Pharmacologic Treatment of Depression

Linda Sobeski Farho, PharmD, BCPS
Assistant Professor, Pharmacy Practice
UNMC College of Pharmacy

Critical Issues in Geriatrics
June 24, 2010
Disclosure

- I have no conflicts or commercial interests related to this presentation
Objectives

1. Describe the common pharmacologic agents used to manage depression in the elderly population.

2. Discuss the efficacy, safety and tolerability of common pharmacologic agents used to manage depression in the elderly.

3. Examine the appropriate selection of antidepressant therapy for an elderly patient with specific symptoms and/or co-morbidities.
Goals of AD Therapy in the Elderly

- Symptom improvement
- Therapeutic response (50% decrease in symptoms)
- Therapeutic remission (asymptomatic)
- Reduction in disability
- Improved functional status
- Improved quality of life

Complications:
- **Relapse:** ↑ in symptoms within 6 months of remission
- **Recurrence:** new episode >6 months after remission
- **Resistance:** no to partial response to trial of 2 or more antidepressants

Pharmacology

- Biochemical theory
- Antidepressant drugs work by:
  - Increasing serotonin
  - Increasing norepinephrine
  - Increasing both
Influence of Age on AD Therapy

- Altered drug pharmacokinetics:
  - Decreased rates of drug absorption and onset of action
  - Increased elimination half-life of drugs
  - Alterations in plasma protein binding
  - Variable decrease in hepatic clearance
  - Decreased renal clearance of active metabolites

Influence of Age on AD Therapy

- Altered receptor sensitivity or neurotransmission:
  - Decreased baroreceptor reflex
  - Increased serotonergic extrapyramidal effects
  - Increased incidence of SIADH
  - ↑ Noradrenergic effects of medication
  - ↑Anti-adrenergic effects of medication
  - ↑Anticholinergic effects of medication

Principles of Drug Selection

- Changes in pharmacokinetics and pharmacodynamics
- Comorbid medical and psychiatric conditions
- Concomitant drug therapy
- Expected side-effect profile
- Previous response to therapy (if known)
- Cost of therapy or formulary restrictions
Special Considerations in the Elderly

- All antidepressants are equally efficacious
- SSRIs are first line due to improved tolerability
- Start low and go slow
- Dose adjustment in renal impairment: mirtazapine
- Fewer drug interactions with:
  - Citalopram, escitalopram, sertraline, venlafaxine, mirtazapine
- Compliance may be difficult to achieve
- Response time may be longer in elderly: >6-12 weeks
- Higher risk of relapse in elderly: continue >2 years after remission
Pre-Pharmacotherapy Evaluation

- History and physical
- Blood pressure (include orthostatic measurements)
- Liver and renal studies
- Electrocardiographic findings
  - Left bundle branch block, bifascicular block, second-degree AV block, QT prolongation, atrial fibrillation
### Medications Associated with Depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Agents</td>
<td>Benzodiazepines, alcohol, levodopa, amantandine, major tranquilizers, stimulants (rebound)</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>β-blockers, clonidine, methyldopa, prazosin, digitalis, procainamide, thiazides, hydralazine</td>
</tr>
<tr>
<td>Chemotherapeutics</td>
<td>Vincristine, vinblastine, L-asparaginase, azathioprine, bleomycin, cisplatin, cyclophosphamide interferon, tamoxifin</td>
</tr>
<tr>
<td>Steroids</td>
<td>Prednisone, estrogen agents</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Primidone, phenytoin, phenobarbital, carbamazepine, ethosuximide</td>
</tr>
<tr>
<td>Others</td>
<td>Cimetidine, non-steroidal anti-inflammatory agents (NSAIDs), disulfiram, phenylephrine</td>
</tr>
</tbody>
</table>

## Drug Classes for Depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI s</td>
<td>fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine</td>
</tr>
<tr>
<td>SNRI s</td>
<td>venlafaxine, desvenlafaxine, duloxetine</td>
</tr>
<tr>
<td>TCAs</td>
<td>Tertiary amines: amitriptyline, doxepin, imipramine, Secondary amines: desipramine, nortriptyline</td>
</tr>
<tr>
<td>MAOIs</td>
<td>phenelzine, tranylcypromine, selegiline</td>
</tr>
<tr>
<td>Others</td>
<td>mirtazapine, bupropion</td>
</tr>
</tbody>
</table>
Selective Serotonin Reuptake Inhibitors

