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Depression in Later Life: Epidemiology, Assessment, and Treatment

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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

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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

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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.

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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.

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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

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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

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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% [1]
- Depression is common in primary care settings [2]
  - 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 [3]

1. Steffens et al. 2000; 2. Garrard JL et al. J Gerontology Medical Sciences. 1998; 3. Brown et al. J Am Geriatr Soc. 2002;50(1):69-76.

* Geriatric Depressive Syndromes: Adverse Outcomes

- Functional Decline / Increased disability[1,2]
- Increased use of non-mental health services[1]
- Increased risk of cancer [2]
- Increased mortality rate[3]
  - Increased cardiac mortality[4]
  - Increased CVA mortality[5]
- Increased suicide rate

1. Beekman et al. 1997; 2. Penninx et al. 1998; 3. Penninx et al. 1999; 4. Frasure-Smith et al. 1993; 5. House et al. 2001

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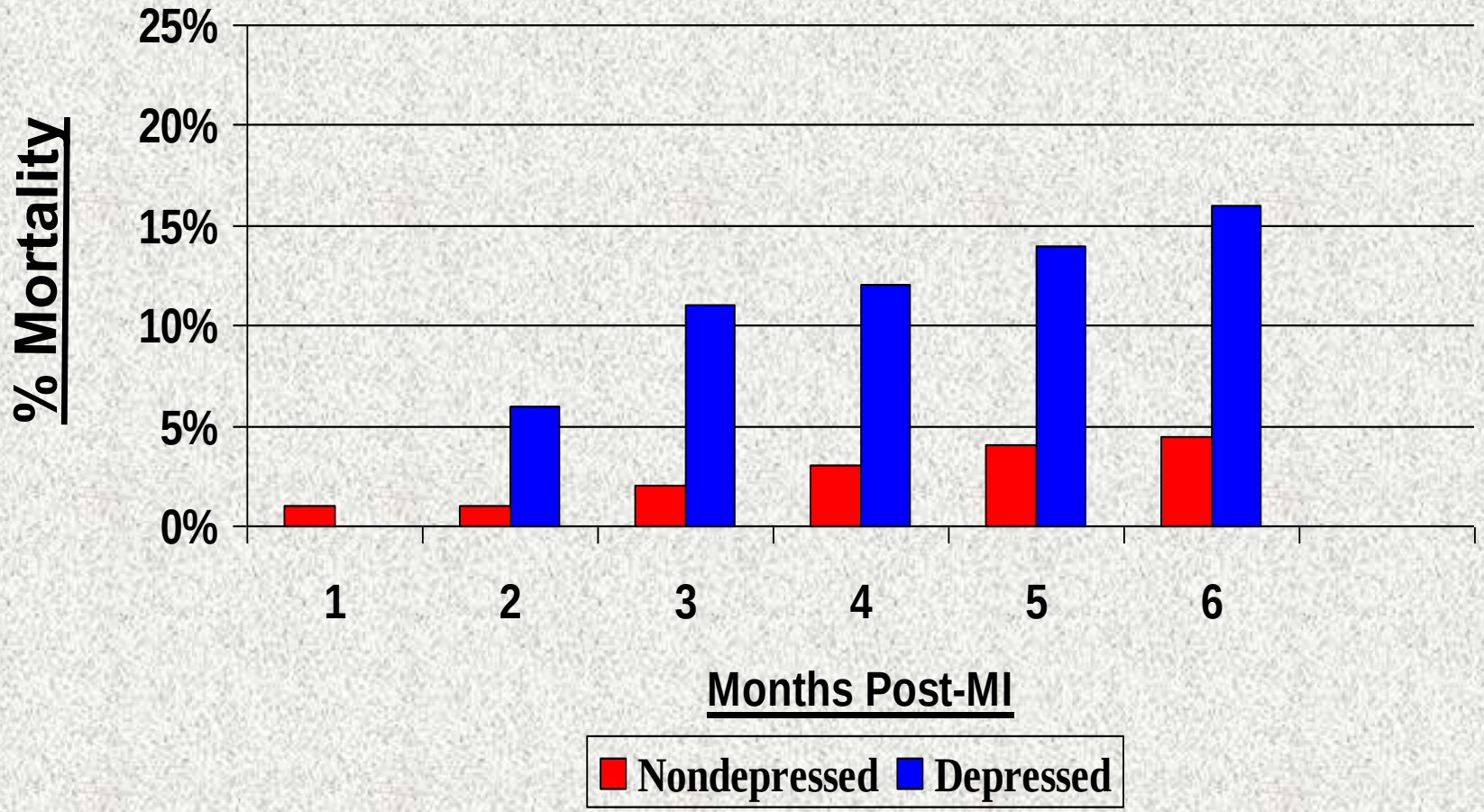
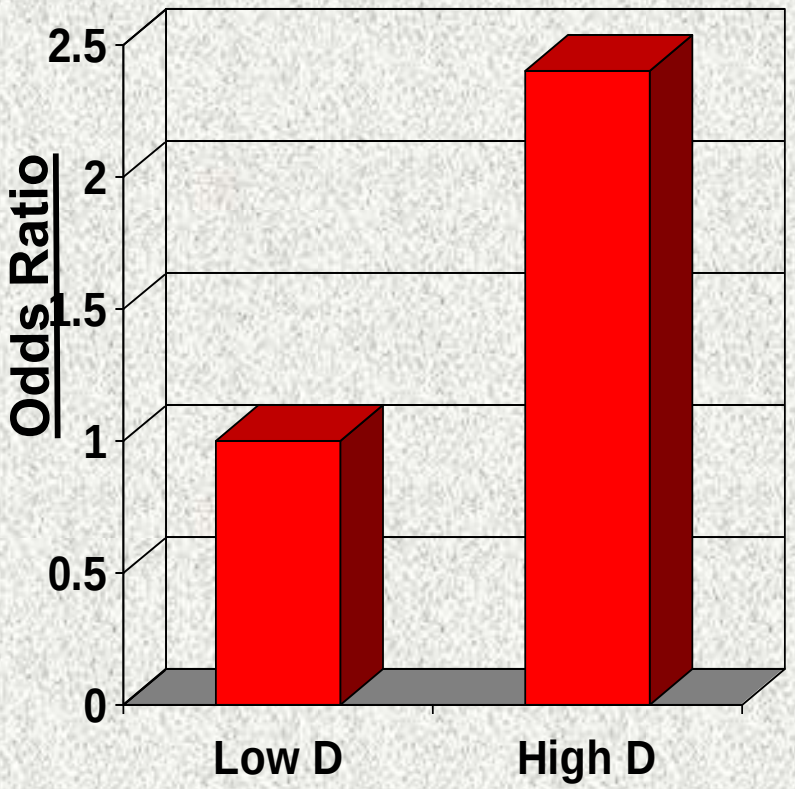
Cumulative Mortality for Depressed and Non-depressed Patients 6 Months After MI



