

# **Depression in Later Life: Epidemiology, Assessment, and Treatment**

**Gary W. Small, M.D.**

**Parlow-Solomon Professor of Aging**

**UCLA School of Medicine**

**Professor of Psychiatry & Biobehavioral Sciences**

**Director, UCLA Center on Aging**

**James M. Ellison, M.D., MPH**

**Clinical Director, Geriatric Psychiatry Program**

**McLean Hospital**

**Associate Professor of Psychiatry, Harvard Medical School**

**Self-Assessment Question 1:**  
**Which of the following statements is most correct?**

- A. Major depressive disorder is less prevalent in older than in younger adults.
- B. Major depressive disorder in late life is associated with increased morbidity and mortality from medical illnesses and suicide.
- C. Major depression is not a normal concomitant of ageing.
- D. Numerous published randomized controlled treatment trials are available to help guide the treatment choices for older adults with major depressive disorder.
- E. All of the above are true

**Self-Assessment Question 2:**  
**Which of the following statements is most correct?**

- A. White matter hyperintensities are the most replicated neuroimaging abnormality in late life depression.
- B. White matter hyperintensities and late-life depression have a direct cause-effect relationship.
- C. White matter hyperintensities represent deposition of beta amyloid plaques in the prefrontal white matter.
- D. The most common location of white matter hyper intensities in vascular depression is occipital.
- E. None of the above

### **Self-Assessment Question 3:**

**Which of the following forms of psychotherapy has/have been empirically validated for the treatment of depression in older adults?**

- A. Cognitive Behavior Therapy
- B. Problem Solving Therapy
- C. Interpersonal Therapy
- D. All of the above
- E. None of the above.

**Self-Assessment Question 4:**  
**Which of the following statements is most correct?**

- A. Efficacy of serotonin reuptake inhibitors in treating late life depression is similar to that of TCAs, though TCA side effects may be less tolerable.
- B. For nonpsychotic late life depression, the combination of psychotherapy and medication is recommended.
- C. Older adults are more vulnerable than younger adults to anticholinergic side effects of antidepressants.
- D. Older adults typically take more concurrently prescribed medications than younger adults, necessitating careful attention to drug/drug interaction possibilities when an antidepressant is prescribed.
- E. All of the above

**Self-Assessment Question 5:**  
**Which of the following statements is not correct?**

- A. ECT is usually less efficacious than antidepressants in treating late life depression with psychotic features.
- B. Intracranial mass lesion, recent CVA, or recent MI can complicate the safe administration of ECT.
- C. Informing patient and family about potential memory disturbance associated with ECT will help them understand and tolerate this usually transient aspect of treatment.
- D. Demented patients may experience intolerable cognitive worsening during the course of a series of ECT treatments.
- E. Unilateral nondominant ECT is associated with fewer cognitive side effects.

# Major Teaching Points

- ❖ Depression in later life is an important, under-recognized illness with severe consequences in function and mortality
- ❖ Psychotherapy, medication, and ECT have each been shown to be effective treatments and enough information is available to individualize treatment approach to a specific patient's needs

# Outline

- 1. Prevalence and significance of depressive symptoms and depressive syndromes in later life**
- 2. Characteristic presentations and assessment process**
- 3. Treatment approaches**
  - ❖ Psychotherapy**
  - ❖ Medications**
  - ❖ ECT**
- 4. Treatment resistance**
- 5. Maintenance treatment issues**

# The High Prevalence of Depressive Symptoms in Later Life

- ❖ Minor depressive disorders are more common than major depressive disorders among older adults
  - ❖ Minor depression ~ 8-10%
  - ❖ Major depression ~ 3-4% <sup>1</sup>
- ❖ Depression is common in primary care settings <sup>2</sup>
  - ❖ Depression or depressive sx in 17% to 37%
  - ❖ 35% to 50% reporting sx were not diagnosed by PCP
- ❖ Depression is highly prevalent and undertreated in LTC settings <sup>3</sup>

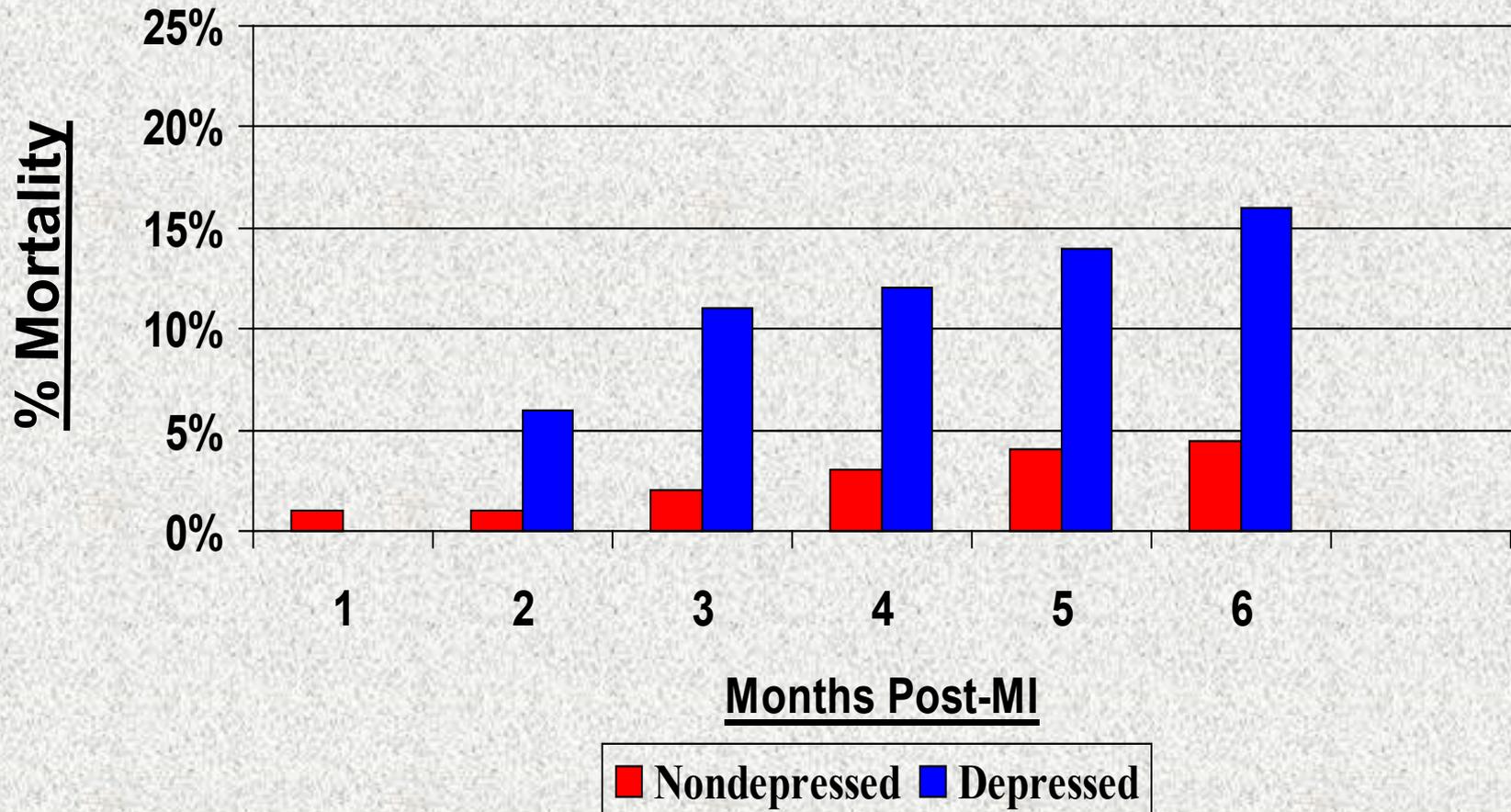


# Failure to Treat Depression Promotes Adverse Outcomes

- ❖ Functional Decline / Increased disability<sup>1</sup>
- ❖ Increased use of non-mental health services<sup>1</sup>
- ❖ Increased mortality rate
  - ❖ Overall<sup>2</sup>: >4x rate of death over 15 months
  - ❖ Cardiac<sup>3</sup>: 4x rate of death within 4 mo after MI
  - ❖ Suicide<sup>4</sup>: 13% of population and 18% of suicides

1. Beekman et al. 1997; 2. Bruce and Leaf 1989; 3. Romanelli et al. 2000;  
4. <http://www.cdc.gov/ncipc/wisqars/default.htm>