- First-line therapy due to safety and tolerability
  - Low potential for fatal overdose
  - Low incidence of anticholinergic and sedative effects
  - Little to no influence on cognition
  - Few adverse cardiovascular side effects
- Once daily dosing
- Effective for mood and anxiety
- Common adverse effects:
  - Nausea (slow titration, take with food)
  - Diarrhea
  - Anxiety
  - Sleep disturbance
  - Headache
  - Sexual dysfunction (15-30%)
Other ADEs of SSRIs in Elderly

- Platelet dysfunction and gastrointestinal bleeding
- Apathy
- Anorexia
- Extrapyramidal symptoms
- Hyponatremia and SIADH (12-25%)
- Serotonin syndrome
  - TCAs, MAOIs, tramadol, dextromethorphan, meperidine

### SSRIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>10-60</td>
<td>Long half-life, once weekly dose available; many drug interactions; insomnia, wt loss, agitation, EPS; available in liquid; Beers list</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-200</td>
<td>Insomnia, EPS</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100-300</td>
<td>Many drug interactions; anticholinergic effects, wt loss; less sexual dysfunction</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20-60</td>
<td>Available in liquid; less EPS/bleeding risk</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10-20</td>
<td>Limited dosing range</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-50</td>
<td>Many drug interactions; anticholinergic effects (dose dependent), EPS, sedation; available in liquid; withdrawal symptoms common</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Selective Serotonin/NE Reuptake Inhibitors

- First or second-line therapy
- Dual mechanism
- Effective for mood and anxiety
- May be useful in treatment resistant depression
- Risk of serotonin syndrome combined with certain drugs
- Common adverse effects:
  - Nausea
  - Irritability
  - Insomnia
  - Sexual dysfunction
  - Tremor
SNRIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>venlafaxine</td>
<td>75-225</td>
<td>Dose dependent hypertension; available in XR</td>
</tr>
<tr>
<td>duloxetine</td>
<td>20-60</td>
<td>Many drug interactions; FDA: peripheral neuropathy</td>
</tr>
</tbody>
</table>


Tricyclic Antidepressants (TCAs)

- Effective and inexpensive
- Beneficial in neuropathic pain
- Poorly tolerated in elderly due to extensive ADEs
- NOT first line therapy
- High fatality risk with overdose (cardiotoxicity)
- Common adverse effects:
  - Sedation
  - Cardiac conduction abnormalities
  - Decreased seizure threshold
  - Anticholinergic effects
  - Orthostasis
  - Confusion
  - Weight gain
TCAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>100-200</td>
<td>Less anticholinergic effect, less sedation</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>75-125</td>
<td>Less anticholinergic effect, less orthostasis</td>
</tr>
</tbody>
</table>


Unutzer J. Late-life depression. NEJM 2007;357;2269-2276.
Monoamine Oxidase Inhibitors

- Tranylcypromine, phenelzine, selegiline
- Side effect profile limits use in older adults
- Numerous drug-drug and drug food interactions
  - Must comply with tyramine-free diet
    - No diet restriction with selegiline at lower doses
  - Meperidine, narcotics, decongestants
- Reserved for treatment resistant depression (3rd line)
- Prescriber should be experienced with MAO-I use
- Adverse effects:
  - Orthostasis
Bupropion

- ↑ Activity of dopamine and NE
- Generally safe and well-tolerated
- Dosage range: 200-300mg/d
- Available in SR and XL forms
- Useful in patients with lethargy, sedation, fatigue
- May be helpful in smoking cessation
- Lacks sexual side effects and weight gain
- Low risk of overdose
- Adverse effects:
  - Seizures
  - Irritability, anxiety, agitation
  - Insomnia
  - GI symptoms
Mirtazapine

- Serotonergic at low doses; noradrenergic at higher doses
- Dosage range: 15-45mg/HS
- Available in sublingual form
- Lacks sexual side effects
- Lacks significant drug interactions
- Low doses (<30mg): sedation & appetite stimulation
- Clearance reduced in renal impairment
Trazodone

