increased chance of showing signs of AD when they get older.

– Timely and appropriate treatment for anxiety and depression may help lower this chance.
However...

• Not everyone who was anxious or depressed earlier will develop dementia later.

• Many people who get dementia have never been anxious or depressed before.

• Some people become anxious or depressed for the first time when they are older.
Among those who become anxious and depressed for the first time in late adulthood:

• In some, the anxiety and depression may simply be a reaction to their increasing difficulties with remembering, organizing, and thinking that are due to their AD.

• In others, the anxiety and depression may be the first symptoms of the brain changes of AD, appearing even before memory loss.
Depression and Dementia: the clinician’s perspective

- Clinicians often see older patients who are both depressed and cognitively impaired.
- Cognitive functioning often improves when depression is treated.

¿ Does this information have clinical implications for prognosis and treatment of patients?

¿ Does this information help us understand the underlying relationship and/or mechanisms?
What does the research tell us?

Different studies appear to have conflicting results, depending on:

✓ The setting/population for the study.
✓ The design of the study.
✓ The assessments/measurements used in the study.
✓ The specific research question being asked (hypothesis being tested) in the study.
WHERE ARE THE PATIENTS SEEN?
WHO PARTICIPATED IN THE STUDY?
What was the design of the study?

- **Who participated?** Memory clinic patients? Primary care patients? Volunteers? Randomly selected community members? Nursing home residents?
- **Time-line:** Was the study cross-sectional, retrospective, or prospective?
- Were participants **depressed or depression-free** at the time of selection?
- Were participants **cognitively impaired or cognitively intact** at the time of selection?
- What was the **outcome** studied? Cognitive decline? Clinical dementia? Brain imaging findings? Autopsy findings? Biomarkers (e.g. plasma or CSF amyloid)?
What did different studies/articles mean by “Depression?”

- **Scores on Depression Symptom Scales:**
  - Self-report questionnaires, e.g., CES-D, GDS, PHQ-9
  - Clinician-rated scale, e.g., Ham-D
  - Prime-MD

- **Depressive Syndromes:**
  - Standard diagnostic criteria: DSM, ICD.
    - Clinician diagnosis
    - Diagnostic algorithm, e.g., SCID, CIDI

- **Depressive Disorders:**
  - Major depression (unipolar), bipolar disorder.
  - Depression secondary to other disorders *
  - Dysthymia
  - “Subsyndromal” or sub-threshold depression

*Including neurodegenerative and vascular brain disease*
What is meant in different studies by “Cognitive Impairment?”

- **Self-report:** subjective difficulty with memory, concentration, organization.
  - Spontaneous complaints.
  - History elicited by questioning.
- **Performance on objective cognitive tests.**
  - Brief general mental status test, e.g., MMSE, MoCA.
  - More extensive global test, e.g. 3MS, Mattis DRS.
  - Neuropsychological tests of specific cognitive domains (attention, processing speed, learning/recall, language, visuospatial/constructional, executive functioning)
  - Need appropriate norms for age, race/ethnicity, gender, education, language/dialect.
- **Cognitive impairment resulting in functional impairment.**
What is meant in different studies by “Functional Impairment?”

• **Basic** self-maintenance Activities of Daily Living (**ADLs**):
  – Self-maintenance: feeding, toileting, grooming, mobility

• **Instrumental ADLs**:
  – Familiar household items, appliances.
  – Driving car, cash management, medication management.
  – Higher-order activities.

• Change in everyday functioning *related to cognitive impairment* (Clinical Dementia Rating- **CDR** scale):
  – Memory, orientation, judgment, home/hobbies, community activities, self-care.
What do different studies mean by “Cognitive Decline?”

- **Subjective**: reports by individual or family (or observation by clinician) of **CHANGE**: loss of cognitive ability compared to previous level.

- **Objective**: **decline** in scores on cognitive tests, demonstrated by **repeated** testing.
  
  ? More than expected for age? (norms available?)