# Cumulative Mortality for Depressed and Non-depressed Patients 6 Months After MI



# **Suicide Rate in Late Life Exceeds That of Other Age Groups**

- ❖ **9th leading cause of death in US population**
  - ❖ **12/100,000**
- ❖ **Among the elderly:**
  - ❖ **19.1/100,000 over age 65**
  - ❖ **22.9/100,000 ages 75-84**
- ❖ **Depression is the most frequent mental disorder preceding suicide**
- ❖ **Physical illness is the most frequent stressor in suicides over 80 years of age**

# **Major Depressive Episode (DSM IV TR)**

- ❖ **Depressed mood or anhedonia of at least 2 weeks with at least 4 of the following:**
  - ❖ **↓ interest or pleasure most of the time**
  - ❖ **Significant change in weight when not dieting**
  - ❖ **Insomnia or hypersomnia**
  - ❖ **Psychomotor agitation or retardation**
  - ❖ **Fatigue or loss of energy**
  - ❖ **Feelings of worthlessness, inappropriate guilt**
  - ❖ **↓ concentration or thinking, indecisiveness**
  - ❖ **Recurrent thoughts of death or suicide**
- ❖ **No medical/substance etiology/mixed episode/other psych**
- ❖ **Significant distress or impairment**
- ❖ **Not uncomplicated bereavement**

# Geriatric Depression: Can Look Different from Adult Depression

Symptom Domain	Adult Presentation	Geriatric Presentation
Mood	Depressed Anhedonic Suicidal thoughts	Weary, Hopeless, Angry Anxious Thoughts of death
Somatic	↓↑ Sleep ↓↑ Appetite ↓↑ Psychomotor ↓↑ Increased pain	↑ Pain, and Somatic symptoms overlap with effects of medications, comorbid disease
Cognitive	↓ Concentration Indecisiveness	↓ Selective attention ↓ Working memory/retrieval ↓ New learning ↓ Processing speed ↓ Executive function

Gallo et al. 1997; Geiselman and Bauer 2000; Devanand 1994;  
Mazure et al. 2002; Lezac 1994; Lavretsky and Kumar 2002

# **Evaluation of Late Life Mood/Anxiety**

## **Disorders:**

### **1. Psychiatric History**

- ❖ Informant may shed light
- ❖ Atypical presentation is typical
- ❖ Psychosocial factors can mislead
- ❖ Delusions are more common
- ❖ Medical comorbidity is relevant
- ❖ That includes substance abuse
- ❖ Treatment adherence may be poor



# Evaluation of Late Life Mood/Anxiety Disorders:

## 2. Consider Use of Objective Depression Scale

### ❖ Why?

- ❖ May facilitate symptom reporting
- ❖ Estimates severity
- ❖ Provides benchmark for treatment evaluation

### ❖ What?

- ❖ Geriatric Depression Scale
- ❖ Cornell Scale for Depression in Dementia

# GDS 15

1. Are you basically satisfied with your life ?
2. Have you dropped many of your activities and interests ?
3. Do you feel that your life is empty ?
4. Do you often get bored ?
5. Are you in good spirits most of the time ?
6. Are you afraid that something bad is going to happen to you ?
7. Do you feel happy most of the time ?
8. Do you often feel helpless ?

9. Do you prefer to stay at home, rather than going out and doing new things ?
10. Do you feel you have more problems with memory than most?
11. Do you think it is wonderful to be alive now ?
12. Do you feel pretty worthless the way you are now ?
13. Do you feel full of energy ?
14. Do you feel that your situation is hopeless ?
15. Do you think that most people are better off than you are ?

GDS is in the Public Domain, can be freely reproduced and used. Score 1 pt for each "Yes" on 2,3,4,6,8,9,10,12,14,15 or "No" on 1,5,7,11,13. A score of 6 or higher suggests need for definitive diagnostic evaluation. (<http://www.stanford.edu/~yesavage/GDS.html>)

# Cornell Scale for Depression in Dementia

## **Scoring System**

A = unable to evaluate 0 = absent 1 = mild or intermittent 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview.

No score should be given in symptoms result from physical disability or illness.

## **A. Mood-Related Signs**

- |   |   |   |   |   |
|---|---|---|---|---|
| 1. Anxiety: anxious expression, ruminations, worrying | a | 0 | 1 | 2 |
| 2. Sadness: sad expression, sad voice, tearfulness    | a | 0 | 1 | 2 |
| 3. Lack of reactivity to pleasant events              | a | 0 | 1 | 2 |
| 4. Irritability: easily annoyed, short-tempered       | a | 0 | 1 | 2 |

## **B. Behavioral Disturbance**

- |   |   |   |   |   |
|---|---|---|---|---|
| 5. Agitation: restlessness, handwringing, hairpulling         | a | 0 | 1 | 2 |
| 6. Retardation: slow movement, slow speech, slow reactions    | a | 0 | 1 | 2 |
| 7. Multiple physical complaints (score 0 if GI symptoms only) | a | 0 | 1 | 2 |
| 8. Loss of interest: less involved in usual activities        | a | 0 | 1 | 2 |

(score only if change occurred acutely, i.e. in less than 1 month)

# Cornell Scale for Depression in Dementia (2)

## **C. Physical Signs**

- |  |         |
|--|---------|
| 9. Appetite loss: eating less than usual   | a 0 1 2 |
| 10. Weight loss (score 2 if greater than 5 lb. in 1 month)   | a 0 1 2 |
| 11. Lack of energy: fatigues easily, unable to sustain activities<br>(score only if change occurred acutely, i.e., in less than 1 month) | a 0 1 2 |

## **D. Cyclic Functions**

- |   |         |
|---|---------|
| 12. Diurnal variation of mood: symptoms worse in the morning        | a 0 1 2 |
| 13. Difficulty falling asleep: later than usual for this individual | a 0 1 2 |
| 14. Multiple awakenings during sleep                                | a 0 1 2 |
| 15. Early morning awakening: earlier than usual for this individual | a 0 1 2 |

## **E. Ideational Disturbance**

- |   |         |
|---|---------|
| 16. Suicide: feels life is not worth living, has suicidal wishes,<br>or makes suicide attempt | a 0 1 2 |
| 17. Poor self esteem: self-blame, self-depreciation, feelings of failure                      | a 0 1 2 |
| 18. Pessimism: anticipation of the worst  | a 0 1 2 |
| 19. Mood congruent delusions: delusions of poverty, illness, or loss                          | a 0 1 2 |

# Evaluation of Late Life Mood/Anxiety Disorders:

## 3. Include Cognitive Screen with MSE

### ❖ Why?

- ❖ Depression as prodrome
- ❖ Comorbid cognitive symptoms in depression
- ❖ Depression and excess functional impairment

### ❖ What?

- ❖ Mini-Mental Status Examination
  - ❖ Per-use fee and permission required<sup>1</sup>
- ❖ Montreal Cognitive Assessment (public domain)<sup>2</sup>

1. [http://www3.parinc.com/uploads/pdfs/MMSE\\_Copyright\\_PermReq.pdf](http://www3.parinc.com/uploads/pdfs/MMSE_Copyright_PermReq.pdf)

2. [www.mocatest.org](http://www.mocatest.org)

# **Psychiatric Differential** **Diagnosis**

- ❖ **Bereavement/Adjustment Disorder**
- ❖ **Bipolar Disorder**
- ❖ **Substance Abuse Disorders**
- ❖ **Anxiety Disorders**
- ❖ **Personality Disorder**
- ❖ **Schizophrenia**

# Organic Differential Diagnosis

- ❖ **Medication toxicities**
- ❖ **Cardiopulmonary disorders**
- ❖ **Neurological disorders**
- ❖ **Endocrine/Metabolic disorders**
- ❖ **Nutritional deficiencies**
- ❖ **Sleep disorders**
- ❖ **Infectious disorders**
- ❖ **Neoplasms**

# **Confusing Comorbidity:** **Depression in Demented Patients**

- ❖ **50% of patients with dementia or other neurological impairments are depressed**
  - ❖ **17-31% of Alzheimer's patients**
  - ❖ **High rates in Parkinson's and post-stroke**
- ❖ **Detection may require collateral informants**
- ❖ **Treatment is of potential value when mood symptoms are present.**

# Dementia Syndrome of Depression (DSD) vs. Alzheimer's Disease (AD)

	<b>DSD</b>	<b>AD</b>
<b>Symptom duration</b>	<b>Short</b>	<b>Long</b>
<b>Prior psychiatric history</b>	<b>Usual</b>	<b>Unusual</b>
<b>Patient complaint</b>	<b>Frequent</b>	<b>Variable</b>
<b>Behavior congruent with cognitive deficits</b>	<b>Unusual</b>	<b>Usual</b>
<b>Mood disorder</b>	<b>Autonomous</b>	<b>Reactive</b>
<b>Recognition memory</b>	<b>More intact</b>	<b>Impaired</b>
<b>Effort on tasks</b>	<b>Poor</b>	<b>Good</b>
<b>Prompting effect</b>	<b>Helpful</b>	<b>Less helpful</b>

Adapted from Kaszniak and Christenson, in Storandt and VandenBos, *Neuropsychological Assessment of Dementia and Depression in Older Adults: A Clinician's Guide*.

