TREATMENT OF DEPRESSION IN LATE LIFE

Robert Kohn, MD
WHY TREAT ELDERLY PERSONS

- Major depression is not a normal part of aging
  - The rates are lower than younger cohorts
  - The prevalence rates are still high
  - Females are at markedly higher risk than males
# NCS-R DSM-IV

12-MONTH PREVALENCE (%)

<table>
<thead>
<tr>
<th></th>
<th>18 - 44</th>
<th>45 - 64</th>
<th>65+</th>
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</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>8.2</td>
<td>6.5</td>
<td>2.3</td>
<td>3.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1.5</td>
<td>1.9</td>
<td>0.5</td>
<td>0.5</td>
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</tr>
<tr>
<td>Bipolar I &amp; Bipolar II</td>
<td>1.9</td>
<td>1.2</td>
<td>0.2</td>
<td>0.4</td>
<td>0</td>
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Gum, King-Kallimanis, Kohn 2009
### NCS-R DSM-IV

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Gum, King-Kallimanis, Kohn 2009
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Gum, King-Kallimanis, Kohn 2009
WHY TREAT THE ELDERLY

- Very painful for the patient
  - They are truly suffering
    - High risk of suicide
    - Among all individuals in the world it is the fourth leading cause of disability
    - Among all disorders it across the age spectrum it results in the most years lived with disability
SUICIDE BY AGE USA 2000-2004

The graph shows the rate of suicide by age group in the USA from 2000 to 2004. The x-axis represents age groups, and the y-axis represents the number of suicides per 100,000 people. The graph includes data for both males and females, with different lines representing each gender.
LETHALITY IS EXPONENTIAL

Friedmann & Kohn, 2008
DALYS AND YLD

- Among all individuals in the world it is the fourth leading cause of disability
  - Among all disorders it across the age spectrum it results in the most years lived with disability
THE AMERICAS (AMRO) PERCENT TOTAL DALYS, 2004
THE AMERICAS (AMRO) PERCENT TOTAL YLD, 2004

- Neuropsychiatric; 41%
- Musculoskeletal diseases; 5%
- Injuries; 9%
- Diabetes mellitus; 3%
- Cardiovascular diseases; 4%
- Sense organ disease; 10%
- Respiratory diseases; 7%
- HIV/AIDS; 0%
- Infectious diseases; 3%

- Unipolar depressive disorders; 14%
- Bipolar disorder; 2%
- Schizophrenia; 3%
- Epilepsy; 1%
- Parkinson disease; 0%
- Alcohol use disorders; 6%
- Alz & other dementias; 2%
- Multiple sclerosis; 0%
- Drug use disorders; 3%
- Post-traumatic stress; 1%
- Obsessive compulsive; 1%
- Panic disorder; 1%
- Insomnia (primary); 1%
- Migraine; 2%
- Mental retard, lead-caused; 2%
- Other neuropsych; 2%
DALYS AND YLD

- Major depression in those over 60 though only accounts 1.7% of DALYS and 1.3% of YLD
  - The low percent of DALYS and YLD in older age is misleading
    - Most people developing major depression when they are young
    - Physical health problems having a prominent role with age
WHY TREAT THE ELDERLY

- Compromises other medical problems
WHY TREAT THE ELDERLY

- Treatable, controllable, and preventable
  - Most people are easy to treat
COLLABORATIVE DEPRESSION STUDY (CDS) ADVANTAGES

- Systematic assessment
- Up to 15 years of follow-up
- Frequent short interval prospective interviews

Muller, Kohn, Leventhal et al. 2004
COLLABORATIVE DEPRESSION STUDY (CDS) METHODS (CONTINUED)

- **Statistical Methods**
  - Outcomes of Interest
    - Time to recovery from intake
    - Time to recurrence to major depressive episode
      - Survival Analysis, Kaplan Meier product limit
      - Predictor analysis for recovery and recurrence
        - Cox regression

