Disclosures

• Dr. Nguyen and Dr. Zdanys have no conflicts of interest to disclose.
• Non-FDA approved indications will be discussed.
Outline

• Epidemiology of late-life depression
• Forms of depression in older adults
• Suicide risk in the elderly
• Relationship of depression and dementia
• Identifying depression vs. dementia
• Treatment approaches
Late-Life Depression (LLD)

- “Depression” may fall into one of many categories
- Symptoms may vary even within a single diagnostic category
- Biological, Psychological, and Social components
Biological Factors

- Female Gender
- Neurotransmitter Dysfunction
  - serotonergic neurotransmission
- Endocrine Changes
  - Sustained increases in cortisol associated with chronic stress
  - Lower testosterone
- Genetics
  - Multi-factorial, inconclusive
  - Twin studies more robust in earlier life
- Vascular Changes
- Medical Illness
- Co-morbid psychiatric disorders
Psychological and Social Factors

- Psychological
  - Personality attributes / coping skills
  - Cognitive distortions

- Social
  - Stressful life events / loss
  - Chronic stress
  - Low socioeconomic status
Epidemiology

• Community survey of 1300 adults > age 60
  – 27% reported depressive symptoms
  – 19% mild dysphoria
  – 4% symptomatic depression
  – 0.8% major depressive episode
  – 1.2% mixed depression / anxiety
Epidemiology

– Major depression prevalence ~1%-3%
– Prevalence major depression higher in long-term care facilities ~6-14.4%
– Anxiety disorders ≥ depression, ~5.5%
– For both depression and anxiety, prevalence is higher in females
– Prevalence of symptoms is much higher than prevalence of disorders
Types of LLD

- Major Depressive Disorder
- Grief
- Bipolar Disorder
- Psychotic Depression
- Dysthymia
- Adjustment Disorder with Depressed Mood
- Depression Associated with Medical Illness
- Dementia-related
Major Depressive Disorder (MDD)

– 5+ of the following:
  • Depressed mood—either subjective or observed by others
  • Markedly diminished interests / pleasure
  • Change in more than 5% body weight in a month or change in appetite
  • Insomnia or hypersomnia
  • Psychomotor agitation or retardation
  • Fatigue / loss of energy
  • Feelings of worthlessness / inappropriate guilt
  • Poor concentration / indecisiveness
SIGECAPS

- Sleep
- Interests
- Guilt
- Energy
- Concentration
- Appetite
- Psychomotor
- Suicidal thoughts
Depression vs. Grief

• DEPRESSION
  – Persistent depressed mood
  – Inability to anticipate pleasure / happiness
  – Pervasive unhappiness
  – Self-critical, guilty feelings, pessimistic
  – Worthlessness
  – Suicidal thoughts

• GRIEF
  – Predominant emptiness / loss
  – Decreases in intensity days to weeks
  – Occurs in waves
  – May experience positive emotions / humor
  – Self-esteem preserved
  – Morbid thoughts about “joining” deceased
Psychotic Depression

• Delusions
  – Incurable illness, focus on abdomen
  – Persecution
• Guilt
  – Trivial episode from past
• Worthlessness
• Psychomotor retardation
• Increased suicidal ideation
• May stop eating
Dysthymia

- Also called “Persistent Depressive Disorder”
- Unremitting depressive symptoms
  - 2+ symptoms
  - More days than not
  - At least 2 years
  - Never more than 2 months without symptoms
- Associated with psychosocial stressors
- Can co-exist with major depressive disorder
Adjustment Disorder

• Maladaptive reaction to an identifiable stressor
  – Family / relationship stress
  – Loss of social role
  – Change in housing
• Results in impairment of functioning (social, occupational)
• In addition to depressed mood, may have:
  – Anxiety
  – Mixed Anxiety / Depressed Mood
  – Mixed Disturbance of Emotions / Conduct
Bipolar Disorder

• Also called “manic-depressive disorder”
• May start in childhood, adolescence, early adulthood, or later adulthood
• Characterized by major swings in highs and lows
Bipolar Disorder