Washington, DC, American Psychological Association, 1994.

# Vascular Depression

## ❖ Observations:<sup>1</sup>

- ❖ High rate of depression with HT, DM, CAD
- ❖ High rate of depression following CVA
- ❖ Prevalence of silent CVA & white matter hyperintensities in late-onset depression
- ❖ Lower prevalence of family history for mood disorders in post-CVA depression



# Vascular Depression: Definition of Syndrome

## ❖ Defined by:

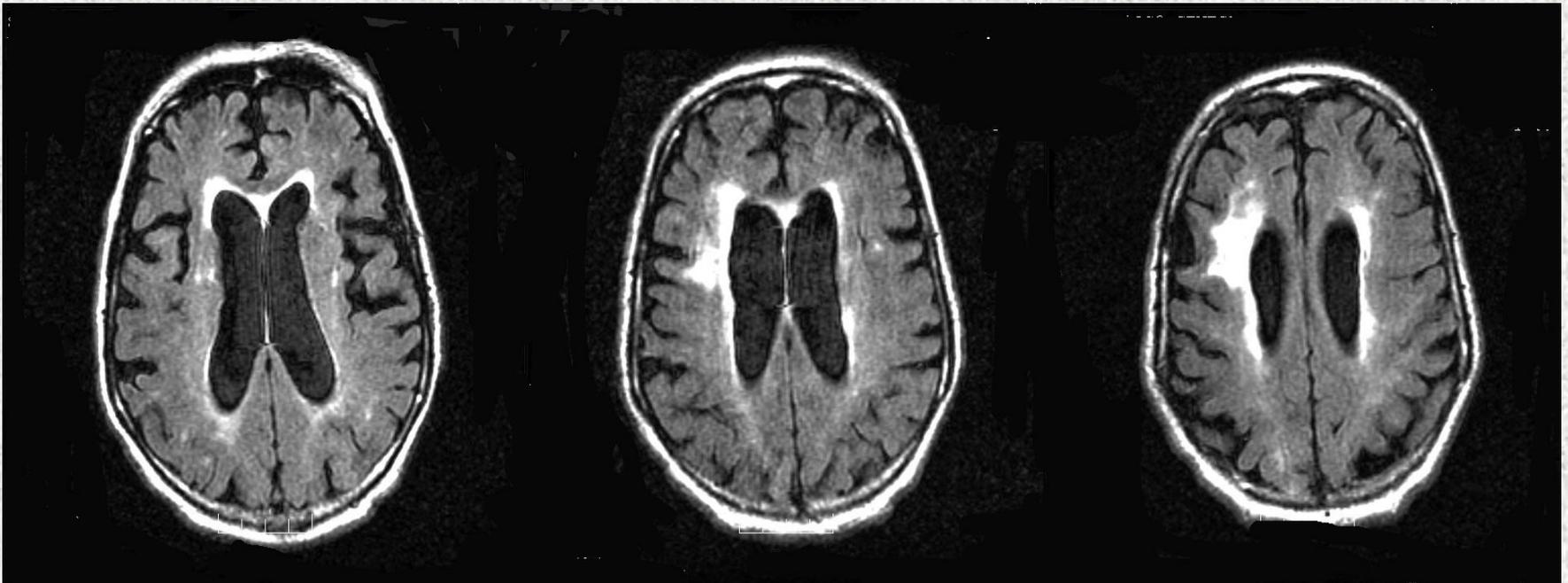
- ❖ First onset of depression at or after 60 years of age
- ❖ Presence of HT and/or TIA or surgery for vascular disease

## ❖ Associated with:

- ❖ reduced depressive ideation
- ❖ Increased psychomotor retardation
- ❖ Cognitive dysfunction
  - ❖ Impaired fluency/naming
  - ❖ Lack of insight
  - ❖ Executive dysfunction
- ❖ MRI findings: Left frontal and left putamen deep white matter hyperintensities<sup>2</sup>

1. Alexopoulos 1997;  
2. Greenwald et al. 1998

# T2 Hyperintensities on MRI



Courtesy of Martin Goldstein MD

# **Assessment of Late Life Depression:**

## **1. Psychiatric History**

- ❖ **Use of informant**
- ❖ **Atypical symptom presentation**
- ❖ **Psychosocial factors**
- ❖ **Medical factors**
- ❖ **Medications and treatment adherence**
- ❖ **Nutrition and deficiencies**
- ❖ **Use of additional substances**

# **Assessment of Late Life Depression:**

## **2. Medical History and Physical Examination**

- ❖ **Essential component of work up**
- ❖ **Cardiopulmonary history/examination**
- ❖ **Cerebrovascular history/examination**
- ❖ **Neurological examination**
- ❖ **Sleep history/assessment**

# **Assessment of Late Life Depression:**

## **3. Mental Status Examination**

- ❖ **Baseline cognitive assessment**
- ❖ **Appearance and self-care**
- ❖ **Variant presentations of mood**
  - ❖ **Withdrawal**
  - ❖ **Weariness**
  - ❖ **Comorbid anxiety**
- ❖ **Mental Content**
  - ❖ **Somatic preoccupations, Pain**
  - ❖ **Complaints re cognitive functioning**

# **Assessment of Late Life Depression:**

## **4. Use of Diagnostic Instruments**

- ❖ **Consider formal depression instrument**
  - ❖ **Hamilton Depression Rating Scale**
  - ❖ **Montgomery Asberg Depression Rating Scale**
  - ❖ **Geriatric Depression Scale**
  - ❖ **Minimum Data Set Depression Rating Scale**
  - ❖ **Cornell Scale for Depression in Dementia**
- ❖ **Include cognitive screening**
  - ❖ **MMSE**
  - ❖ **Functional assessments**
  - ❖ **Tests of executive function**

# Rating Scales: GDS

- ❖ Self report, 30 item<sup>1</sup>
- ❖ Short version (15 item), cutoff 5/15<sup>2</sup>
  - ❖ Sensitivity 92%
  - ❖ Specificity 81%
- ❖ Limited validity with MMSE less than 15<sup>3</sup>

1. Yesavage 1983; 2. Lyness et al. 1997; 3. McGivney et al. 1994

# GDS 15

1. Are you basically satisfied with your life ?
2. Have you dropped many of your activities and interests ?
3. Do you feel that your life is empty ?
4. Do you often get bored ?
5. Are you in good spirits most of the time ?
6. Are you afraid that something bad is going to happen to you ?
7. Do you feel happy most of the time ?
8. Do you often feel helpless ?
9. Do you prefer to stay at home, rather than going out and doing new things ?
10. Do you feel you have more problems with memory than most?
11. Do you think it is wonderful to be alive now ?
12. Do you feel pretty worthless the way you are now?
13. Do you feel full of energy ?
14. Do you feel that your situation is hopeless ?
15. Do you think that most people are better off than you are ?

# **Assessment of Late Life Depression:**

## **5. Laboratory Assessment**

### **❖ Hematology**

- ❖ WBC, differential**
- ❖ HGB/HCT, MCV**
- ❖ Platelets**

### **❖ Urine**

- ❖ Urinalysis**
- ❖ Culture and sensitivity**

### **❖ Chemistry**

- ❖ Lytes, BUN, Creatinine**
- ❖ Liver function tests**
- ❖ Thyroid function tests**
- ❖ ESR**
- ❖ B12 or methylmalonic acid**
- ❖ Folate or RBC folate**
- ❖ Testosterone level (males)**

# Assessment of Late Life Depression:

## 6. Ancillary Studies

- ❖ Neuropsychological Testing\*
  - ❖ Cognitive/memory testing\*
  - ❖ Assessment of executive functions\*
- ❖ Neuroimaging Studies\*
  - ❖ Structural (CT, MRI)\*
  - ❖ Functional (fMRI, SPECT, PET)\*

# Treatment

- ❖ Psychotherapy
  - ❖ Consensus recommendations
- ❖ Pharmacotherapy
  - ❖ Acute
  - ❖ Continuation
  - ❖ Maintenance

# Evidence-Based Psychotherapies for Older Adults

- ❖ Interpersonal psychotherapy (IPT)
- ❖ Cognitive behavior therapy (CBT)
- ❖ Problem-solving therapy (PST)
- ❖ Brief psychodynamic therapy