Frasure-Smith et al. 1993

Depressive Symptoms 1 Month After Stroke Predict Increased Mortality at 12 and 24 Months

- 448 hospitalized CVA patients assessed at 1 month after stroke
- OR for mortality at 12 and at 24 months more than doubled with high score on depression subscale (GHQ-D) of General Health Questionnaire-28



House et al. 2001

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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

APA 2000

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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; Geiselmann and Bauer 2000; Devanand 1994; Mazure et al. 2002; Lezac 1994; Lavretsky and Kumar 2002

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Psychiatric Differential Diagnosis

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

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Organic Differential Diagnosis

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

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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)

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

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

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Vascular Depression

- **Observations:**[1]
  - **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**

1. Alexopoulos 1997

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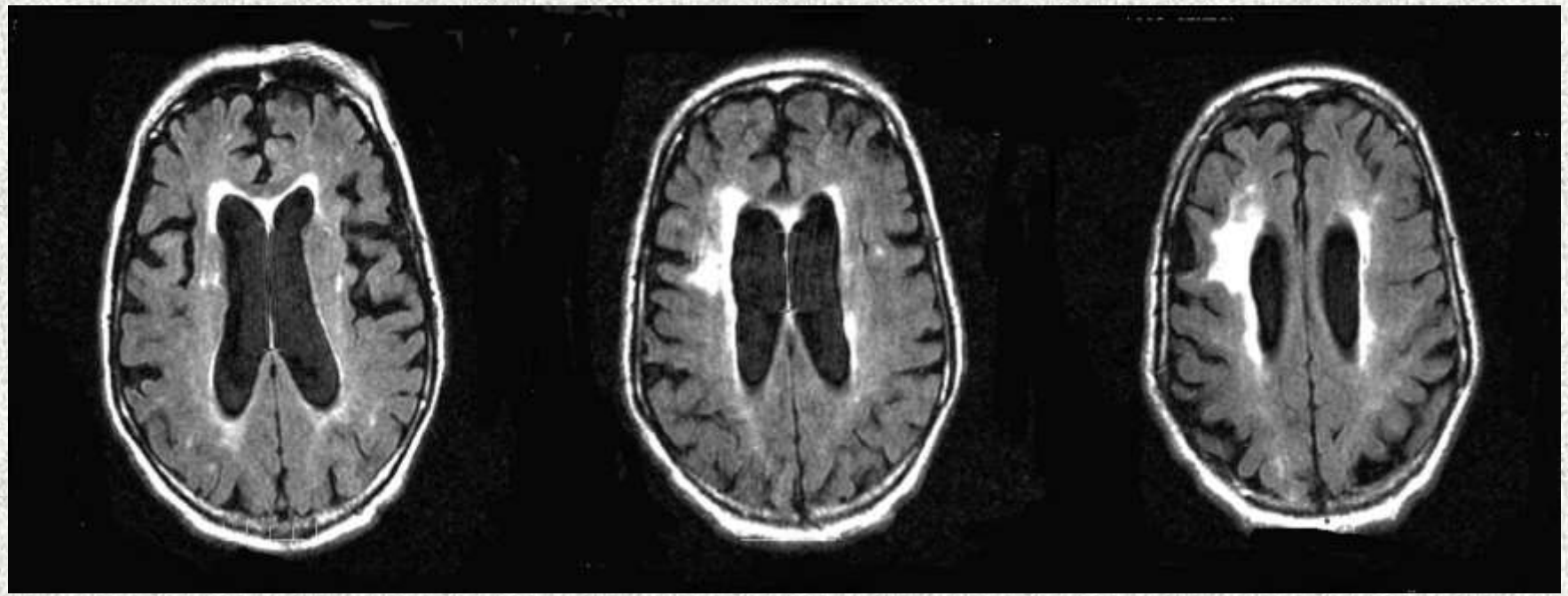
Vascular Depression: Definition of Syndrome

- **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[2]**

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

T2 Hyperintensities on MRI



Courtesy of Martin Goldstein MD

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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

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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[1]
- Short version (15 item), cutoff 5/15[2]
  - Sensitivity 92%
  - Specificity 81%
- Limited validity with MMSE less than 15[3]

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

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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 no
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 tha you are ?

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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)

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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)*

*Not considered “routine”

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Treatment

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

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Evidence-Based Psychotherapies for Older Adults

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

Arean PA, Cook BL. *Biol Psychiatry.* 2002;52:293-303.

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

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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**
  - Phenelzine (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)

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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)

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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

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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

Wilson and Mottram 2004;Int J Geriatr Psychiatry 19:754-762.

Adherence in the Elderly

- 40-70% overall noncompliance[1]
- 10% take drugs prescribed for others[2]
- 20% take drugs not currently prescribed[2]
- 40% stop drugs too soon[3]

1. Ostrum et al. 1988; 2. Lamy et al. 1992; 3. Jackson et al. 1984

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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

Roose SP: Treatment of depression in patients with heart disease. Biological Psychiatry 2003;54:262-268

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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 β-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

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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

Zubenko and Sunderland 2000; Cadieux 1999

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%)*
++ moderate effect (50%-150%)*
+ mild effect (20%-50%)*
+++ substantial effect (>150%)*

Preskorn SH. *J Psychiatr Pract*. 2003;5:228-236.

*Percent increase in plasma levels of a co-administered drug dependent on this CYP enzyme for its clearance.

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, hyponatremia, drug interactions and high 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 hepatotoxicity, a rare but serious adverse effect.**
- **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**

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For Persistent Depressive Symptoms: To Switch or To Augment?