• Mania:
  – Grandiosity / increased self esteem
  – Decreased need for sleep
  – Flight of Ideas
  – Talkativeness
  – Psychomotor Agitation
  – Distractability
  – Spending sprees
Depression Associated with Medical Illness

• Depressive disorders associated with:
  – Cancer
  – Cardiovascular disease
  – Stroke
  – Parkinson’s disease

• Physiological effects in brain
• Psychological reaction to disability
• Associated life changes
Depression in Cancer

- Not all cancer patients get depressed
- “Desire for hastened death” more common in depressed / hopeless cancer patients (Breitbart et al. 2000)
- Depression in cancer known to increase mortality (Brown et al. 2003)
Depression in Heart Disease

• Cardiovascular mortality is increased in depressed patients (Glassman and Shapiro 1998)

• Myocardial Infarction (Schleifer et al. 1989)
  – 45% patients met dx criteria for major or minor depression within 10 days of MI, 18% MDD
  – 3-4 months post-MI 33% still met criteria for depression including 77% of those who previously met criteria for MDD
Depression in Stroke

- MDD up to 25%, minor depression another 30%
- Peak 3-6 months post-stroke, may persist several years
- May have had pre-existing vascular depression
- More common in women
Depression in Parkinson’s

- Up to 60% PD patients have depression
- Associated with decreased time to medication for motor symptoms
- Treating depressive symptoms may improve motor symptoms
Suicide Risk

• Suicide rate among all age groups is highest for older men (50/100k vs. 22/100k younger men)
  – Caucasian
  – >75 y.o.
Suicide Risk

• Older women worldwide are >3x as likely to die from suicide than young women (15.8/100k vs. 4.9/100k)
  – In US, 30% more likely
Depression vs. Dementia

• Can be difficult to distinguish!
Depression-Related Dementia

• Someone who is very depressed “looks” demented
  – Slow
  – Confused
  – Disoriented
  – Apathetic
  – Non-communicative
Depression-Related Dementia

• Theoretically, treating depression improves cognitive symptoms
• Even if improved, 40% will develop dementia within 3 years
• Is depression an early sign of dementia?
Work-Up

- History
- Screening
- Physical Examination
- Laboratory tests
- Polysomnography
- MRI
History

- Duration of current episode
- Current symptoms / severity
- Impact on functioning
- History of previous episodes
- Substance abuse
- Response to previous treatments
- Family history
- Recent stressors
- Collateral from family / caregiver
Functioning

• Activities of Daily Living
  – Ambulation, Eating, Dressing, Toileting, Bathing

• Instrumental Activities of Daily Living
  – Telephone, Medications, Finances, Driving, Shopping, Cooking, Housework
## Screening

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you basically satisfied with your life?</td>
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<tr>
<td>Have you dropped many of your activities or interests?</td>
</tr>
<tr>
<td>Do you feel that your life is empty?</td>
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<tr>
<td>Do you often get bored?</td>
</tr>
<tr>
<td>Are you in good spirits most of the time?</td>
</tr>
<tr>
<td>Are you afraid that something bad is going to happen to you?</td>
</tr>
<tr>
<td>Do you feel happy most of the time?</td>
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<tr>
<td>Do you feel helpless?</td>
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<tr>
<td>Do you prefer to stay at home, rather than go out and do things?</td>
</tr>
<tr>
<td>Do you feel that you have more problems with memory than most?</td>
</tr>
<tr>
<td>Do you think it is wonderful to be alive now?</td>
</tr>
<tr>
<td>Do you feel pretty worthless the way you are now?</td>
</tr>
<tr>
<td>Do you feel full of energy?</td>
</tr>
<tr>
<td>Do you feel that your situation is hopeless?</td>
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<tr>
<td>Do you think that most people are better off than you are?</td>
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</tr>
<tr>
<td>1. Little interest or pleasure in doing things</td>
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<tr>
<td>2. Feeling down, depressed, or hopeless</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
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<tr>
<td>4. Feeling tired or having little energy</td>
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<tr>
<td>5. Poor appetite or overeating</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
</tr>
</tbody>
</table>