# Age-Related Factors Inhibiting Therapeutic Engagement

- Patient's own perceptions of aging:
  - Time as limited
  - Self as fixed and unchangeable (eg, "old dog . . .")
- Physical limitations
  - Hearing/vision loss
  - Ambulatory/mobility problems
  - Urinary urgency/incontinence
  - Physical discomfort
  - Transportation difficulties
- Cognitive limitations
  - Retention/recall difficulties
- Reimbursement

# **Antidepressant Treatment of Late Life Depression Is Evidence-Based**

- Over 70 Randomized Controlled Trials of pharmacotherapy of geriatric depression
- >25 comparisons of 1 AD to placebo, >50 comparisons of two active antidepressants to each other or to placebo
- Many trials use older antidepressants, optimal rather than typical populations and settings
- Efficacy supported, with limited EBM support for greater side-effect superiority of newer agents

# Some Marketed Antidepressants Used for Late Life Depression

## ❖ Tricyclics

- ✗ Nortriptyline (Pamelor, Aventyl)

## ❖ MAO Inhibitors

- ✗ Phenzelzine (Nardil)
- ✗ Tranylcypromine (Parnate)

## ❖ SSRIs

- ✗ Fluoxetine (Prozac)
- ✗ Sertraline (Zoloft)
- ✗ Paroxetine (Paxil)
- ✗ Fluvoxamine (Luvox)
- ✗ Citalopram (Celexa)
- ✗ Escitalopram (Lexapro)

## ❖ SNRIs

- ✗ Venlafaxine (Effexor)
- ✗ Duloxetine (Cymbalta)

## ❖ Others

- ✗ Bupropion (Wellbutrin)
- ✗ Mirtazapine (Remeron)
- ✗ Nefazodone (Serzone)

# **Strategies for Drug Treatment**

- ❖ **Select initial antidepressant on basis of efficacy, cost, side effect profile, concurrent medical illness, and drug/drug interactions**
- ❖ **Start low, go slow, and don't undertreat**
- ❖ **Monitor side effects actively**
- ❖ **Avoid non-essential polypharmacy**
- ❖ **Adjust one medication at a time**

# **Choosing An Antidepressant: Efficacy Is Not The Guide**

- ❖ **Clinical trials indicate generally similar efficacy among all the antidepressants that are FDA-indicated for depression**
- ❖ **Discontinuation rate is somewhat lower with SSRIs based on side effect profile differences between SSRIs and TCAs**
- ❖ **Controversy remains whether heterocyclics are more effective for melancholia (despite side effects)**

# Choosing an Antidepressant: Consider Cost

- ❖ Coverage issues / Medicare Part D
- ❖ Formularies/guidelines
- ❖ **Generic new antidepressants:**
  - ❖ Fluoxetine
  - ❖ Fluvoxamine
  - ❖ Paroxetine
  - ❖ Mirtazapine
  - ❖ Citalopram
  - ❖ Bupropion IR/SR
- ❖ **Not yet generic**
  - Sertraline (Zoloft)
  - Escitalopram (Lexapro)
  - Paroxetine CR (Paxil CR)
  - Bupropion XL (Wellbutrin XL)
- ❖ Samples vs. Patient assistance programs

# **Choosing An Antidepressant:** **Consider Side Effect Profile**

- ❖ 11 RCT comparisons of antidepressants in elderly subjects suitable for metaanalysis of side effects
- ❖ “Classical” TCAs had increased withdrawal rate (24.4%) vs SSRIs (18%)
- ❖ TCA side effects: dry mouth, constipation, drowsiness, dizziness, lethargy
- ❖ SSRI side effects: Nausea/vomiting, sleep disturbance



# Antidepressant Treatment is Safe and May Be Medically Beneficial in Cardiac Patients

- ❖ SADHART<sup>1</sup> showed that treatment is well-tolerated
  - ❖ Sertraline 50-200 mg/d x 24 weeks
  - ❖ No change with sertraline vs placebo in:
    - ❖ Left ventricular ejection fraction
    - ❖ Heart rate
    - ❖ Blood pressure
    - ❖ ECG
  - ❖ Trend with sertraline vs placebo toward lower incidence of death, recurrent MI, CVA, Heart failure, hospitalization for angina
- ❖ ENRICH<sup>2</sup> study found SSRI decreased life threatening outcomes among highly at risk cardiac depressed patients

# Adherence in the Elderly

- ❖ 40-70% overall noncompliance<sup>1</sup>
- ❖ 10% take drugs prescribed for others<sup>2</sup>
- ❖ 20% take drugs not currently prescribed<sup>2</sup>
- ❖ 40% stop drugs too soon<sup>3</sup>

## **Choosing An Antidepressant:** **Consider Comorbid Medical Illness**

- TCAs: (Class I antiarrhythmics) potentially arrhythmogenic
- SSRIs:
  - Not anticholinergic (except for paroxetine)
  - Possibly beneficial antiplatelet effect
  - No significant overall changes in HR, HR variability, BP, conduction intervals (though individual differences can occur)
- Fluoxetine, paroxetine, sertraline in IHD patients show considerable safety (sertraline in SADHART and other studies)
- Bupropion, venlafaxine can be associated with mild BP increases

# **Choosing An Antidepressant:** **Consider Age-Related Changes in** **Pharmacokinetics and Pharmacodynamics**

- ❖ **Reduced GI, renal and liver function**
- ❖ **Lower albumin levels**
- ❖ **Increased fat/muscle ratio**
- ❖ **Increased receptor-site sensitivity for many drugs (decreased  $\beta$ -adrenergic)**
- ❖ **Polypharmacy leading to drug-drug and drug-disease interactions**

# **Drug Interactions Can Take Place on Five Levels**

- ❖ **Gastrointestinal absorption**
- ❖ **Protein binding**
- ❖ **Hepatic metabolism**
- ❖ **Renal excretion**
- ❖ **Receptor site competition**

# Choosing An Antidepressant: Consider CYP 450 Drug/Drug Interactions

## ❖ **Some CYP 2D6 substrates**

- ❖ TCA, fluoxetine, paroxetine, trazodone, venlafaxine
- ❖ selegiline
- ❖ donepezil
- ❖ morphine, dextromethorphan, codeine, meperidine, oxycodone, tramadol
- ❖ encainide, flecainide, lidocaine, mexiletine
- ❖ metoprolol, bisoprolol, propranolol, timolol, labetolol

## ❖ **Two CYP1A2 substrates**

- ❖ clozapine
- ❖ warfarin

## ❖ **Some CYP 3A4 substrates**

- ❖ alprazolam, midazolam, triazolam, clonazepam
- ❖ carbamazepine, lamotrigine
- ❖ donepezil
- ❖ acetaminophen
- ❖ codeine
- ❖ clarithromycin, erythromycin
- ❖ ketoconazole
- ❖ tamoxifen, vinblastine, doxorubicin
- ❖ amiodarone, quinidine
- ❖ calcium channel blockers
- ❖ lovastatin, simvastatin, atorvastatin, fluvastatin, pravastatin
- ❖ estradiol, cortisol, prednisone, testosterone
- ❖ omeprazole

# Inhibitory Effect of SSRIs on Specific Cytochrome P450 Isoenzymes in Vivo

	1A2	2C9/10	2C19	2D6	3A3/4
Citalopram 40 mg/d	•	•	•	++	•
Escitalopram 20 mg/d	•	•	•	++	•
Fluoxetine 20 mg/d	•	+++	++	+++	+
Fluvoxamine 150 mg/d	+++	+++	+++	•	+++
Paroxetine 20 mg/d	•	•	•	+++	•
Sertraline 100 mg/d	•	•	•	+	•

• no or minimal effect (<20%)\*  
 + mild effect (20%-50%)\*

++ moderate effect (50%-150%)\*  
 +++ substantial effect (>150%)\*

# **Antidepressant Choices: Tricyclic Antidepressants (TCAs)**

- ❖ **Advantages**: proven efficacy, availability of blood levels for selected agents, low cost
- ❖ **Disadvantages**: sedation, cardiovascular effects, autonomic side effects (hypotension), toxicity.
- ❖ **Examples**: nortriptyline 10 to 150 mg daily (guide treatment by plasma level of 50 – 10 ng/ml); desipramine 10 to 150 mg daily

# **Antidepressant Choices:** **Serotonin Reuptake Inhibitors (SRIs)**

- ❖ **SSRIs vs SNRIs**
- ❖ **Advantages:** Effective with minimal toxicity, avoidance of autonomic side effects, less sedation, ease of administration
- ❖ **Disadvantages:** Overstimulation/insomnia, G.I. symptoms, sexual side effects, hyponatremia, drug interactions, cost
- ❖ **Examples:** fluoxetine 10 to 80 mg/day, sertraline 25 to 200 m/day, paroxetine 10 to 50 mg/day, citalopram 10 to 40 mg/day; venlafaxine XR 37.5 mg/d; duloxetine 20-30 mg/d

# **Antidepressant Choices:** **Ungrouped Agents**

- ❖ **Mirtazapine** (start: 15 mg/day) may cause sedation and increased appetite.
- ❖ **Bupropion** (start: 37.5 mg BID or bupropion SR 100 mg q d) may increase risk for seizures at higher doses, is not approved for treating anxiety disorders, and is contraindicated with comorbid eating disorder.
- ❖ **Nefazodone**: rarely used as primary therapeutic agent because of concerns about rare but serious hepatotoxicity.
- ❖ **Trazodone**: rarely used as primary therapeutic agent because of limited potency and significant side effects (sedation, hypotension, priapism) but can be used as an hypnotic in conjunction with SSRI.