- **Sample Size**
  - 32 = Age 65 and older
  - 399 = Age 64 and younger

Muller, Kohn, Leventhal et al. 2004
MEDIAN TIME TO RECOVERY

Time Until Recovery

Muller, Kohn, Leventhal et al. 2004
MEDIAN TIME TO FIRST RECURRENCE

Muller, Kohn, Leventhal et al. 2004
Summary

- Elderly had a similar MDD course of recovery.
- Elderly more likely to experience recurrence after controlling for demographic and clinical factors.
- Baseline severity of depression played less of a role for the elderly, and not a good predictor.
- Primary or secondary depression played less of a role for the elderly.
- Mortality rate during 15 years for the elderly was high 50%.
- Risk of suicide remained high in the elderly.
- Medical problems not a good predictor.

Muller, Kohn, Leventhal et al. 2004
# PHARMOKINETIC CHANGES IN LATE LIFE

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Decreases in passive absorption, saliva and gastric acid production, esophageal and gastrointestinal motility, intestinal blood flow and gastric and intestinal villous surface area: overall decreased rates of drug absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Increase in total body fat and decreases in lean body mass and total and extracellular water volumes: increased elimination half-life of antidepressants (since they are fat soluble) Increase in α1-acid glycoprotein: decreased free concentrations of tricyclic antidepressants Decrease in albumin: increased free concentrations of selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Decreases in hepatic blood flow, liver mass and high-throughput cytochrome P450 system: variable decrease in hepatic clearance</td>
</tr>
<tr>
<td>Excretion</td>
<td>Decreases in renal blood flow, glomerular filtration rate and tubular secretory capacity: decreased renal clearance of active metabolites</td>
</tr>
</tbody>
</table>

Rajji et al. 2008
PHARMACODYNAMIC CHANGES IN LATE LIFE

Age-related altered receptor sensitivity or cholinergic and monoaminergic neurotransmission can result in:

- Decreased baroreceptor reflex, resulting in increased susceptibility to blood pressure-lowering effect of some antidepressants
- Increased serotonergic-related extrapyramidal adverse effects
- Increased incidence of serotonergic-related syndrome of inappropriate antidiuretic hormone
- Increased noradrenergic (e.g. dry mouth, urinary retention, tachycardia, hypertension, tremor) and anti-adrenergic antidepressant effects (e.g. bradycardia, exacerbation of congestive heart failure, hypotension)
- Increased anticholinergic antidepressant effects of many antidepressants (e.g. constipation, urinary retention, delirium)

Rajji et al. 2008
TREATMENT PHASES OF MAJOR DEPRESSION

Fig. 1. Relationship between the treatment phases of major depressive disorder and the phases of the illness (modified from Kupfer[31] with permission). 1 = not including depressed mood or anhedonia; 2 = relapse and recurrence refer to the return of sufficient symptoms to fulfill criteria for a major depressive episode (MDE); the same index MDE in relapse vs a distinct MDE in recurrence.

Rajji et al. 2008
TREATMENT RESPONSE

- Age of onset does not influence rate of short or long term treatment response
  - Early onset major depression in the elderly may have a slower speed of remission
    - Due to higher number of previous episodes

- ECT response
  - Older age has a greater likelihood of achieving remission
ACUTE TREATMENT

- Acute trial 4 – 12 weeks
- Start with SSRI
  - Favorable adverse side effect profile
  - Limited drug-drug interaction
  - More likely to be tolerated at appropriate dosages
  - Less likely to be discontinued
- Goal is to achieve remission not just response
  - Residual symptoms are associated with
    - Functional impairment
    - Increased health care utilization
    - Decreased quality of life

Rajji et al. 2008
ACUTE TREATMENT

- Depressed elderly respond as well as mid-life depressed patients
  - Respond at a slower rate

Rajji et al. 2008
ACUTE TREATMENT

- A Meta-analysis of 90 RTCs
  - 40 published SSRI studies
  - 9 SNRI studies
  - 49 Heterocyclics
  - 8 MAOI
  - 3 Buprioprion
  - 3 Mirtazapine
  - 19 Agents not available in USA

