Geriatric Mood and Anxiety Disorders

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Normal Aging

• Ageism
• “Normal” Aging
Late-life stressors

- Physical Illness***
- Surgery, immobility
- Sensory deprivation
- Social isolation / Rejection
- Economic / Living Conditions
- Loss of significant other
- Retirement
Core symptoms + Physiological + Psychological

Psychological
- Hopelessness
- Helplessness
- Guilt
- Suicidal

Physiological
- Sleep
- Appetite
- Weight
- Energy
- Concentration

CORE SYMPTOMS
Depressed Mood or Lack of Interest & Pleasure

In older adults:
Less mood symptoms
Somatic symptoms
Agitation & Anxiety
Psychotic symptoms

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Depression & Psychosocial Disability

Asymptomatic Status  Subsyndromal Depressive Symptoms  Minor Depressive Disorders  Major Depressive Disorders

Psychosocial Disability & Global Functioning  Level of Depression

Global Functioning in Depression
1=very good, 2=good, 3=fair, 4=poor

Judd LL, Akiskal HS, et al. Psychosocial disability during the long-term course course of unipolar major depressive disorder. Arch Gen Psychiatry 2000;57:375-380
Depression in Older Adults
Epidemiology: Prevalance by Setting

<table>
<thead>
<tr>
<th>Setting</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>1-3%</td>
<td>15%</td>
</tr>
<tr>
<td>Primary care</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Medical / Surgical</td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td>Long Term Care</td>
<td>15%</td>
<td>30%</td>
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<tr>
<td></td>
<td>13% annual incidence of new episodes in nursing homes</td>
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</tbody>
</table>


Suicide Rate Increases with Age

U.S. Suicide Rates by Age, Gender, and Racial Group

Common in young people and elderly men.

Suicide Rate Per 100,000

Source: National Institute of Mental Health Data:
Centers for Disease Control & Prevention, National Center for Health Statistics
Natural history in the community
N=277 / 6 YEARS

- Syndromal depression is relatively rare but has the worst prognosis.
- Subsyndromal depression is common, serious and chronic in many cases, high risk of developing DSM affective disorders.
- Outcomes clear gradient: subthreshold disorders best outcome, followed by those with major depressive disorder, dysthymic disorder, and double depression.
- Symptom severity remains above the 85th percentile.
- Symptoms were short-lived in only 14%, remissions in 23%, an unfavorable but fluctuating course in 44%, and a severe chronic course in 32% (percentages do not total 100 because of rounding).

CONCLUSIONS:
The natural history of late-life depression in the community is poor.

The natural history of late-life depression: a 6-year prospective study in the community.
CUMULATIVE DURATION of depressions and hippocampal size


NO correlation with age or the number of depressives episodes

\[ R^2 = 0.36 \]
\[ p = 0.002 \]
Hippocampal Volumes

• Significantly reduced in the patients with MDD.

• Negative association with duration of the index episode & duration of illness

Hippocampal volume reduction and HPA-system activity in major depression.
Depression: A Risk for CAD & Stroke

- Depression and Heart Disease ¹
  - 13 prospective studies with structured assessments
  - 10 studies included samples of 1000 or more
  - 9 of 13 found that depression increased the risk

- Depression and Stroke ²
  - Prospective 6-year study of 10,294 elders

¹ Musselman DL et al. [Review:] Arch Gen Psychiatry. 1999.
Depression causes MI

13-Year Follow-up Study of 1551 Individuals in the ECA Study Without Cardiac Disease at the Outset

- Hypertension
- Male Gender
- Dysphoria
  - 2 weeks
- Major Depression

Odds Ratio

Achieving Remission:
When Are The Chances Greatest?

Keller et al, Arch Gen Psych, 1992; 49: 809-816
Depression is treatable.