  ? Accounting for learning/practice effects?

  ? All potential causes considered?
What do different studies mean by “DEMENTIA?”

- Clinical Dementia Rating (CDR) *(based on functional loss only)*
- DSM-diagnostic criteria? *(loss of memory and other cognitive domains sufficient to interfere with functional independence)*
- ICD criteria?
- Neuropsychological definition *(test scores >=2 standard deviations below the mean in two cognitive domains)*?
- A specific etiologic subtype of dementia *(Alzheimer’s, vascular, other)*?
What do different studies mean by “Mild Cognitive Impairment (MCI)?”*

- A cognitive state **intermediate** between normal-for-age and dementia. (**intermediate** ≠ **transitional**)
- Has elevated probability of progressing to dementia.
- In memory clinic populations, majority with MCI progress to dementia (usually Alzheimer’s) *(many studies)*
- In the community at large, the majority remain mildly impaired *(many studies)*
- Current criteria are International Working Group 2004 *(Winblad et al.)* but studies vary in how they interpret and implement the criteria.

(*Petersen et al., 1999; Winblad et al., 2004*)
Normal cognition for age

Mild cognitive impairment

Severe cognitive impairment = dementia
What do the data tell us?

• Late-life depression is characterized by slowed information processing, which affects all realms of cognition.  
  Butters MA et al. 2004

• Most older individuals who are cognitively impaired during a depressive episode remain impaired when their depression remits.

• A lot of older depressed patients who are cognitively intact when depressed are likely to be impaired one year later, although their depression has remitted.  
  Bhalla R et al. 2006
Depressive symptoms in cognitively intact elderly were associated with increased probability of subsequent MCI, independent of vascular disease.  

*Barnes et al., 2006*

Depressive symptoms predict cognitive decline in old age.  

*Wilson et al., 2004*

Clinically significant *depressive symptoms* in women aged 65 or older are independently associated with greater incidence of MCI and probable dementia.  

*Goveas et al., 2011*

There was no increased risk of developing dementia in amnestic MCI patients with depression. In contrast, amnestic MCI patients with *apathy* had significantly increased risk of progressing to dementia.  

*Palmer et al., 2010*
Dividing people into one group who later developed dementia and another group who remained dementia-free,

- Depressive symptoms are cross-sectionally associated with cognitive impairment, especially in those who continued to remain dementia-free.
- Dementia-free individuals undergo minimal cognitive decline over time;
- Depression is not associated with rate of subsequent cognitive decline in either group.

Ganguli et al., 2006
• Depressive symptoms were significantly more likely to be present in individuals after the onset of dementia than in persons without dementia.

• Depressive symptoms appeared to be early manifestations, rather than predictors, of Alzheimer’s disease in this community sample.

Chen et al., 1999
...after partially controlling for genetic influences, late-life depression for many individuals may be a prodrome rather than a risk factor for dementia.

Bromelhoff et al., 2009
Maybe it’s not one-time depression but the course of depression over time

“Fifty Shades of Blue”

Graziane et al., 2015
Dual trajectories of depression and cognitive trajectories over time

• Moderate depressive symptoms, and low-grade but increasing symptoms, were the most strongly associated with consistently poor cognitive function.

• High-grade depressive symptoms were not strongly associated with consistently poor cognitive function except in attention/processing speed.

Graziane et al., 2015
Systematic Reviews and Meta-Analyses

• A **history** of depression may confer an increased later risk of developing AD, and may be an independent risk factor.  
  \[Ownby\ et\ al.,\ 2006.\]

• **Interval** between diagnoses of depression and AD was positively related to increased risk of AD.