Switch

- Preferred to augmentation?
- Simpler
- Less costly
- Avoids potential drug-drug interactions
- Side effects fewer/more easily attributable
- With side effect intolerance, may switch within class
- Choice of “different mechanism” has been proposed

Augmentation

- Builds on current improvement in partial responders
- Extends potentially successful current trial
- Prevents discontinuation-related treatment delays
- Popular “add-on” drugs include:
  - T3 or Li Carbonate*
  - Atypical antipsychotics*
  - Bupropion*
  - Mirtazapine*
  - TCA (e.g. nortriptyline)*
  - Stimulants (e.g. methylphenidate)*
  - Modafinil

*some evidence base in younger adults

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Stimulants for Geriatric Depression

- Use remains controversial
- Effect is often rapid
- May be justified with:
  - apathy/psychomotor retardation
  - concurrent medical illness
  - intolerance of antidepressants
  - need for rapid response
- Effect can be lasting

Wallace et al 1995; Kaplitz 1975;Katon and Raskin 1980, Pickett et al. 1990; Askinazi et al. 1986

MPH acceleration of Citalopram Response in Late Life Depression

- **Open trial** – 9 of 11 completed
- 6 responders (3 remitters)
- 3 worsened on discontinuation of MPH
- Dosing: 2.5 start, double after 3 days and 6 days, increase again, to 20 mg/d by end of week 3 if still symptomatic
- Tapered weeks 8-10

Lavretsky et al. 2003

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Augmentation with Atypical Antipsychotics

- Two small studies available in younger adults
  - Risperidone open study, n=8, small doses, increased antidepressant response[1]
  - Olanzapine controlled trial, n=28 fluoxetine-treated patients randomized to olanzapine vs placebo, showed possible superiority over fluoxetine alone[2]
- Limited support for addition of atypical antipsychotic to antidepressant in geriatric depression after 2 failed antidepressant trials[3]

1. Ostroff and Nelson 1999; 2. Shelton et al. 2001; 3. Alexopoulos et al: J Clin Psychiatry 2004;65 Suppl 2:5-99

Atypical Antipsychotic Augmentation (1)

- Lower EPS than typicals, but associated with other significant adverse effects (e.g. metabolic, vascular)
- Proposed mechanisms:
  - Antagonism of $5HT_2$ receptors (all atypicals)
  - Antagonism of $5HT_{1a}$ receptors (ziprasidone, aripiprazole)
  - Antagonism of $5HT_{1d}$ autoreceptors (ziprasidone, risperidone)
  - D_2 agonist activity (aripiprazole)
  - Reuptake inhibition for NE, 5HT, DA (ziprasidone)
  - Increased prefrontal levels of DA and NE (olanzapine)

Nelson C. J Clin Psychiatry 2003;64[suppl 1]:5-12

Support for Atypical Antipsychotic Augmentation in Younger Adults

- Risperidone: Several positive open-label studies support use with SSRI, typical dose 0.5 to 1 mg/d
- Olanzapine: Several small studies and 1 double-blind trial (dose 5-20 mg/d with fluoxetine) support augmentation of SSRI
- Ziprasidone+SSRI: 20-80 mg bid, open label
- Aripiprazole+SSRI or SNRI: 2.5-5 mg/d, open label
- Only anecdotal support for antidepressant augmentation with quetiapine, clozapine

Papakostas GI. Essential Psychopharm 2005;6:209-220;
Nemeroff CB. J Clin Psychiatry 2005;66[suppl8]:13-21

Augment SSRI or Switch to Venlafaxine?

- N=53 elderly subjects who failed paroxetine trial + IPT
- treated with augmentation (buproprion vs nortriptyline vs lithium) vs N=9 subjects who failed paroxetine + IPT +/- augmentation trials treated with switch (venlafaxine XR)
- Results:
  - Responses for augmentation of paroxetine 40 mg/d:
    - Bupropion (50 – 450 mg/d): 45%
    - Nortriptyline (80 – 120 ng/ml): 31%
    - Lithium (0.5 – 0.7 meq/l): 43%
  - Responses for switch to venlafaxine (37.5 – 300 mg/d): 42%

Whyte et al. J Clin Psych 2004;65:1634-41.

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 and 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).