- **Severe: Major depression:**
  - Use Meds / ECT.
  - treated successful in very old & early old. (1)

- **Advanced Minor Depression/Dysthymia:**
  - Use Meds
    - SSRI (Paroxetine) showed moderate benefit. (3)

- **Mild Minor Depression:**
  - May not need meds / High Placebo response.
    - SSRI (Paroxetine) not clearly superior to placebo...may help more severely ill patients (2)

Antidepressants are safe and effective in the treatment of late-life depression. (4)

WHY DO WE HAVE SO MUCH DIFFICULTY WITH TREATING THESE PEOPLE?
Complicated by:

- Attitude: “Depression is normal in old people”
- Pain, sleep, medications.
- Poor energy due to medical illness.
- Bereavement / Grief
- Dementia-like presentation superimposed on it

Leads to under-detection and under-treatment
Depression Presenting as Dementia

✓ Loses interest, social activity
✓ Exaggerates cognitive loss
✓ “Don’t know” answers
✓ Poor concentration
✓ Marked self-depreciating ideas
✓ Vegetative s/s, suicidal neglect
✓ Rapid onset?
✓ Past Hx of depression?

DO NOT BE FOOLED BY THE MMSE SCORE
Depression or Normal Grief?
Look at symptoms and course

Symptoms
- Motor Retardation
- Suicidal
- Worthlessness
- Sadness
- Sleep Problems
- Concentration

Course
- Bursts vs. enduring
- Triggered vs. autonomous
- Lessening vs. persistent

• Time since loss is NOT clinically useful

Depressed patients MUST be treated:
Medication + Psychotherapy
Major Depression in Older vs. Younger Adults

- Less: Gender difference
- More: Unipolar, less bipolar
- More: Recurrent, more chronic
- More: Melancholia (psychomotor changes, late insomnia, weight/appetite changes, marked guilt).
- More: Comorbidity (Alcohol, Medical)

Depression can be a risk factor for dementia

- Depressed elderly with cognitive impairment

  After antidepressant treatment

  - Do not regain normal cognition, particularly in memory and executive functions.

High risk of developing progressive dementia:
Must follow closely for dementia

Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, Reynolds CF 3rd.
Sleep and Depression

- Poor sleep → higher suicide risk.
- Fewer benzos used due to A/E's in all ages
- “Other” class drugs increase in use with severity: TCAs, MAOIs, Li+, mood stabilizers
- Trazodone & Nefazodone: sleep & anxiety
- Buspirone augmentation: helps some pts.

Sleep and Depression

• Sleep of chronic users of zopiclone is no better than that of drug-free patients with insomnia.

• 41% of patients treated pharmacologically for insomnia also had sleep apnea.


Sleep and sleep disorders in chronic users of zopiclone and drug-free insomniacs.
Factors related to sleep problems:
very old age, poor self-rated health, one or more chronic disease, nonpsychotropic drug use, hypnotic-sedative use, female gender, depression, pain.

• 1/3 have sleep problems. (1)
• Sleep problems and depression:
  Only 20% used antidepressants,
  but 46.2% used hypnotics-sedatives.
• Sleep problems and pain:
  63% used analgesics,
  but 47.0% used hypnotics-sedatives.
• Sleep hygiene: first-line therapy.
• Nonbenzodiazepine hypnotics, antidepressants, or antipsychotic may be needed. (2)

For Sedation:
• Trazodone: OK for sleep
• Mirtazapine
  ✓ Good antidepressant
• Seroquel
  ✓ Good antipsychotic


2) Schneider DL. Geriatrics 2002 May;57(5):24-6 Insomnia. Safe and effective therapy for sleep problems in the older patient.
PAIN

- **Chronic pain** (1)
  - osteoarthritis, low back pain, and neuropathy.
  - Effective pain management important.

- **Pain & Disability**: (2)
  - Degree of disability and illness attitudes pain and depression.
  - No direct relationship between pain and depression

MUST TREAT DISABILITY FROM ALL PAINFUL SYNDROMES.


2) Dickens C, Jayson M, Sutton C, Creed F
   - Psychosomatics 2000 Nov-Dec;41(6):490-9
Chronic Pain & Antidepressants

- Rx of chronic pain → multimodal approach
- ADs in low and therapeutic doses demonstrates similar response rates.
- TCAs (2 & 3 amines), SSRI/SNRIs and atypicals, all appear to show similar favorable response rates.