# **Antidepressant Choices:** **Monoamine Oxidase (MAO)** **Inhibitors**

- ❖ **Advantages:** MAO levels increase with age, low cardiac effects, effectiveness for atypical depression.
- ❖ **Disadvantages:** Dietary restriction, potential hypertensive crisis, orthostatic hypotension, drug interactions.
- ❖ **Examples:** phenelzine 15 mg bid to tid, tranylcypromine 10 mg bid to tid

# To Switch or To Augment?

## Switch

- Simpler, less costly
- Avoids drug-drug interactions
- Reduces side effects
- Introduces “different mechanism”
- Implementation is slower
- Outpatient setting

## Augmentation

- More complex and costly
- Risks drug-drug interactions
- Risks side effect increase
- Avoids loss of partial response effect
- Implementation is faster
- Inpatient setting

# Antidepressant “Augmenters”

<b>Augmenter</b>	<b>Evidence in Adults</b>	<b>Evidence in Late Life Depression</b>
<b>Lithium carbonate</b>	<b>+</b>	<b>Mixed results</b>
<b>Triiodothyronine</b>	<b>+</b>	<b>No specific study</b>
<b>Atypical antipsychotic</b>	<b>+</b>	<b>+ Open trial: aripiprazole</b>
<b>Modafinil</b>	<b>+/-</b>	<b>+/- case reports</b>
<b>Testosterone</b>	<b>+ Hypogonadal men</b>	<b>+ ? Hypogonadal men</b>
<b>Buspirone</b>	<b>+/-</b>	<b>No specific study</b>
<b>Estrogen</b>	<b>+ Peri/postmenopausal women??</b>	<b>+ Peri/postmenopausal women</b>
<b>Lamotrigine</b>	<b>?</b>	<b>?</b>

+ signifies presence of credible evidence base for use



# Augmenters: Atypical Antipsychotics

- ❖ Small, mostly open label, studies support atypicals as SRI augmenters in depressed nongeriatric nonpsychotic adults<sup>1</sup>
  - ❖ Risperidone: 0.5 to 1 mg/d
  - ❖ Olanzapine: 1 RCT at 5-20 mg/d
  - ❖ Ziprasidone: 20-80 mg bid
  - ❖ Aripiprazole: 2.5-5 mg/d
  - ❖ Quetiapine: Anecdotal support for augmentation
  - ❖ Clozapine: Anecdotal support for augmentation
- ❖ In elderly, 1 open and limited trial of aripiprazole<sup>2</sup>



# Prescribe Atypicals with Caution in Elderly Patients

- ❖ FDA warnings re use in psychosis/dementia geriatric patients
  - ❖ CVA risk
  - ❖ Overall mortality risk
- ❖ Concerns re metabolic effects
  - ❖ Weight gain
  - ❖ Glucose
  - ❖ Lipids
- ❖ Safety and risk-management considerations



# Augmenters: Testosterone

- ❖ Low total testosterone level predicts higher incidence of depressive illness among older men (enhanced with comorbid medical morbidity).<sup>1</sup>
- ❖ One RCT found testosterone +SSRI = placebo + SSRI in older hypogonadal men<sup>2</sup>, while others have supported testosterone coadministration<sup>3</sup> including in SSRI-resistant hypogonadal<sup>4</sup> or eugonadal<sup>5</sup> men
- ❖ Prescreen: Contraindicated with prostate cancer, may cause hepatotoxicity and other adverse effects.

# Antidepressant “Co-Prescribing”

<b>Augmenter</b>	<b>Evidence in Adults</b>	<b>Evidence in Late Life Depression</b>
TCA + SSRI/SNRI	+	+ Nortriptyline/paroxetine <sup>1</sup>
SSRI/SNRI + bupropion	+	+ Bupropion/paroxetine <sup>1</sup>
SSRI/SNRI + mirtazapine	+	No specific study
Stimulant	+	+/- Methylphenidate, (dextroamphetamine)

1. Dew et al. 2007; 2. Orr and Taylor 2007

+ signifies presence of credible evidence base for use



# Electroconvulsive Therapy

- ❖ Underused modality, especially suitable with:
  - ❖ Antidepressant intolerance or non-response
  - ❖ Prior positive response to ECT
  - ❖ Delusions
  - ❖ Catatonia
  - ❖ Mania
  - ❖ Emergency
- ❖ High response rates documented<sup>1</sup>

# ECT and Medical Status Concerns

- ❖ **Rarely contraindicated in appropriate setting**
- ❖ **Cardiac:** Recent MI, unstable angina, arrhythmias, severe valvular diseases, CHF, hypertension
- ❖ **Pulmonary:** COPD, asthma, infections
- ❖ **Gastrointestinal:** Aspiration or laryngospasm risk factors
- ❖ **Musculoskeletal:** Stress to bones, joints, vertebrae during treatment or in subsequent falls
- ❖ **Neurologic:** Intracranial lesions “substantially increase” risk<sup>1</sup>

# ECT and Memory Loss

- ❖ A major concern of patients and families
- ❖ ECT may improve depression-impaired cognition but exacerbate impaired cognition of dementia
- ❖ Preparation:
  - ❖ Education of patient/family
  - ❖ Pre-screen to establish baseline
  - ❖ Monitor of memory throughout treatment course
  - ❖ Decrease treatment frequency when pronounced
  - ❖ Treat unilaterally when possible



# Psychosis: A Source of Treatment Resistance?

- ❖ Delusional depression is more prevalent among older vs younger depressives
- ❖ Associated with:
  - ❖ Hypochondriacal and nihilistic delusions
  - ❖ Delusional relapses
  - ❖ Worse response to antidepressant monotherapy
  - ❖ Longer hospitalizations
  - ❖ High relapse rate



# Treatment of Late Life Delusional Depression

- ❖ Adjunctive antipsychotic important in younger adults but evidence is less secure in later life
  - ❖ Atypicals vs typicals? 2 positive delusional depression treatment studies support use of olanzapine in younger adults – no evidence base in older adults.
- ❖ No RCTs guide choice of antipsychotic or antidepressant in geriatric psychotic depression
- ❖ Expert consensus: Use APD + AD<sup>1</sup>
- ❖ ECT may be more effective<sup>2</sup>

1. Alexopoulos et al. 2004; 2. Flint and Rifat 1998.

# **Hormone Treatments for Late-Life Mood and Cognitive Disorders**

- ❖ **Several hormones may influence mood and cognition in late life**
- ❖ **Estrogen, historically used as an antidepressant augmenter, was supported by limited evidence but is used infrequently to treat depression following the WHI and other studies raising concern about the safety of estrogen treatment.**
- ❖ **Testosterone has been used to treat depression in men with low testosterone levels absent risk factors (e.g. prostatic hypertrophy, cancer, or elevated PSA).**