Ellison et al. 2009
MAINTENANCE TREATMENT

- High rates of relapse and recurrence occur
  - Long term maintenance reduces relapse by 50%
  - Without continuation treatment the relapse rate in 4-6 months is about 50%
  - In absence of maintenance treatment, 30-90% who achieve recovery experience recurrence in 8 to 48 months

Rajji et al. 2008
MAINTENANCE TREATMENT

- It is argued that treating patients for only 6-12 months may not be optimal
- 4-6 months of continuation treatment is needed to consolidate remission and consolidate recovery
- Maintenance has been shown to be beneficial
  - Recurrent depression up to 3 years
  - Single episode up to 2 years

Rajji et al. 2008
NON-REMISSION

- Failure rate with SSRIs is up to 77%
- What to do
  - Augmentation
    - One study showed augmenting with buprioprion, lithium, or nortriptyline achieved only 40% remission
    - One study with aripiprazole 50% remission
  - Switch antidepressants
    - Best rates in studies are 50% remission
- Data is limited and results are not optimal

Rajji et al. 2008
ANTIDEPRESSANTS: TRICYCLICS

- Examples: Imipramine (Tofranil), Desipramine (Norpramin), Amitriptyline (Elavil), Nortriptyline (Pamelor)
- Anticholinergic
  - Constipation, dry mouth, blurred vision, weight gain, drowsiness, delirium
  - Theoretically could worsen dementia
- Orthostatic hypotension and risk for falls
- Arrhythmia and EKG changes
  - Increases QT interval
  - Contraindication Left Bundle Branch Block
- Lethal in overdose
- May be more effective than SSRIs
ANTIDEPRESSANTS: MONOAMINE OXIDASE INHIBITORS (MAOIS)

- Examples: Selegiline (Emsam - Patch), Phenelzine (Nardil), Tranylcypromine (Parnate)
- MAOI diet and limited medication regimen
  - Risk of hypertensive crisis
  - Tyramine free diet
  - SSRIs and antihistamines are contraindications
- Fluid retention
- Orthostatic hypotension and risk for falls
- Used when all else fails
  - Patient or caregiver must be reliable
  - Niche Dysthymia
ANTIDEPRESSANTS: SEROTONIN SELECTIVE REUPTAKE INHIBITORS (SSRIS)

- Examples: Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil), Citalopram (Celexa), Escitalopram (Lexapro)
- Safe in the elderly with minimal side effects
- Common side effects
  - Headaches, nausea, loose stools, sexual dysfunction, loss of appetite
- Easy to dose
- First line agents
ANTIDEPRESSANTS: OTHER NEW GENERATION AGENTS

- **NSRI**: Venlafaxine (Effexor), Duloxetine (Cymbalta), Desvenlafaxine (Pristiq)
  - Good next choice if SSRIs fail
  - Monitor for hypertension
  - Better relapse prevention
  - Neuropathic pain

- **Bupropion** (Wellbutrin or Zyban)
  - Used in augmentation strategies and bipolar depression
  - Quit smoking and treat depression
  - Low risk for sexual dysfunction
  - Increased risk for seizures
ANTIDEPRESSANTS: OTHER AGENTS COMMONLY USED

- **Nefazedone (Serzone)**
  - Touted for the anxiously depressed
  - Sedating
  - Wide dosing range
  - Monitor liver function, have been rare deaths (black box)

- **Mirtazepine (Remeron)**
  - Sedating and histaminic
  - May have a niche in augmentation strategies
  - Appetite stimulating

- **Trazodone (Desyrl)**
  - Most view it as a poor antidepressant in clinical practice
  - Great non-benzodiazepine sleeping aide
  - Useful in Alzheimer’s Disease management
# WHICH SSRI: PHARMACOKINETIC CONSIDERATIONS