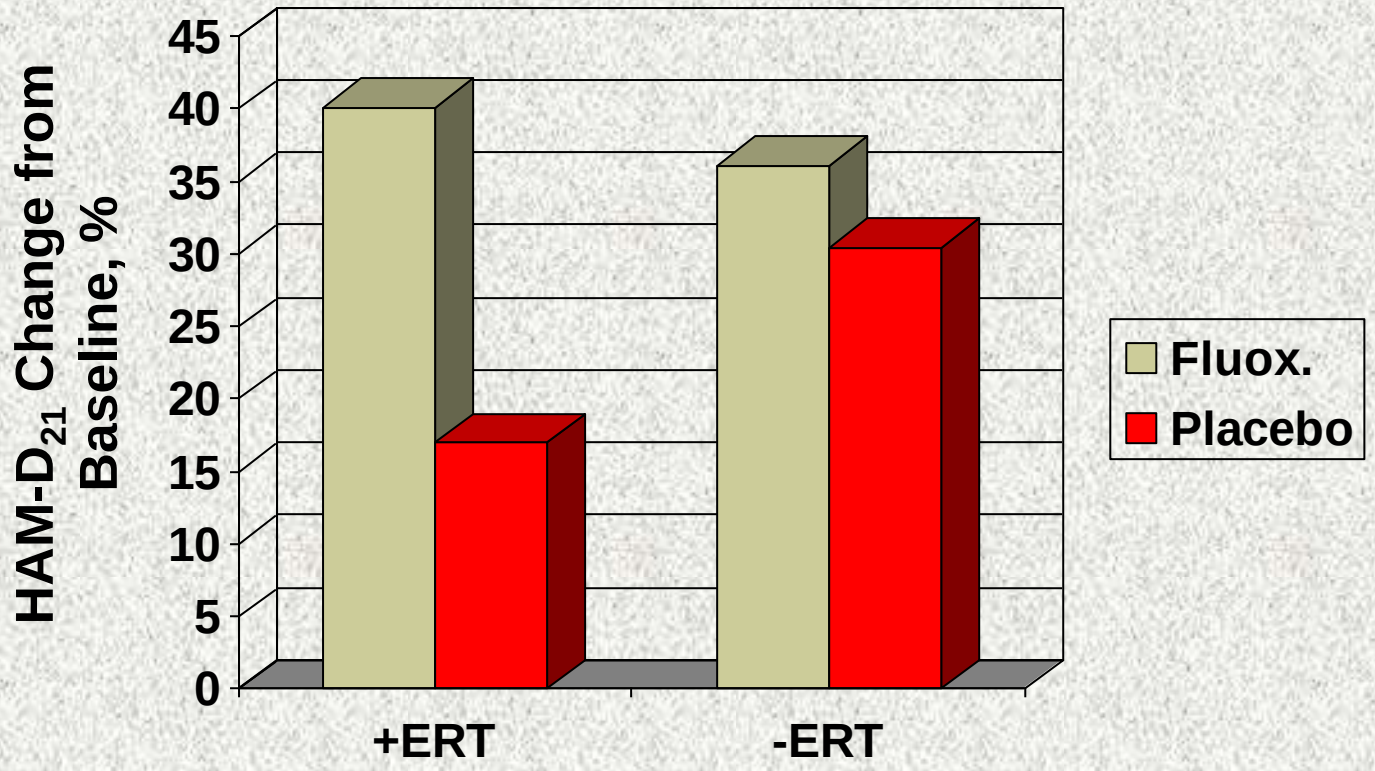
Estrogen Replacement Therapy and Response to Fluoxetine

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

- **Compared the response of 72 elderly depressed women outpatients (DSM-III-R, $HAMD_{17}$ 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)