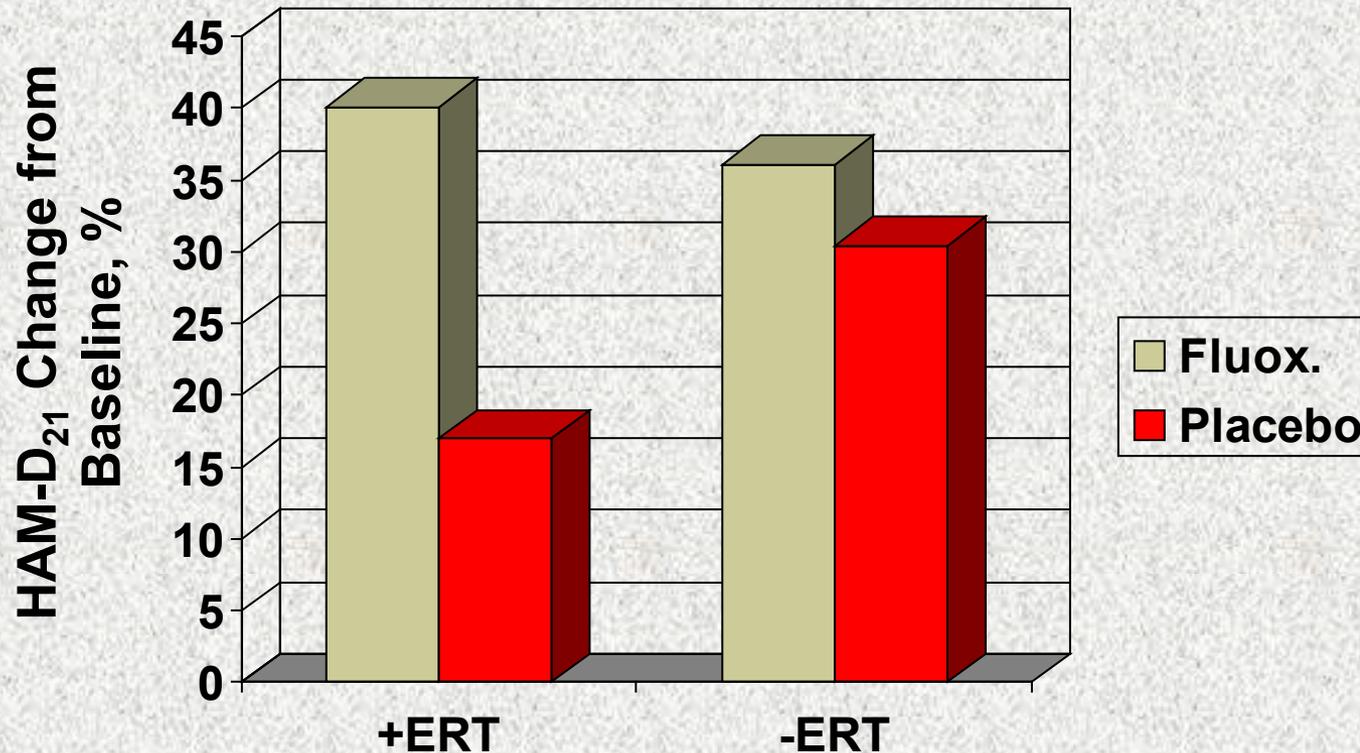
# **Estrogen Replacement Therapy** **and Response to Fluoxetine**

(Schneider et al, *Am J Geriatr Psychiatry* 1997;5:97-106)

- ❖ **Compared the response of 72 elderly depressed women outpatients (DSM-III-R, HAMD<sub>17</sub> scores = 16) receiving ERT to that of 286 not receiving ERT**
- ❖ **Data from a six-week, randomized, placebo-controlled, double-blind, multicenter trial of fluoxetine (20mg/d) vs. placebo**

# Outcome of Patient by ERT Status and Treatment Assignment: Fluoxetine vs. Placebo in Geriatric Major Depression

(Schneider et al, Am J Geriatr Psychiatry 1997;5:97-106)



**P=.015 (LOCF analysis) for interaction between tx & ERT status**  
**Main ERT tx effect: p=.13 (LOCF) % p=.055 (completer)**

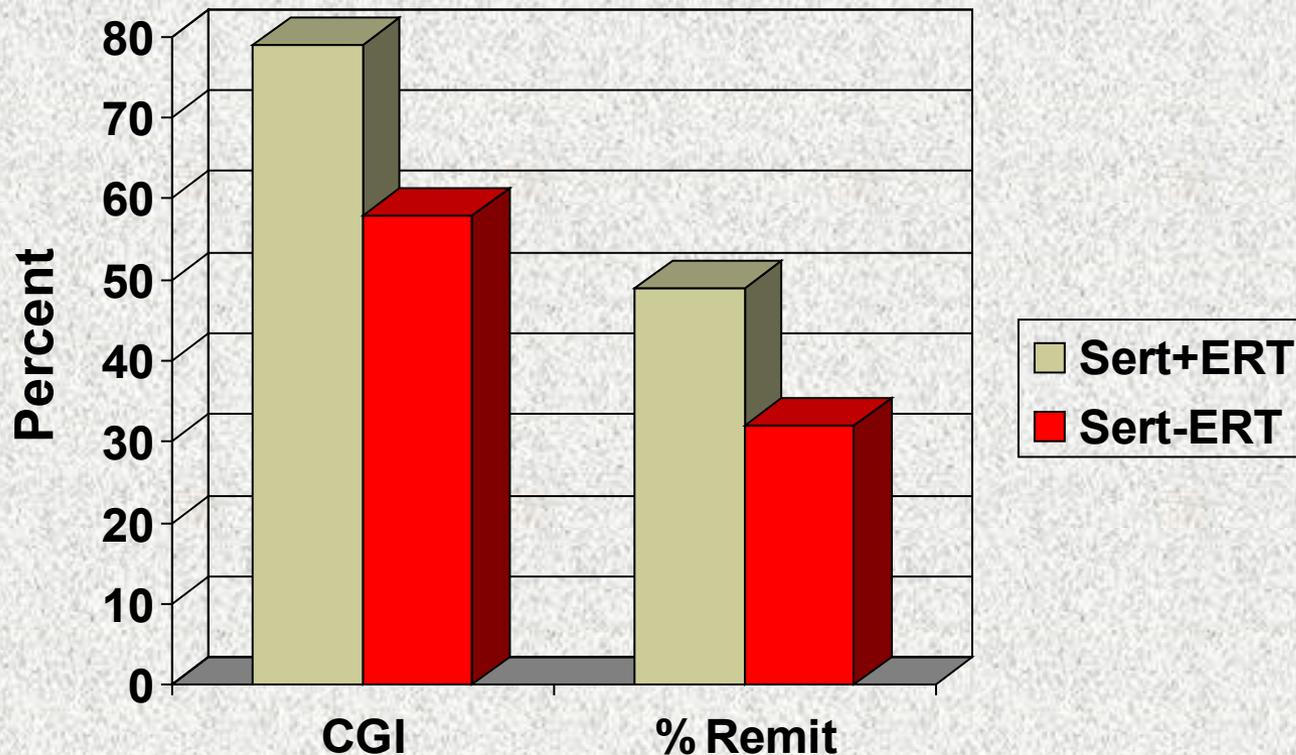
# **Estrogen Replacement Therapy and Response to Sertraline**

(Schneider LS, et al. *APA New Research Abstracts* 1998; NR426:182)

- ❖ **Compared sertraline response of 34 depressed women receiving ERT to 93 not receiving ERT**
- ❖ **Data from two 12-week, randomized, double-blind, multisite trials comparing sertraline (50-150 mg/d) with fluoxetine or nortryptiline**

# Outcome of Patient by ERT Status and Treatment Assignment: Sertraline vs. Placebo in Geriatric Major Depression

(Schneider LS, et al. *APA New Research Abstracts* 1998;NR426:182)



**CGI = % “much improved” or “very much improved” (p=0.04)**

**% Remit = proportion remitting (HAM-D<sub>17</sub> ≤ 7)**

# Limitations of Studies

- ❖ **Women not randomized**
- ❖ **Women who take estrogen are more highly educated**
- ❖ **Results complicated by effects of progesterone that might minimize antidepressant effects of estrogen**

# Delusional Depression

- ❖ More prevalent among older than younger depressives
- ❖ Associated with:
  - ❖ Hypochondriacal and nihilistic delusions
  - ❖ Worse response to antidepressant monotherapy
  - ❖ Longer hospitalizations
  - ❖ High relapse rate
  - ❖ Delusional relapses



# Treatment of Late Life Delusional Depression

- ❖ ECT may be more rapidly effective
- ❖ No RCTs guide choice of agent (antipsychotic or antidepressant) in treatment of geriatric psychotic depression
- ❖ Antipsychotic adjunctive treatment shown important in younger adults
  - ❖ Expert consensus: APD + AD is first line treatment for geriatric psychotic major depression<sup>1</sup>
  - ❖ Atypicals vs typicals? Two positive delusional depression treatment studies support use of olanzapine in younger adults – no evidence base in older adults.



