Depression and Anxiety in the Elderly: An Evolving Framework

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Depression & Anxiety in the Elderly: One “Disease” or Two?

- Often co-morbid
- Diagnosis often not clear
  - Often difficult to distinguish
- Same treatments are 1st-line for both

Good Mental and Emotional Health is the Normal Outcome in Old Age

- Anxiety and depression are not normal or expectable reactions to old age
  - Among elders with preserved brain reserve capacity
- Elders cope better than younger people
  - Higher satisfaction with life
  - Higher level of happiness

Rule of Thumb No. One:
Never Assume Severe Depression or Anxiety is an Understandable, Normal Reaction to Old Age.

Why Do People With No Past Psychiatric History Develop Anxiety-Depression in Old Age?

Good Brain Reserve Capacity
Poor Brain Reserve Capacity

STRESSFUL EVENT

Evolving Paradigm Shift in Psychiatry: Relevance in Geriatrics

- PSYCHODYNAMIC (Freudian)
  - Treatment is driven by psychological theory
  - Brainless mind
- “BIOLGICAL PSYCHIATRY” (1960’s to present)
  - Chemical black box
  - Neurotransmitters (current psychopharmacopia)
    - Treatment is driven by clinical symptoms
- NEURAL NETWORK PSYCHIATRY (Emerging)
  - Dimensionally based
  - Neural circuits, networks, mental functions
  - Psychopathology is due to aberrant connectivity
    - Targeted therapies based on dynamic brain imaging and other biomarkers
Late-Life Anxiety-Depression: Comorbid Conditions of Phenotypic Continuum?

Depression

Prefrontal Cortex
• DLPFC
• Cingulate Cortex

Amygdala

Anxiety

Proposed Brain Networks

White Matter Tractography
Diffusion Tensor Imaging

White matter tracts connecting different brain regions, showing anatomical connectivity.

Mechanisms

Cerebrovascular
Neurodegenerative
Autonomic hyperarousal
HPA Activation
Inflammation
Oxidative Damage
Modifiable Risk Factors for Late-Life Neuropsychiatric Disorders

- Exercise
- Diet
- HTN
- Diabetes
- Hypercholesterolemia
- B12, folate deficiency, homocysteinemia
- Chronic inflammation
- Chronic stress
- Chronic or recurrent depression, PTSD
- Drugs – Benzodiazepines – Anticholinergic agents
- Education
- Social and cognitive engagement
- TBI
- Obesity

Cerebral Reserve and Disease Onset

Rule of Thumb No. 2

- Patients 55+ presenting for the first time with clinically significant psychiatric symptoms should be presumed to have a psychiatric disorder due to another medical condition, including pre-senile dementia.

Primary Care Focus

- Late-Life Anxiety & Depression are common in primary care settings
- The vast majority of the mental healthcare the elderly receive (if they receive any at all) is from primary care clinicians.
  - Detection of mental health problems
  - Proper diagnostic evaluation
  - Vigilant primary care and medical management of common geriatric conditions and syndromes.
    - e.g., Hypothyroidism, vitamin deficiencies.
    - e.g., Fall risk management
  - Iatrogenic problems
    - Geriatric pharmacology

Depression
Anxiety
Diabetes
Stroke
HTN
Chronic inflammation
Oxidative stress

Subjective Cognitive Complaints
Mild Cognitive Impairment
Dementia

Brain Failure
Increased Psychiatric/Sx
Behavioral Sx

Rule of Thumb 3:
Avoid treating symptoms, treat syndromes or diagnoses!

CASE ONE:

- 82 YO woman living alone on the 4th floor of an upscale retirement community
  - CC: Anxiety about leaving her apartment
  - Dx: Agoraphobia – Ativan started
  - Correct Dx: Alzheimer’s disease with wayfinding difficulty, fear of getting lost/social embarrassment/NF placement
  - Proper treatment: D/C anticholinergic drugs, start donepezil, OT for cognitive training
Rule of Thumb 3: Avoid treating symptoms, treat syndromes or diagnoses!

CASE TWO
– 78 YO woman living alone in own home. Has mild Alzheimer’s disease but fully independent except doesn’t drive.
  • CC: "depressed" – “Mom has no interest in doing anything and just wants to stay in bed all day”.
  • Dx: Depression – sertraline 25 mg qD started
  • DDox: Apathy, Sleep apnea.
    – SSRIs not indicated: Can cause abulia, apparently exacerbating apathy.

Atypical Geriatric Presentations of Anxiety
• Dementia – worry/fear of task failure
  – Treatment: Treat dementia
• Fear of falling
  – Treatment: Gait assessment/PT assessment/PT gait training
• Fear of incontinence

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Treatment of Geriatric Anxiety Disorders
• Exercise
• Mindfulness practices
• Psychotherapy
  • Behavioral – Relaxation Tx.
  • Cognitive -behavioral Tx
• Access and patient preference may be issues

Why Do SSRIs Treat Anxiety and Depression?