<table>
<thead>
<tr>
<th></th>
<th>Celexa</th>
<th>Zoloft</th>
<th>Prozac</th>
<th>Paxil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>35 hours</td>
<td>26 hours</td>
<td>4-6 days</td>
<td>21 hours</td>
</tr>
<tr>
<td>Metabolite half-life</td>
<td>n/a</td>
<td>62-104 hours</td>
<td>4-16 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Metabolite activity</td>
<td>Less active</td>
<td>Less active</td>
<td>As potent</td>
<td>Less active</td>
</tr>
<tr>
<td>Pharmokinetics</td>
<td>Linear</td>
<td>Linear</td>
<td>Non-linear</td>
<td>Non-linear</td>
</tr>
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## WHICH SSRI: PHARMACOKINETIC CONSIDERATIONS P450 ACTIVITY

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<tr>
<td><strong>P450 3A4 inhibition</strong></td>
<td>Not likely to be clinically significant</td>
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</tr>
<tr>
<td><strong>P450 2D6 inhibition</strong></td>
<td>Weak inhibitory effect</td>
<td>Weak inhibitory effect</td>
<td>Inhibits activity</td>
<td>May have significant inhibitory activity</td>
</tr>
</tbody>
</table>
WHICH SSRI: SEROTONIN WITHDRAWAL SYMPTOMS

- Paxil: dizziness, 16%; paresthesia, 12%; lethargy, 12%; nausea, 6%; lowered mood, 2%; anxiety, 4%; vivid dreams, 4%; insomnia, 4%; movement related, 16%
- Zoloft: dizziness, 2.2%
- Prozac: none
DOSING ANTIDEPRESSANTS IN FRAIL ELDERLY

- In frail elderly start low and go slow
  - Increase once every week or two only if out patient
  - Monitor drug-drug interactions and side effects

- Administration
  - Prozac and Celexa have a liquid forms
  - May crush most
  - Effexor can pour capsule as pellets not capsule is time release
  - Remeron melt in your mouth soluble tablets

- If not frail may be more aggressive

- Do not under treat

- Do not wait weeks or months to adjust medications in symptomatic patients
DOSING ANTIDEPRESSANTS

- Get up to a therapeutic dose or what can be tolerated without significant side-effects
- A good drug trial is one that has achieved therapeutic dose and lasted at least 8 weeks
  - About 60-70% will respond
- Maintenance treatment
  - Severity of episode
  - Reoccurrence
TREATING CONCOMITANT PROBLEMS

Psychosis
- Use an antipsychotic
- Examples: Haldol, Risperdal, Zyprexa, Seroquel
  - Watch for TD and EPS
  - Avoid anticholinergic antipsychotics
  - Geodon increases QT interval
  - Parkinson’s syndrome Seroquel or Clozaril

Sleep and Anxiety
- May resolve with antidepressant treatment
- Sleep: Trazodone, Remeron, short acting benzodiazepine, Ambein, Sonata, Lunesta, Rozeram
- Benzodiazepine may be need for anxiety
  - Avoid if possible
  - Effexor and SSRIs are anxiolytics
TREATMENT RESISTANCE

- Try another class of antidepressant
- Augmentation
  - Lithium
    - Monitor levels
    - Caution in renal failure
    - Monitor for hypothyroidism
  - Second antidepressant
    - Remeron, Effexor, Wellbutrin
- Thyroid supplement
- ECT
There are no “absolute” medical contraindications to ECT

Conditions with increased risk

- Unstable or severe cardiovascular conditions
  - Recent myocardial infarction; Unstable angina; Poorly compensated congestive heart failure; Severe valvular cardiac diseases
- Aneurysm or vascular malformation that might be susceptible to rupture with increased blood pressure
- Increased intracranial pressure
  - Brain tumor; Other space occupying lesion
- Recent cerebral infarction
- Pulmonary conditions
  - Severe chronic obstructive pulmonary disease; Asthma; Pneumonia
- Patient status rated as ASA level 4 or 5
"Depression remains the most treatable psychiatric disorder of late life."