# Electroconvulsive Therapy

- ❖ Underused modality, especially suitable with:
  - ❖ Antidepressant intolerance or non-response
  - ❖ Prior positive response to ECT
  - ❖ Delusions
  - ❖ Catatonia
  - ❖ Mania
  - ❖ Emergency
- ❖ High response rates documented<sup>1</sup>

# ECT and Medical Status Concerns

- ❖ **Rarely contraindicated in appropriate setting**
- ❖ **Cardiac:** Recent MI, unstable angina, arrhythmias, severe valvular diseases, CHF, hypertension
- ❖ **Pulmonary:** COPD, asthma, infections
- ❖ **Gastrointestinal:** Aspiration or laryngospasm risk factors
- ❖ **Musculoskeletal:** Stress to bones, joints, vertebrae during treatment or in subsequent falls
- ❖ **Neurologic:** Intracranial lesions “substantially increase” risk<sup>1</sup>

# ECT and Memory Loss

- ❖ A major concern of patients and families
- ❖ ECT may improve depression-impaired cognition but exacerbate impaired cognition of dementia
- ❖ Preparation:
  - ❖ Education of patient/family
  - ❖ Pre-screen to establish baseline
  - ❖ Monitor of memory throughout treatment course
  - ❖ Decrease treatment frequency when pronounced
  - ❖ Treat unilaterally when possible

# Depression/Exec Dysfunction: Different Approach to Treatment?

- ❖ Executive dysfunction (by impaired IP on DRS) but not memory impairment predicted:
  - ❖ Delayed antidepressant response<sup>1</sup>
  - ❖ Greater risk of relapse, recurrence and symptom fluctuation following response<sup>2</sup>
- ❖ White matter hyperintensities predicted executive dysfunction<sup>3,4</sup> and poorer treatment response<sup>4</sup> (but not in all studies<sup>5</sup>)

1. Kalayam et al. 1999; 2. Alexopoulos et al. 2000; 3. Boone et al. 1992; 4. Hickie et al. 1995; 5. Salloway et al. 2002



# Is DEDS Treated Differently?

- ❖ Current approach is “treatment as usual”
- ❖ Attention to cerebrovascular risk factors is urged
- ❖ Hypothetical microvascular damage to frontostriatal (CSPTC) pathways suggests that glutamatergic, GABA-ergic, dopaminergic, cholinergic, and enkephalin pathways may be of importance<sup>1,2</sup>
- ❖ D<sub>3</sub> agonists, modafinil, nimodipine<sup>3</sup> or other novel agents may be of interest

1. Alexopoulos et al. 2000; 2. Alexopoulos GS 2001; 3. Taragano et al. 2005



# Post-Stroke depression

- ❖ CVA: 600,000 per year in US
- ❖ At 3-6 months s/p CVA, 9-34% show MDD
- ❖ Depression associated with:
  - ❖ Left anterior lesions
  - ❖ Left basal ganglia lesions
  - ❖ Lesions closer to frontal pole
- ❖ Minor depression is also common
- ❖ Assessment complicated by neurological symptoms
- ❖ Treatment
  - ❖ No antidepressant clearly superior (Flx, Nor studied)
  - ❖ ECT
  - ❖ ?Role for stimulants

# Depression & AD: Positive Drug Trials (3 of 8 published RCTs)

- ❖ In 6 wk RCT, n=726 inpatients with cognitive impairment (mostly AD) and depression by DSMIII & HAMD, HAMD improved with **moclobemide** dosed up to 400 mg/d max<sup>1</sup>
- ❖ In 6 wk RCT, n=149 inpatients and outpatients with AD and depression by DSMIII & HAMD, **citalopram** 30 mg/d max showed HAMD effect vs placebo<sup>2</sup>
- ❖ In 12 wk RCT, n=22 outpatients with DSMIV AD & Depression, **sertraline** 150 mg/d max showed CSDD but not HAMD effect vs placebo<sup>3</sup>

# Anxiety Symptoms Are Highly Prevalent in Late Life

- ❖ 10-20% of adults over 65 show clinically significant new or recurring anxiety symptoms<sup>1</sup>
- ❖ Symptom picture may confusingly emphasize agitation rather than worry; physical/cognitive rather than affective symptoms, such as sweating, restlessness, pacing, palpitations, poor concentration, fatigue, dizziness, dry mouth, GI symptoms, tremor, aches, pains
- ❖ Anxiety even more prevalent among the medically ill elderly

# Anxiety Symptoms are Commonly Associated with:

## ❖ Medications / Drugs of abuse

- ❖ Stimulants or sympathomimetics
- ❖ Withdrawal of CNS depressants
- ❖ Thyroid hormones
- ❖ Nicotine
- ❖ Antidepressants
- ❖ Antipsychotics
- ❖ Corticosteroids

## ❖ Conditions

- ❖ Post-CVA
- ❖ Coronary artery disease
- ❖ IBS
- ❖ Endocrine
- ❖ Dementia
- ❖ Depression

# Differentiating Anxiety from Depression

- ❖ Difficult, because they share disturbances of sleep, appetite, and cognitive functioning<sup>1</sup>
- ❖ Initial insomnia, fear, loss of confidence more typical of anxiety<sup>2</sup>
- ❖ Anxiety is often associated with depression in the elderly<sup>3</sup>

1. Colenda and Smith: AJGP 1993;1:327-338; 2 Salzman C: Conclusion. In: Salzman C, Liebowitz BD, eds: Anxiety in the Elderly: Treatment and Research 1991; 3. Fernandez et al. J Clin Psychiatry. 1995;56(suppl 2):20-29

# Depression with Anxiety: Treatment Recommendations

- ❖ The claim for superiority of sedating antidepressants with anxious, insomniac depressed patients has limited evidence base.
- ❖ These antidepressants are FDA-Indicated for GAD:
  - ❖ Paroxetine
  - ❖ Venlafaxine
  - ❖ Escitalopram
- ❖ Other useful agents may include sertraline, citalopram, mirtazapine, tricyclic antidepressant, buspirone as adjunct
- ❖ Avoid chronic benzodiazepines when possible

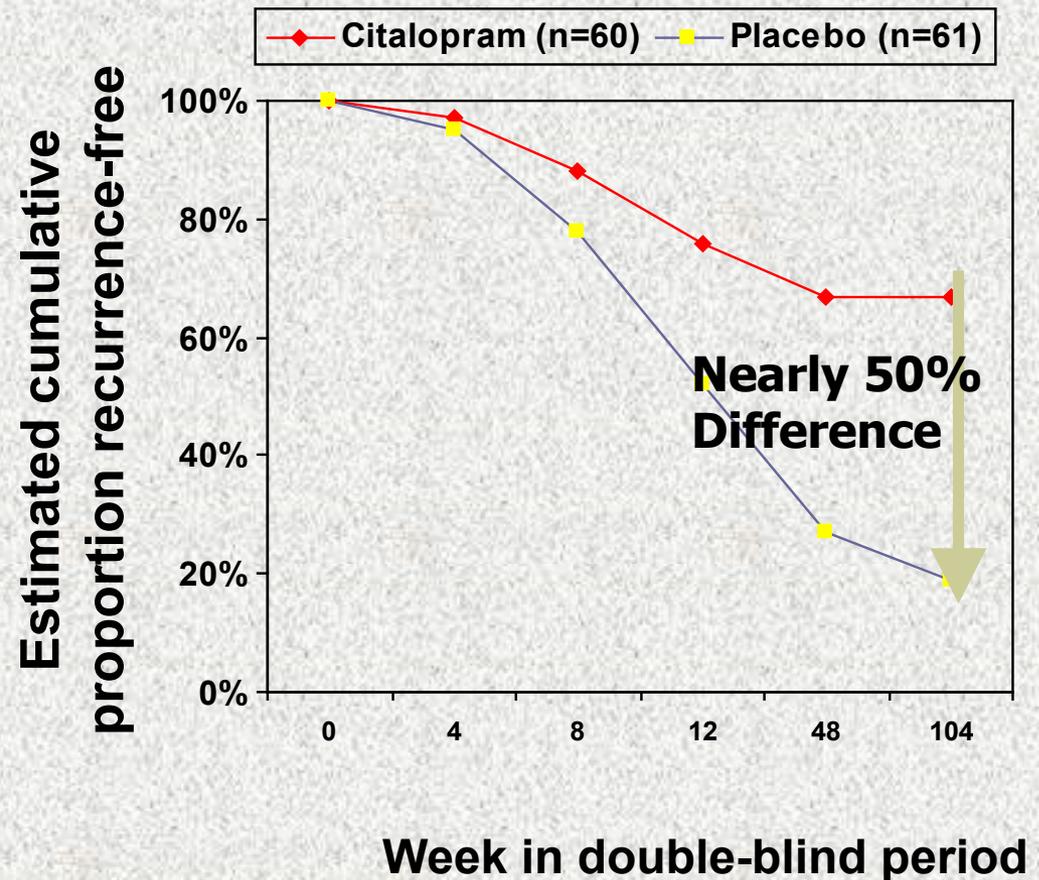
# Maintenance Treatment: What do Experts Recommend?

❖ 1 episode:	Continue for	1 year
❖ 2 episodes:	Continue for	1-3 years
❖ 3 episodes	Continue for	>3 years

Alexopoulos GS, Katz IR, Reynolds CF III, et al. Postgrad Med Special Report. 2001 (October):1-86.