Low and therapeutic doses of antidepressants are associated with similar response in the context of multimodal treatment of pain.
Anxiety and Depression:

- Comorbid anxiety & MDD (moderate-severe) → higher suicide rates
- Type of depression associated with suicidal ideas is an agitated, irritable, and especially mentally overactive syndrome
- Clinically prudent to avoid the prescription of antidepressant monotherapy to such patients

Akiskal HS, Benazzi F. Does the FDA proposed list of possible correlates of suicidality associated with antidepressants apply to an adult private practice population? J Affect Disord. 2006 Aug;94(1-3):105-10. Epub 2006 Jun 12.
Greater use of atypicals in severe MDD

- Increase use severe depression
- “Atypical antidepressants”
- Severely ill ➔ agitated, suicidal, psychotic
- Manic or mixed states
- Lower switch rates vs. ADs
- Do they work quicker?
- Fewer available inpatient beds & services a factor.

Association Between Depression and Medical Illness

Depression is associated with disability caused by variety of diseases:

- **CNS:**
  - Stroke
  - Alzheimer’s disease
  - Parkinson disease

- **Cardiac:**
  - Myocardial infarction

- **Cancer**

- **Endocrine disorders**
  - Hypothyroidism
  - Diabetes
  - High level of glucocorticoids

- **Orthopedic:**
  - Hip fracture

- **Rheumatic:**
  - Arthritis

- **Pulmonary:**
  - COPD

- **Gastrointestinal**
  - IBS
• Placebo Trials:

  • The response to placebo in published trials of antidepressant medication for MDD is highly variable and often substantial and has increased significantly in recent years, as has the response to medication.

  **DRUGS: NECESSARY BUT NEVER SUFFICIENT ALONE!!**

  *Placebo response in studies of major depression: variable, substantial, and growing.*

  Walsh BT, Seidman SN, Sysko R, Gould M.
Teaching an old dog new tricks!
It may be difficult but it IS possible!

"Okay your father managed to get a mouse. Now how do we use it?"
Depression in the Elderly: Treatment Program

- Strong doctor-patient relationship
- Environmental, Social, Recreational, Supportive & Spiritual Interventions
- Psychoeducation
  - include Family
- Medication
  - Drug: TCAs, SSRIs & Novels
  - Dosage
  - Duration
- ECT for severe cases
Development of Antidepressant Treatment

- **1950**: TCA (Non-selective tricyclic AD)
- **1960**: MAOI (Mono-amine oxidase inhibitor)
- **1970**: SSRI (Selective serotonin re-uptake inhibitor)
- **1980**: SNRI (Serotonin noradrenaline re-uptake inhibitor)
- **1990**: NaSSA (Noradrenergic and specific serotonergic antidepressant)
- **2000**: Escitalopram, Duloxetine
Geriatrics and Depression
Selecting an antidepressant

- Severity of depression & Previous response
- Comorbid conditions / other medication
- Half-life / kinetics / dynamics
- Risk of overdose & drug interactions
- Tips:
  - Compliance
  - Avoid anticholinergic drugs
  - Avoid cardiotoxic drugs
Adverse Effects of Neurotransmitter Activity and Receptor Binding

- Sedation/drowsiness
  - Weight gain

- Psychomotor activation
  - Psychosis

- DA reuptake inhibition

- Sexual dysfunction
  - Activating side effects

- Blurred vision
  - Dry mouth
  - Constipation
  - Sinus tachycardia
  - Urinary retention
  - Memory dysfunction

- ACh block

- 5HT2 Stimulation

- 5-HT3 Stimulation

- 5-HT reuptake inhibition

- NE reuptake inhibition

- Postural hypotension
  - Dizziness
  - Reflex tachycardia

- Alpha1 block

- Alpha2 block

- Nausea

- GI disturbances
  - Activating effects

- Priapism

- Dry mouth
  - Urinary retention
  - Activating effects
  - Tremor

Adapted from Richelson E. Current Psychiatric Therapy. 1993;232-239
SSRIs compared in older patients

CONCLUSIONS:

• Efficacy is about the same for all SSRIs.
  Also for depression secondary to stroke or dementia and those with other comorbid physical disorders.