For office coding: __0__ + __1__ + __2__ + __3__

=Total Score: ___
Suicide Risk Assessment

• Do you ever think about dying?
• Do you ever think about killing yourself, or wish you were dead?
• If yes:
  – When you think about dying, do you have a plan about how to do it?
  – Do you have the means to carry out your plan?
  – Is there a history of previous suicide attempts? How many?
Physical Exam

- Weight loss
- Pulmonary (sleep study?)
- Cardiac
- Neurologic
  - Laterality (vascular)
  - Rigidity or gait changes (Parkinson’s)
Lab Work

• Thyroid panel
• Complete blood count
• B12
• Folate
• Consider D3
For Possible Dementia…

- MRI of the brain
- Neuropsychological testing referral
Take-Home Point

• If you are thinking depression, look for dementia.

• If you are thinking dementia, look for depression.
References

Alexopoulos et al. Biol Psychiatry 1993;34:141-145
Arve et al: Aging 1999;11:90-95
Steffens et al. Arch Gen Psychiatry. 2006;63(2):130-138
What is “Successful” Aging?

• “...key ideas such as life satisfaction, longevity, freedom from disability, mastery and growth, active engagement with life, and independence.”

• Age related life stressors
  – Impending and/or chronic illness
  – Social losses
  – “lack of person-environment fit”

Later Life Challenges

**PERSONAL:** retirement and financial issues, grandparenthood, bereavement and widowhood, loss of loved ones, caregiver issues

**CLINICAL:** chronic illness, progressive cognitive and physical decline, end of life care

**SYSTEMS:** fearful, pessimistic view of aging stereotyped as old fashioned, rigid, boring, demented, burdensome; institutionalized view of aging
Goals

[Image of a Venn diagram with three overlapping circles labeled: Minimize risk of disease and disability, Continue engagement with life, Maintain physical and cognitive function.]

http://rogenera.com/2015/03/15/what-is-successful-aging/
Non-Pharmacological Approaches

• Senior day programs
  – Structured group activities

• Skills training
  – Social skills
  – Occupational skills
  – Vocational skills
  – Stress management skills
  – Life skills
  – All of above: psychosocial rehabilitation
Lifestyle Changes

• Moderate intensity physical activity
• Improving nutrition
• Increasing engagement in pleasurable activities and social interactions
Evidence-Based Psychotherapies

- Cognitive behavioral therapy (CBT)
- Interpersonal therapy (IPT)
  - Grief
  - Role transition
  - Interpersonal deficits
  - Interpersonal conflict
- Problem solving therapy (PST)
  - Insufficient problem solving skill
  - Abandonment of skill
  - Perceived complexity of problems

Bright Light Therapy

- Indications
  - Seasonal affective disorder
  - Aberrant sleep/wake cycles
- 10,000 lux at 18 inches away
- 20-30 min/day, preferably AM
Pharmacology in Later Life

• Pharmacokinetics: action of the body on the drug
• Pharmacodynamics: mechanism of action
• Polypharmacy and drug-drug interactions
• Safety and adherence
• Less than 1/3 of package inserts have specific dosing recs for elderly patients
Geriatric Pharmacokinetics

1. **Absorption:** gastric pH can increase, gastric and colonic motility can decrease
2. **Distribution:** higher body fat by 50-100%, less total body water by 10-15%, lower albumin
3. **Metabolism in liver:** lower blood flow (40%) leads to lower clearance and decline occurs in certain metabolic enzymes
4. **Elimination:** renal function decreased
Treatment: Consensus Guidelines