# Citalopram Prevents Depression Recurrence in Elderly

- ❖ N=121 outpatients  $\geq 65$  yr
- ❖ 20-40 mg citalopram vs placebo for up to 104 weeks after 2 periods of open-label treatment (up to 24 weeks total) to establish and continue remission
- ❖ No treatment-related serious AEs



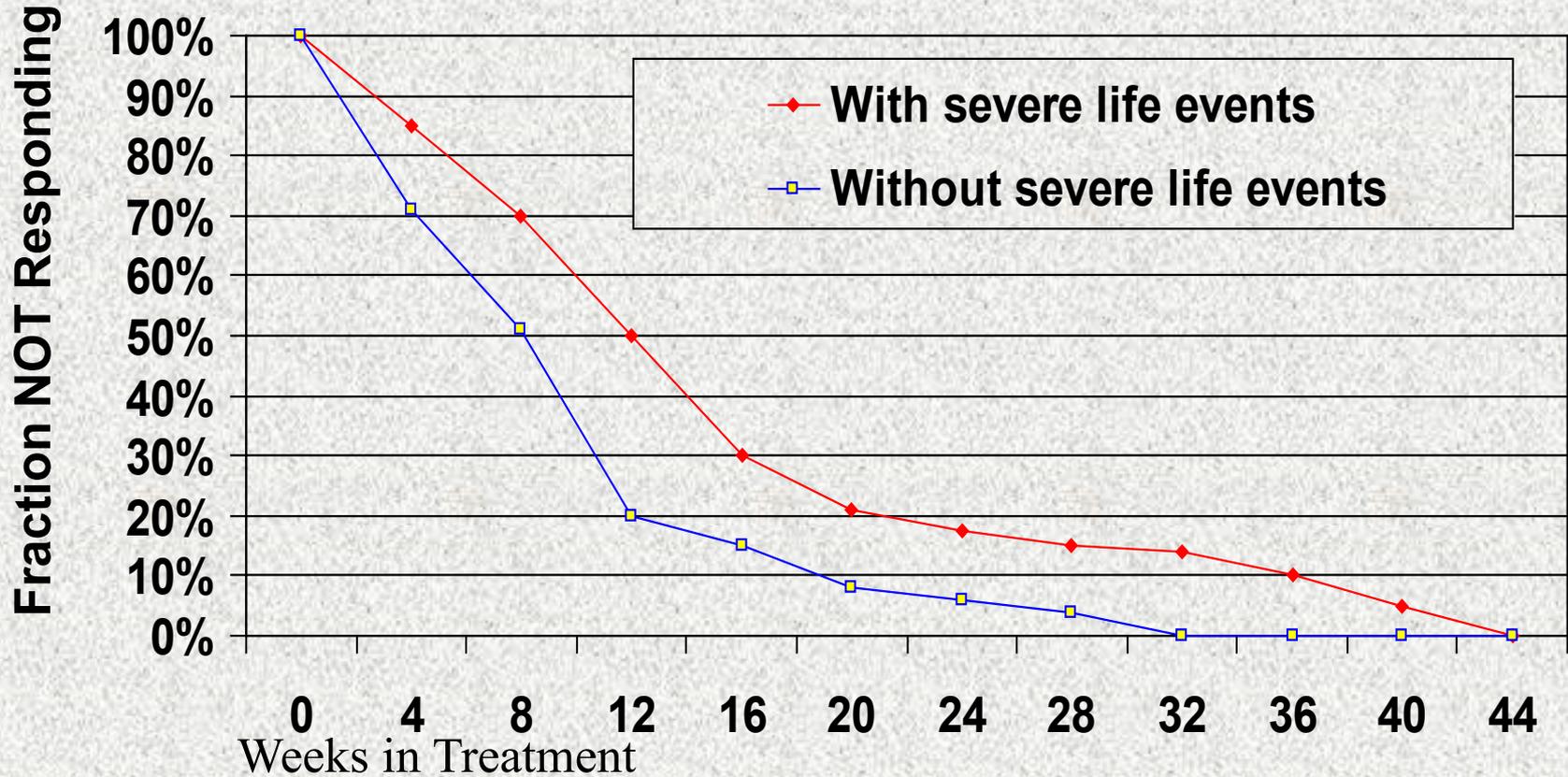
# Recurrence after Recovery from Geriatric Depression

- ❖ Up to 15 years observational follow up (n=380)
- ❖ Recurrence in
  - ❖ 85% of those who had recovered
  - ❖ 58% of those who had remained well at least 5 years
- ❖ Risk factors (not in subgroup with 5 years recovery)
  - ❖ more prior episodes
  - ❖ longer depressive episode before intake
  - ❖ **Low levels of antidepressant treatment**
  - ❖ never marrying
  - ❖ female

# **Suggestions to Improve Adherence for Treatment of Geriatric Depression/Anxiety**

- ❖ Assess for cognitive impairment
- ❖ Assume adherence will be a problem
- ❖ Ask about non-adherence
- ❖ Encourage patient to monitor self-adherence
- ❖ Include family members/other supportive individuals as monitors/helpers
- ❖ Explore patient's conception of illness/treatment
- ❖ Provide clear, easy-to-understand info (repeat frequently, oral/written)
- ❖ Maintain appropriately frequent patient contact
- ❖ Accept limited adherence in some patients but maintain dialog

# Importance of Recognizing Significant Psychosocial Factors: Effect of Severe Life Event on Time to Response in Elderly Depressed Patients



# Summary of General Principles of Pharmacotherapy in Late Life Depression

- ❖ Differential diagnosis and comprehensive treatment planning
- ❖ Consider psychosocial and medical factors
- ❖ Psychotherapy may be important treatment ingredient
- ❖ Individualized consideration of treatment agents' properties
- ❖ Begin with low doses
- ❖ Monitor closely for response, side effects, and compliance
- ❖ Increase dose slowly and carefully
- ❖ Avoid underdosing and premature discontinuation

# **Self-Assessment Question 1:**

## **Which of the following is most correct?**

- A. Major depressive disorder is less prevalent in older than in younger adults.
- B. Major depressive disorder in late life is associated with increased morbidity and mortality from medical illnesses and suicide.
- C. Major depression is not a normal concomitant of ageing.
- D. Numerous published randomized controlled treatment trials are available to help guide the treatment choices for older adults with major depressive disorder.
- E. All of the above are true

## **Self-Assessment Question 2:**

### **Which of the following is most correct?**

- A. White matter hyperintensities are the most replicated neuroimaging abnormality in late life depression.
- B. White matter hyperintensities and late-life depression have a direct cause-effect relationship.
- C. White matter hyperintensities represent deposition of beta amyloid plaques in the prefrontal white matter.
- D. The most common location of white matter hyper intensities in vascular depression is occipital.
- E. None of the above

### **Self-Assessment Question 3:**

**Which of the following forms of psychotherapy has/have been empirically validated for the treatment of depression in older adults?**

- A. Cognitive Behavior Therapy
- B. Problem Solving Therapy
- C. Interpersonal Therapy
- D. All of the above
- E. None of the above.

## **Self-Assessment Question 4:**

### **Which of the following is most correct?**

- A. Efficacy of serotonin reuptake inhibitors in treating late life depression is similar to that of TCAs, though TCA side effects may be less tolerable.
- B. For nonpsychotic late life depression, the combination of psychotherapy and medication is recommended.
- C. Older adults are more vulnerable than younger adults to anticholinergic side effects of antidepressants.
- D. Older adults typically take more concurrently prescribed medications than younger adults, necessitating careful attention to drug/drug interaction possibilities when an antidepressant is prescribed.
- E. All of the above

# **Self-Assessment Question 5:**

## **Which of the following is not correct?**

- A. ECT is usually less efficacious than antidepressants in treating late life depression with psychotic features.
- B. Intracranial mass lesion, recent CVA, or recent MI can complicate the safe administration of ECT.
- C. Informing patient and family about potential memory disturbance associated with ECT will help them understand and tolerate this usually transient aspect of treatment.
- D. Demented patients may experience intolerable cognitive worsening during the course of a series of ECT treatments.
- E. Unilateral nondominant ECT is associated with fewer cognitive side effects.

## Self-Assessment Question Answers

1. E
2. A
3. D
4. E
5. A

# Suggested Further Reading

- ❖ Ellison JM, Verma SK (eds): Depression in Later Life. New York, New York. Marcel Dekker, Inc., 2003.
- ❖ Lebowitz BD. Pearson JL. Schneider LS. Reynolds CF 3rd. Alexopoulos GS. Bruce ML. Conwell Y. Katz IR. Meyers BS. Morrison MF. Mossey J. Niederehe G. Parmelee P. Diagnosis and treatment of depression in late life. Consensus statement update. JAMA. 278:1186-90, 1997.