• Assuming that MCI may be the earliest identifiable clinical state of dementia, **depressive symptoms may be an early manifestation rather than a risk factor** for dementia and Alzheimer’s disease.  
  \[Panza\ et\ al.,\ 2010.\]
Anxiety may mean different things

• Recent onset, acute anxiety was associated with non-amnestic MCI;
• Chronic, severe anxiety was associated with all forms of MCI;
• Chronic, mild worry was not associated with MCI

— Andreescu et al., 2013
Normal cognition for age

Mild cognitive impairment

Severe cognitive impairment = dementia

Depression

Anxiety
One way to resolve the apparent inconsistencies

- Major depression in **early life**, and
- Recurrent major depression and chronic anxiety throughout life, **may be independent risk factors** for dementia.

- New depression/anxiety occurring in **late life** is more likely to be an **early manifestation or prodrome** of a dementing disease.
1. **Glucocorticoid theory:**
Major depression and anxiety is associated with **cortisol elevation**.
Sustained hypercortisolaemia is toxic to the **hippocampus**.
In these patients, the hippocampus becomes particularly vulnerable to neurodegenerative pathology in old age.
Here, depression is an independent risk factor for dementia.
Some Data

• Longer durations of untreated depressive episodes were associated with reduced hippocampal volume.

• No significant relationship between hippocampal volume loss and time depressed while taking antidepressant medication, or with lifetime exposure to antidepressants.

• Antidepressants may have a neuroprotective effect during depression.

  Sheline et al., 2003
Postmortem Study;
Brains of 102 deceased nursing home patients, all with Alzheimer’s disease, half of whom had lifetime history of major depression.

In AD, the presence of a **lifetime history of depression** corresponds to increases in AD-related neuropathological changes in the hippocampus.

*Rapp et al., 2006*
With increasing age, there is increasing cerebrovascular (blood vessel) pathology in the brain.

“Vascular depression” can accompany “vascular cognitive impairment/vascular dementia.”

Here, depression is not an independent risk factor for dementia.
• Prospective study of 3837 primary care patients with diabetes
• Patients with *major depression plus diabetes* had an increased risk of developing dementia compared to those with diabetes alone.
• These data add to recent findings showing that *depression was associated with an increased risk of macrovascular and microvascular complications* in patients with diabetes.

*Katon et al., 2010*
Possible mechanism - 3

• Neurodegenerative disease causes cognitive impairment/dementia.
• Neurodegenerative disease also causes apathy, anxiety, depression, and other behavioral disturbance.
• These behavioral disturbances precede or accompany MCI and may be the first sign of the dementia.
Cross-sectional study of homebound elderly using AD biomarkers Aβ40 and Aβ42

• Patients with depression had lower plasma Aβ42 levels and a higher ratio of Aβ40: Aβ42 than those without depression.

• “Amyloid-associated depression” was associated with greater memory impairment than non-amyloid associated depression.

• “Amyloid-associated depression” may be a prodrome of AD.

Sun et al., 2008
Homeostasis:
• A state of everything being stable in the body.

Allostasis:
• The body’s physiological efforts to keep everything stable (to maintain homeostasis) in the face of challenges and change.

Allostatic Load:
• The “wear and tear” negative consequences on the body of trying to keep everything stable through allostasis.
• Reflected by effects like inflammation, increased cortisol, cardiovascular risk.
Chronic anxiety
(and depression)

HPA axis hyperactivity

Stressor-evoked BP reactivity

Increased Allostatic Load

Accelerated Aging

Inflammatory cytokines

Andreescu C, unpublished, 2015
Combining all models

Koenig, Bhalla, and Butters, JINS 2014
Conclusion

• Depression/Anxiety and Dementia frequently occur in the same people.
• The direction of causality may vary.
• Early onset depression and chronic anxiety may be risk factors for dementia.
• Adequate treatment for depression and anxiety may have a protective effect.
• Late onset depression and anxiety may be an early manifestation of the same disease (degenerative or vascular) that is causing the dementia.
Take-home message

• Don’t walk around being anxious or depressed at any age.

Get help:
  – Medication
  – Talk therapy
  – Exercise
  – Meditate
  – Maintain physically and socially active lifestyle

• You’ll feel better

• You may also reduce your risk of dementia.