Depression
  • Prefrontal Cortex
  • Cingulate Cortex
  • Amygdala

Anxiety
  • Prefrontal Cortex
  • Cingulate Cortex
  • Amygdala

Dysregulation

Rule of Thumb No. 4: Use Benzodiazepines VERY Sparingly
• Use in elderly NOT recommended!
• But, still widely prescribed for anxiety, agitation in dementia, and depression.

Treatment Refractory GAD

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Risks Associated with Benzodiazepines in the Elderly

- Cognitive impairment
  - Excess disability in dementia
- Fall risk
  - Fractures
- Driving Impairment
- Non-motor vehicle accidents
- Addiction
  - Dose escalation
  - “Who cares if Mom gets addicted at her age!”

Evidence-Based Treatment of Depression

- Integrative
  - Exercise, mindfulness practices, L-methylfolate, curcumin, OSRA.
- Psychotherapy
  - CBT, interpersonnal, problem solving.
- Antidepressants
  - Various classes with different MOA may target different sub-syndromes
  - SSRIs treatment of choice in primary care.
  - Add cholinesterase inhibitor to antidepressant for patients with cognitive impairments
- Phototherapy
- Brain stimulation
  - ECT, rTMS, vagus nerve stimulators.
- Treatment must be individualized based on resources, patient preference, type of depression, comorbid conditions, patient med list.

Why Do SSRIs Treat Depression and Anxiety?

- Depression
- Anxiety

Processes of Good Treatment of Depression

- Proper Evaluation
  - History
  - Physical examination
  - Labs
    - CBC and routine chemistry
    - Thyroid studies
    - B-12, folate, homocysteine, zinc, vitamin D
    - Testosterone in younger old men?
    - CRP?

Processes of Good Treatment of Depression

- Adequate Trials
  - 12 weeks at adequate dose
  - If no improvement by 4 weeks (maybe earlier?) adjust treatment.
- Primary care:
  - SSRIs
  - 2 adequate trials (or more)
- 2/3 of geriatric patients do not respond to the first antidepressant tried
  - “Start low, go slow, go all the way.”
- Frequent visits to monitor progress and support patients during response latency
  - No later than 2 weeks after starting or changing treatment.

Rule of Thumb No 6:

Use Watchful Waiting for Sub-Syndromal Depression with onset in the context of Acute Illness

- 50% of geriatric patients with depression complicating a general hospital or rehab stay will improve spontaneously
Processes of Good Treatment of Depression

- Managing treatment resistance
  - Combination psychotherapy & medication
  - Polypharmacy
    - combination - two or more antidepressants
    - Augmentation
      - Lithium
      - Antipsychotic medication
      - Methylphenidate
      - Buspirone
      - Triiodothyronine
      - ECT or rTMS

Maintenance Management

- The dose that makes the patient better is the dose they ought to stay on
- Most older adults better served by ongoing maintenance management
  - Role of monthly adjunctive psychotherapy over 3 years even for patients in stable remission.

Cholinesterase Inhibitors

- A new class of psychoactive medication?
  - For depression or anxiety in Alzheimer's disease and related disorders
  - For depression with cognitive impairment
- Meta-analyses reveal significant improvement in neuropsychiatric symptoms
  - Symptoms already present (including depression)
  - Prevents depression and other psychiatric symptoms from emerging
- Corollary:
  - Reducing anticholinergic burden reduces prevalent neuropsychiatric symptoms

Anticholinergic Potency of Common Drugs
(atropine equivalents)

Aricept Treats Neurobehavioral Symptoms in Alzheimer's Disease

![Graph showing clinical improvement and clinical decline](image-url)
Possible Benefits of Treatment

Possible Benefits of Treatment

Ideal treatment

Disease arrest

Blowed progression

Symptomatic benefit

Delated treatment

Table 1
FDA Approved AChEIs and NMDA Antagonist in Various Stages of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Applicable Stages of AD</th>
<th>FDA Approved Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (AChE inhibitor)</td>
<td>Acetyl</td>
<td>All</td>
<td>1996</td>
</tr>
<tr>
<td>Galantamine (AChE inhibitor)</td>
<td>Brandint</td>
<td>NIAAD to Moderate AD</td>
<td>2001</td>
</tr>
<tr>
<td>Rivastigmine (ChE inhibitor)</td>
<td>Nuartan</td>
<td>Moderate AD to Severe AD</td>
<td>2003</td>
</tr>
<tr>
<td>Memantine (NMDA Antagonist)</td>
<td>Tefdin</td>
<td>All</td>
<td>2000</td>
</tr>
<tr>
<td>Donepezil / Memantine</td>
<td>Nortane</td>
<td>Moderate AD to Severe AD</td>
<td>2010</td>
</tr>
</tbody>
</table>

Adapted from Alz.org

Beers Guidelines

Remember That Psychiatric Illnesses Themselves Carry Serious Risks

- Quality of life
- SUD
- Suicide
- Frailty, falling, disability, long-term care
- Accelerating aging
- Premature death

Pharmacodynamic Effects of Post-Synaptic Receptor Blockade
Drug-Illness Interactions

• Based on pharmacodynamic action of a drug
  – Cholinesterase inhibitors and OAB
  – Lithium and OAB or urge incontinence
  – SSRIs and hyponatremia
  – Anticholinergic drugs and BPH
  – Cholinesterase inhibitors/anticholinergic drugs and IBS-D/IBS-C