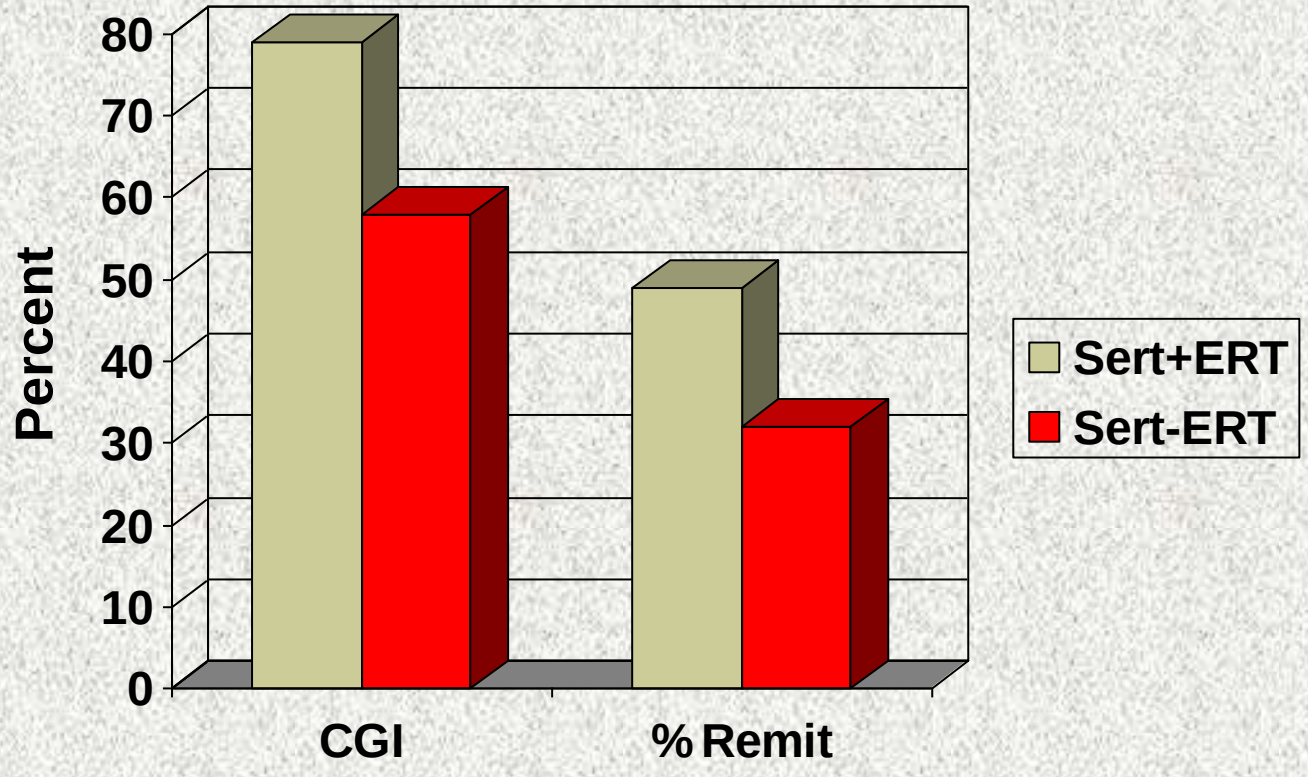
Estrogen Replacement Therapy and Response to Sertraline

(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_{17} ≤ 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

Testosterone

- Low total testosterone level predicts higher incidence of depressive illness among older men (enhanced with comorbid medical morbidity).[1]
- One RCT found testosterone = placebo in older hypogonadal men[2], while others have supported testosterone therapy3 or coadministration[4] including in SSRI-resistant hypogonadal[5] men
- Prescreen: Contraindicated with prostate cancer, may cause hepatotoxicity and other adverse effects.

1. Shores MM et al .J Clin Psychiatry 2005;66:7-14; 2 .Seidman SN et al: J Clin Psych 2001;62:406-12; 3 .Rabkin JG et al. Arch Gen Psych 2000;57:141-7; 4. Pope HG Jr et al .Am J Psych 2003;160:105-11; 5. Seidman SN et al. J Affect Disord 1998;4:157-161.

*

Electroconvulsive Therapy

- Underused modality, especially suitable with:
  - Antidepressant intolerance or non-response
  - Prior positive response to ECT
  - Delusions
  - Catatonia
  - Bipolar states
  - Emergency
- High response rates documented[1]

1. Seiner and Henry 2003

*

ECT and Medical Status Concerns

- **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[1]

1. APA Task Force 2001

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ECT and Memory Loss

- A major concern of patients and families
- ECT may improve depression-impaired cognition but exacerbate impaired cognition of dementia
- Preparation should include:
  - Psychoeducation of patient/family
  - Pre-screening of memory to establish baseline
  - Monitoring of memory throughout treatment course
  - Decreased treatment frequency when memory disturbance is pronounced
  - Use of unilateral treatment when reasonable

Depression/Exec Dysfunction: Different Approach to Treatment?

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

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

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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 in developing alternate approaches[1,2]
- D_3 agonists, modafinil, other novel agents may be of interest

1. Alexopoulos et al. 2000; 2. Alexopoulos 2001

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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[1]
- 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[2]
- In 12 wk RCT, n=22 outpatients with DSMIV AD & Depression, **sertraline** 150 mg/d max showed CSDD but not HAMD effect vs placebo[3]

1. Roth et al. 1996; 2. Nyth et al. 1992; 3. Lyketsos et al. 2000

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[1]
  - Atypicals vs typicals? Two positive delusional depression treatment studies support use of olanzapine in younger adults – no evidence base in older adults.