- Nonpsychotic MDD $\rightarrow$ SSRI/SNRI + psychotherapy
- Psychotic MDD $\rightarrow$ (SSRI/SNRI + antipsychotic) or ECT
- MDD + medical d/o $\rightarrow$ treat both from outset
- Dysthymia $\rightarrow$ SSRI + psychotherapy
- MDD with insomnia $\rightarrow$ sedating antidepressant (trazodone or mirtazapine) or add zolpidem or zaleplon

Choosing a Medication

- Safety profile (e.g., orthostasis, overdose)
- Pharmacodynamic profile (e.g., renal, hepatic effects)
- Drug-drug interaction profile
- Pharmacokinetic profile (e.g., dosing schedule, evenness of plasma levels)
- Tolerability (e.g., anticholinergic effects)
- Beneficial added effects (e.g., sedation)
- Previous response
Other Considerations

• Depression with:
  – Insomnia
  – Poor appetite
  – Pain
  – Hypertension
  – Heart disease
  – Renal disease
  – Liver disease

  – Diabetes Mellitus
  – Alzheimer’s Disease
  – Cerebrovascular disease
Pharmacotherapy Approach

• All antidepressants equally effective
• Adequate trial: 8 weeks at therapeutic dose
• Dosing: start ½ adult dose
• Response: 50-65% to first trial / 30% to placebo
• Remission: 30-40% to first trial / 15% to placebo
Predictors of Delayed or Poor Treatment Response

- Older age
- Longer duration of episode
- Presence of cognitive impairment
  - “Impaired response inhibition”
  - Longer symptom duration and more chronic episodes
- Higher anxiety levels
SSRIs

• Still 1\textsuperscript{st} choice in LLD
• Several well-tested, generic, well-tolerated, with limited DDI, appropriate elimination half-lives:
  – Sertraline
  – Citalopram (note FDA dosage warning)
  – Escitalopram
SSRIs Geriatric Safety

• May reduce platelet aggregation
• Fewer myocardial infarctions than non-SSRI treated patients
• Fluoxetine and sertraline
  – benign in ischemic heart disease (IHD)
FDA warning on citalopram, 2011

- 20 mg/day for patients > 60 years of age
- Dose-dependent QT interval prolongation
  - Torsades de Pointes
  - Ventricular tachycardia
  - Sudden death
SNRIs

- FDA approved, but not first line:
  - Desvenlafaxine (Pristiq)
  - Duloxetine (Cymbalta): neuropathic pain and fibromyalgia
  - Venlafaxine (Effexor): panic disorder and social anxiety
  - Caution with renal or liver disease, alcohol use
SNRI Adverse Effects

- Hypertension or orthostatic hypotension
- EKG changes and arrhythmias
- Anxiety
- Insomnia
- Adrenergic SE: dry mouth, constipation, urinary retention, IOP, transient agitation
Other Antidepressants

- **Buproprion (Wellbutrin)**
  - Less sedation and sexual SE
  - Less helpful with anxiety/psychosis
  - Special contraindications: seizure, case reports for psychosis

- **Mirtazapine (Remeron)**
  - More anxiolytic, less sexual SE, less nausea
  - More weight gain and sedation
  - Exacerbates REM sleep behavior in PD
  - Associated with small risk for neutropenia, agranulocytosis, minimal interaction with warfarin
Newer Antidepressants

- Viibryd (vilazodone)
  - SSRI and partial agonist at 5HT1a
- Brintellix (vortioxetine)
  - SSRI, agonist 5HT1a, partial agonist 5HT1b, antagonist 5HT3a/5HT7
- Fetzima (levomilnacipran)
  - SNRI
Switching Medications

- SSRI non-responsiveness, consider SWITCH to:
  - Venlafaxine: anxiety prominent
  - Bupropion: apathy prominent
  - Mirtazapine: insomnia/anxiety prominent
  - Nortriptyline: melancholic depression
Duration of Treatment

- Single severe episode of MDD
  - Continue AD at least 1 year
- Two episodes of MDD
  - Continue AD for 1-3 years
- Three or more episodes of MDD
  - Continue AD for longer than 3 years