- Not recommended as a primary antidepressant
- Adverse effects:
  - Sedation
  - Orthostasis
  - Priapism (rare)
- Low doses (25-50mg/HS) may be useful for insomnia
Stimulants

- Methylphenidate, dexamphetamine, modafinil
- Data suggest usefulness in specific patient groups
  - Terminally ill patients
  - Medically ill elderly patients
  - Apathy
- Potential advantages:
  - Accelerated response
  - Energizing effect
- **Adverse effects:** insomnia, anxiety, tachycardia, hypertension, tremor, HA, anorexia, wt loss, GI disturbances

# Target Sx and Comorbidity Considerations

<table>
<thead>
<tr>
<th>Symptom/Comorbidity</th>
<th>Drug Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>SSRI or SNRI</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Bupropion or stimulants (methylphenidate)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>BPH</td>
<td>Avoid TCAs</td>
</tr>
<tr>
<td>Dementia</td>
<td>SSRIs or venlafaxine; avoid TCAs and paroxetine</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Venlafaxine, bupropion; avoid TCAs, MAOIs, possibly SSRIs (if with MAOB-I)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>Avoid bupropion, TCAs</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>SSRI, bupropion; avoid TCAs, SSRIs + Ic antiarrhythmics, venlafaxine in HTN</td>
</tr>
</tbody>
</table>
Cost Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>$4</th>
<th>Geriatric Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Yes</td>
<td>Y</td>
<td>Long half-life, drug interactions</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Yes</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Yes</td>
<td>Y</td>
<td>Drug interactions, ADEs</td>
</tr>
<tr>
<td><strong>Citalopram</strong></td>
<td>Yes</td>
<td>Y</td>
<td><strong>Well tolerated</strong></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>No</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Yes</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>No</td>
<td>N</td>
<td>Indication for neuropathic pain</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>No</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Yes</td>
<td>N</td>
<td>Sedation, weight gain</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Yes</td>
<td>N</td>
<td>Seizure risk</td>
</tr>
</tbody>
</table>
Medication Adherence

- Non-adherence rate is as high as 40-75%
- Factors associated with non-adherence
  - Attitudes, perceptions, preferences
  - Beliefs about etiology of depression/treatment
  - Patient/provider communication
  - Cognitive impairment
  - Substance abuse
  - Polypharmacy
  - Cost of treatment
  - Social support
  - Gender/race

Patient Aversion to AD Therapy

- Fear of dependence
- Resistance to viewing depressive symptoms as a medical illness
- Concern that antidepressants will prevent natural sadness
- Prior negative experiences with medications for depressions

Neutraceuticals for Depression

- St. John’s Wort
- American ginseng
- Siberian ginseng
- Gotu kola
- Lavendar
- Schisandra
- Ginkgo biloba
St. John’s Wort

- Hypericin inhibits monoamine oxidase
- Hypericin and hyperforin inhibit serotonin reuptake
- Effective in mild to moderate depression
- Numerous drug interactions
  - ↓ Drug levels of: statins, TCAs, warfarin, nifedipine, cyclosporine, oral contraceptives, protease inhibitors, theophylline, digoxin
  - ↑ Drug effect of: beta-2 agonists, benzodiazepines, SSRIs
- Phototoxicity
Pharmacotherapy is effective in treating depression in older adults

Goals of therapy are to achieve remission, improve functional status, and improve quality of life

Drug selection in the older population is largely based on pharmacokinetics/pharmacodynamics, co-morbid conditions, concomitant drug therapy, drug side effect profiles, previous response to therapy, and cost
# Trade Name Conversion

<table>
<thead>
<tr>
<th>Drug (Trade)</th>
<th>Drug (Trade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Amitriptyline (Elavil)</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>Nortriptyline (Pamelor)</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>Desipramine (Norpramin)</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>Doxepin (Sinequan, Adapin)</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>Imipramine (Tofranil)</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>Clomipramine (Anafranil)</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Phenelzine (Nardil)</td>
</tr>
<tr>
<td>Desvenlafaxine (Pristiq)</td>
<td>Tranylcypromine (Parnate)</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>Selegilene (Emsam)</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>Methylphenidate (Ritalin and others)</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td></td>
</tr>
<tr>
<td>Nefazodone (Serzone)</td>
<td></td>
</tr>
</tbody>
</table>
Questions