1. Alexopoulos et al: J Clin Psychiatry 2004;65 Suppl 2:5-99

*

Tardive Dyskinesia: Rates in Adult vs. Elderly

- Conventional Antipsychotic Medications[1,2] :
  - Year 1: Adult 5% Elderly 33%
  - Year 2: Adult 10% Elderly 50%
  - Year 3: Adult 15% Elderly 60%
- Atypical Antipsychotic Medications[3,4]
  - Year 1 Adult: 0.3-0.6%
  - Year 1 Elderly: 2.6%

1. Kane 1988; 2. Jeste 1999; 3. Csemansky 2002; 4. Jeste 2000

*

Anxiety Symptoms Are Highly Prevalent in Late Life

- 10-20% of adults over 65 show clinically significant new or recurring anxiety symptoms[1]
- 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

[1]Himmelfarb, Murrell. J Psychol. 1984;159-167.

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[1]
- Initial insomnia, fear, loss of confidence more typical of anxiety[2]
- Anxiety is often associated with depression in the elderly[3]

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.
- The following antidepressants 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

*

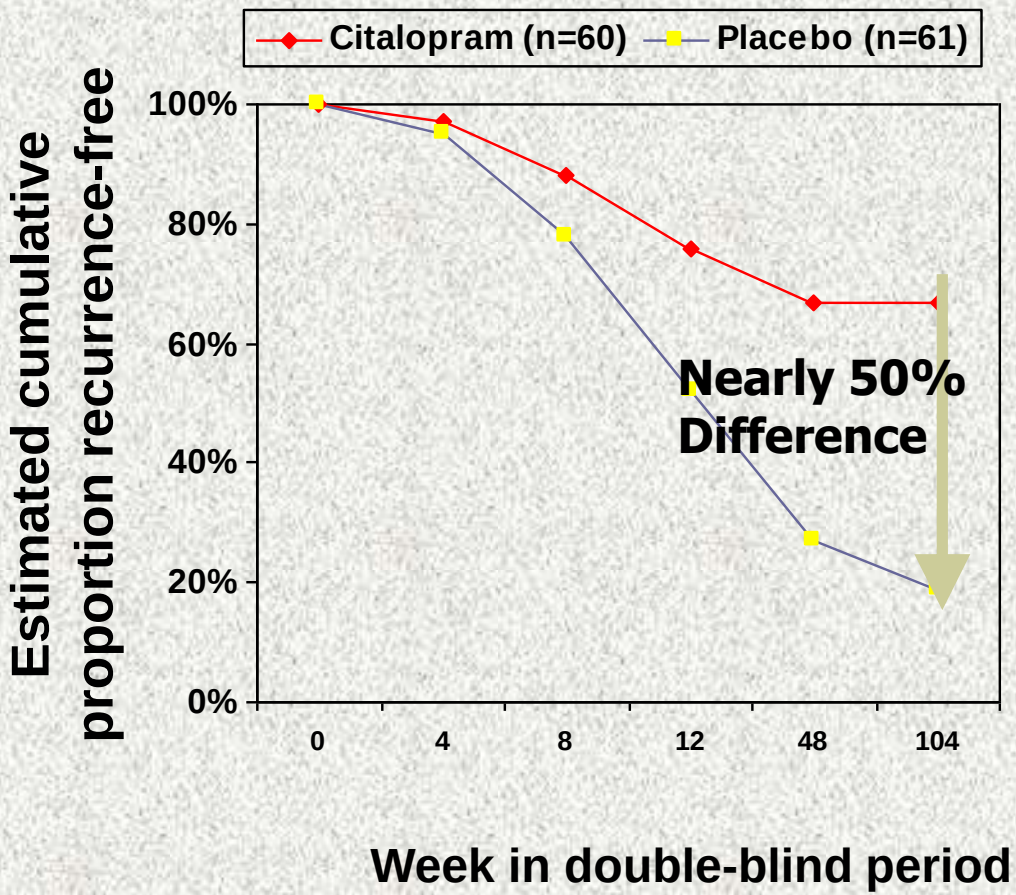
Maintenance Treatment: What do Experts Recommend?

- 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 ≥ 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



Klysner R, et al. *Br J Psychiatry.* 2002;181:29-35.