Source: Adapted from Kupfer, 1989.
TCAs

• Secondary TCAs: nortriptyline, desipramine
  – preferred, selective for NE, less SE
• Tertiary TCAs: imipramine, amitriptyline, clomipramine, doxepine
• Obtain EKG before and after therapeutic level achieved
• Drawbacks in LLD:
  – Anticholinergic effects
  – Postural hypotension
  – Cardiac effects
    • Type 1 antiarrhythmic
    • 2:1 AV block with BBB
MAOIs

- MAOIs – efficacious but rarely used unless failed SSRI, SNRI, TCA
  - Significant hypotension
  - Life-threatening hypertensive or serotonergic crisis
  - Avoid tyramine rich foods
  - DDI with sympathomimetic drugs
- Phenelzine preferred to tranylcypromine
- Selegeline transdermal patch: avoids GI tract and reduces risk of hypertensive crisis
Augmentation Strategies

- Stimulants: methylphenidate
- Lithium
- T3
- Antipsychotics: aripiprazole, quetiapine
- Combination therapy
  - Bupropion, mirtazapine, stimulants
Electroconvulsive Therapy (ECT)

- Elderly have better response to ECT than younger patients
- In the old-old, may be more efficacious and cause less s/e than medications
- 86% response in depressed patients with dementia
- Indications: moderate-severe depression, psychotic features, intolerance to medications, fast response needed, etc

Tew 1999, Manly 2000, APA Practice Guidelines
Other Therapies

- Repetitive Transcranial Magnetic Stimulation (rTMS)
  - More efficacious than sham treatment in older adults, age >50, with vascular depression (n=92)

- Bibliotherapy > waitlist and education for mild-moderate depression
  - Gains maintained at 2 years

*Jorge 2008, Scotin 1989*
Treatment Resistant Depression: ABCD Review

- **Adequacy of prior treatment**
  - Duration and dosage

- **Behavioral/environmental factors**
  - Personality disorders, psychosocial stressors

- **Compliance/adherence**
  - Treatment intolerance, psychoeducation

- **Diagnosis**
  - Missed medical or psychiatric diagnosis, adverse SE
Depression with Dementia

• MDD confounded by deficits in verbal expression and cognitive symptoms

• AD + MDD
  – Presence of 3+ symptoms, not including difficulty concentrating, and nonsomatic symptoms
  – Irritability and social withdrawal

• VaD + MDD
  – More vegetative symptoms
  – Fatigue, muscular weakness, weight loss

Treatment of MDD + Dementia

- Assess severity and “masked” depression
- Consider psychosocial interventions
- Choose medication and target symptoms
- Monitor improvement and adverse effects
- Modify approach based on outcome
- Consider discontinuation
Late Life Delusional Depression

- Expert consensus: antipsychotic + antidepressant
- ECT produces more rapid response than meds
- Compared to younger adults, RCTs guiding treatment choice in LLD with psychotic features much more limited

Medication-Induced Depression

- Acyclovir
- Anabolic steroids
- **ACE inhibitors**
- Anticonvulsants
- Baclofen
- Barbiturates
- Benzodiazepines
- **B-blockers**
- Bromocriptine
- **Calcium channel blockers**
- Ciprofloxacin
- Clonidine

- Corticosteroids
- Digitalis
- Disulfiram
- Estrogen
- Guanethidine
- **H2 receptor blockers**
- Interferon alpha
- Interleukin-2
- Isotretinoin
- **Levodopa**
- Methyldopa
- Metoclopramide

- Metrizamide
- Metronidazole
- **NSAIDS** (indomethacin)
- Opioids
- Pergolide
- Reserpine
- **Sulfonamides**
- Thiazide diuretics
- Topiramate
- Vinblastine
- Vincristine

Ko et al, Jama, 2002
Take Home Points

• Age-related physiological changes and DDI are important considerations for pharmacological interventions
• Depression in late life is treatable, even among older adults with dementia
• Consider psychotherapies in treatment of LLD – strong evidence but not as frequently used!