Fall Risk

• Increased
  – Antidepressants
    • Bupropion is an exception
    • (Depression itself increases fall risk)
  – Anti-psychotics
• Reduced
  – Anti-dementia drugs
  – Methylphenidate

Mechanisms of Drug-Associated Falling

• Lightheadedness
  – Syncope
  – α blockers and other antihypertensives
• Dizziness
  – Vertigo
• EPS
  – Parkinsonism
  – Restlessness
• Sedation/inattention
[Depression increases the risk of falling]

Geriatric Depression Remains Problematic

• Slower to respond
• Response more brittle

Antidepressants

• Selective Serotonin Reuptake Inhibitors
• Serotonin Norepinephrine Reuptake Inhibitors
• Mirtazapine
• Bupropion
• Vilazodone
• Vortioxetine
• Nefazodone
• Tricyclic antidepressants
• Monoamine oxidase inhibitors
• Methylphenidate

SSRI Antidepressants

• Citalopram, escitalopram
  – Well studied in elderly
  – Few interactions
  – Concerns about QT prolongation?
• Sertraline
  – Mild dopamine agonist actions
• Paroxetine
  – Moderately anticholinergic
• Fluoxetine
  – Ultra-long half life
  – Multiple interactions
SSRI Side Effects

- GI – N/V/D
- Insomnia
- Anorexia or weight gain
- EPS – Tremor – akathisia
- Agitation
- Bradycardia
- SIADH
- Falls
- Bleeding – Epistaxis, GI bleeding most common, intracranial rare
- Loss of bone mineral density

Rule of Thumb No. 8: Avoid Prescribing Cascades
- Anti-Parkinson agents for SSRI-induced Parkinsonian tremor

SNRI Antidepressants

- Venlafaxine
  - 5-HT > NE
    - Safe with tamoxifen
- Duloxetine
  - Balanced reuptake inhibition
- Desvenlafaxine

SNRI Side Effects

- UGI
- Diaphoresis
- Headache
- Insomnia
- HTN – 15% venlafaxine
- “Activating”

Define “Activating”

- Anxiety
- Restlessness
  - Akathisia?
- Hyperactivity
- Mania/hypomania
- Over stimulated
- Insomnia
- Relief of psychomotor retardation

Mirtazapine

- Noradrenergic and specific serotonin Antidepressant (NaSSA)
  - Faster onset of action
  - Antagonizes α-2 auto and hetero receptors and blocks 5-HT-2 and 5-HT-3 receptors
    • 5-HT-1a stimulation = therapeutic
    • 5-HT-3 blockade
      - Antiemetic effects
      - Side effects
        • Moderately antihistaminic
Bupropion

- Mechanism?
  - Norepinephrine & dopamine reuptake inhibition
  - Psychostimulant and weak dopamine agonist actions
- Safety advantages
  - Free of sexual, CV, sedating, anticholinergic effects
  - Weight neutral or weight loss
- Side effects
  - Jitteriness
  - GI

Newer Antidepressants

- Vilazodone (Viibryd)
  - SSRI
  - SHT1A partial agonist
    - Same MOA as buspirone
- Vortioxetine (Trintellix)
  - SSRI
  - SHT1A partial agonist
  - SHT7 antagonist
    - Same as mirtazapine

Tricyclic Antidepressants

- More effective in severe depression
  - Inflammation predicts
    - High CRP: NOR > ESC
    - Low CRP: ESC > NOR
  - Balance of serotonin vs. norepinephrine reuptake inhibition varies

Tricyclic Antidepressants

- More Toxic
  - Negative inotropic and chronotropic effects
  - Variably alpha blocking, antihistaminic, anticholinergic
- Nortriptyline
  - Least orthostatic
  - Therapeutic window
    - 80-120 (v 50-150)

Cardiac Patients:

- Contraindications
  - Absolute
    - Post MI
      - CAST study
        - TCAs are type one ANTIARRHYTHMICS
  - Relative
    - Rate-dependent cardiac ischemia
    - CHF
    - Orthostatic hypotension

Cardiac Patients and TCAs
Don’t Forget MAOIs

- MAO levels increase with aging, especially in Alzheimer’s disease
- Challenging to use
  - “cheese effect” requires special diet
  - Many side effects
    - Hypotension
    - Weight gain

Antidepressant Response Latency: How Long Do You Wait?

- Response rate is higher at 12 weeks than at 8 weeks
- At 4 weeks <30% response \(\rightarrow\) 80% chance of not achieving remission
- At 4 weeks >45% response \(\rightarrow\) 80% of remission at 12 weeks.

Definition of TRD

- 2 trials of SSRIs or other antidepressants
  - 12 weeks each at therapeutic dose

Treatment Refractory Depression

- Predictors
  - Anxiety
  - Executive dysfunction
  - T2 weighted white matter hyperintensities
  - Vascular depression

Help is Available

DHMC - Healthy Aging Brain Care Clinic

New Hampshire Hospital Geriatric Psychiatry Consultation Program

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