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

Mueller et al 2000

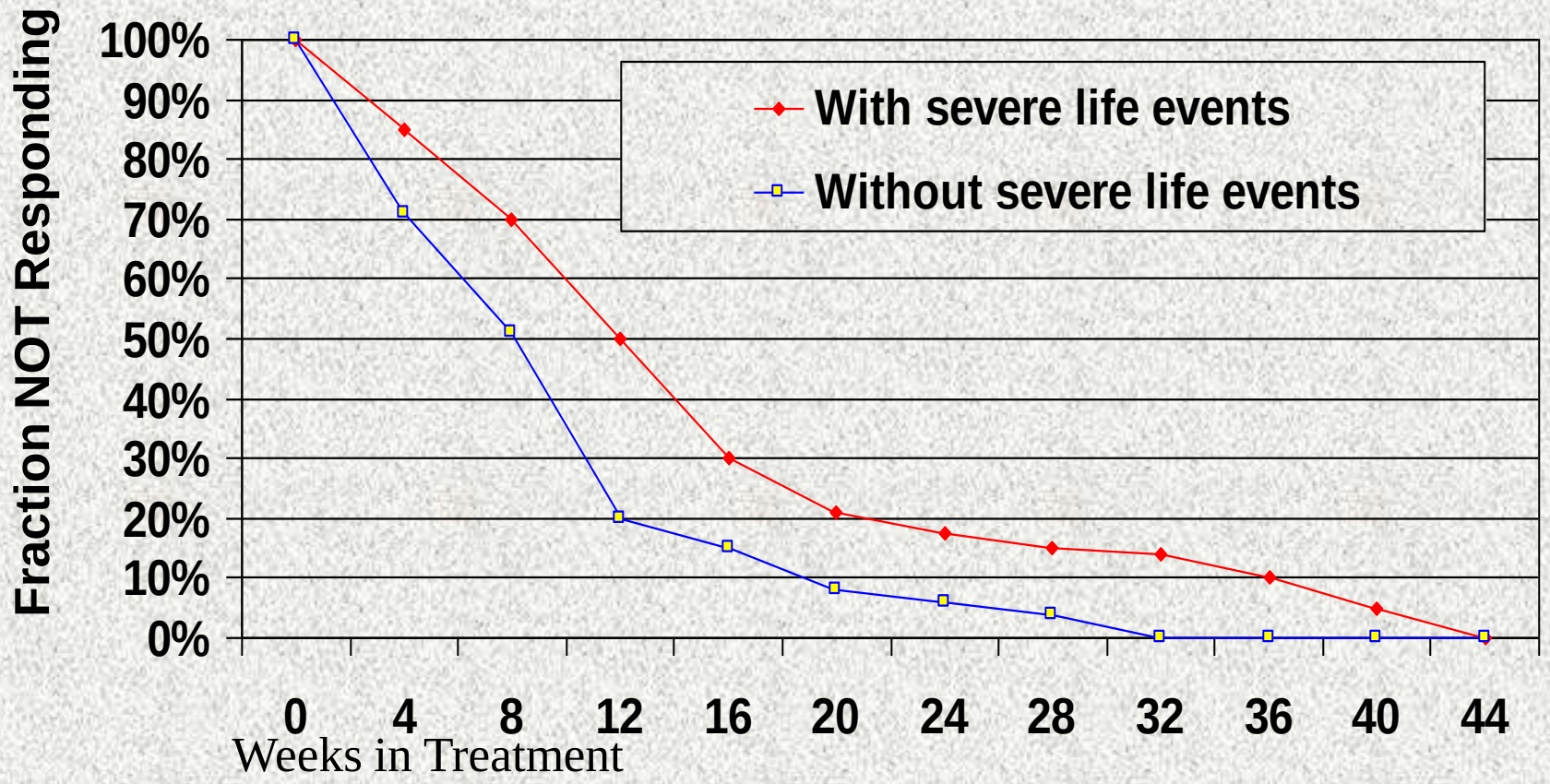
Suggestions to Improve Adherence for Treatment of Geriatric Depression/Anxiety

- 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

Wetherell JL, Unutzer J. *CNS Spectr.* 2003;8(12 suppl 3):48-59.

Importance of Recognizing Significant Psychosocial Factors:

Effect of Severe Life Event on Time to Response in Elderly Depressed Patients



Adapted from Karp et al. 1993

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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.