• Distinguishing features may influence the choice of agent.


SSRIs in Depression plus Dementia

Citalopram vs Placebo

Change in GBS Rating¹ (Baseline to Week 4)

* P < 0.005  ** P < 0.01 (within groups)
† P < 0.05   Δ P < 0.01 (between groups)

¹ GBS = Gottfries-Brane-Steen Dementia Rating Scale
Nyth and Gottfries, Br. J. Psychiatry 1990; 157: 894-901
Comparative Remission Analysis by Age: Venlafaxine/Venlafaxine XR vs. SSRIs*

Remission=HAMD-17 ≤7

Women <50 Years of Age (week 8)

Women ≥50 Years of Age (week 8)

*SSRIs=fluoxetine, fluvoxamine, and paroxetine.
†P≤0.05 drug vs. placebo. ‡P≤0.05 VEN vs. SSRI.
Thase M, et al. Poster presented at: First World Congress on Women’s Mental Health; March 2001; Berlin, Germany.
# Neurotransmitters, Receptors and Their Clinical Relevance

<table>
<thead>
<tr>
<th>Neurotransmitter system</th>
<th>Receptor action</th>
<th>SEROTONIN</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt; Stimulation</td>
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<tr>
<td>Clinically relevant effects</td>
<td>Antidepressant effect</td>
<td>Serotonergic adverse events</td>
</tr>
<tr>
<td>Type of adverse effects</td>
<td>Anxiolytic effect</td>
<td>Agitation</td>
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<tr>
<td></td>
<td></td>
<td>Nervousness</td>
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<td></td>
<td></td>
<td>Insomnia</td>
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Adapted from: Richelson, 1994; Dubovsky, 1995

Sleep & Anxiety Improved with block
Mirtazapine vs. Venlafaxine in Sleep Improvement

(HAMD-17 Sleep Disturbance; LOCF)

Venlafaxine (n=79)

Mirtazapine (n=78)

*p < 0.05

Guelfi, 2001
Mirtazapine vs. Venlafaxine

Conclusions: Tolerability

- More patients dropped out due to adverse events in the venlafaxine group (statistically significant difference)

- The main differences in side-effect profile were:
  - More weight gain on mirtazapine
  - More nausea, constipation, dizziness, increased sweating and weight loss on venlafaxine
Efficacy in Long-Term Treatment
Sustained Response (HAMD ≤ 7); Mean Duration 2 Years

- **Mirtazapine** (n=74)
  - 20 Weeks: 72%
  - Endpoint: 77%

- **Amitriptyline** (n=86)
  - 20 Weeks: 62%
  - Endpoint: 57%

- **Placebo** (n=57)
  - 20 Weeks: 44%
  - Endpoint: 44%

* Mirtazapine or amitriptyline better than placebo (p<0.05), pairwise x²-test.
† Mirtazapine better than amitriptyline (p<0.05), pairwise x²-test.

Montgomery et al., 1998
Newer Antidepressants and CYP 450 System

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>1A2</th>
<th>2C19</th>
<th>2D6</th>
<th>3A3/4</th>
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<tbody>
<tr>
<td>Citalopram</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>Venlafaxine</td>
<td>0.8</td>
<td>0.8</td>
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<tr>
<td>Wellbutrin</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>Sertraline</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td>Paroxetine</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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</tbody>
</table>

CYP 450 Enzymes: 1A2, 2C19, 2D6, 3A3/4
SSRIs & P450

- **2D6:** Blocks pain relief of codeine & raise its level.
- **3A4:** Caution with terfenadine, astemizole, cisapride some benzos (triazolam / alprazolam), carbamazepine, propranolol,
- **1A2:** Caution theophylline, clozapine
- **2C9/10, 2C19:** fluoxetine + phenytoin
  sertraline + tolbutamide
  fluvoxamine + warfarin
SSRIs

- Tricyclics: increase [TCA] 2D6
- Alprazolam: increased with fluoxetine, nefazodone, fluvoxamine
- Warfarin: increase with fluvoxamine
- MAOIs & St. John’s Wart: Serotonin Syndrome
- Phenytoin: increases with SSRI
- Carbamazepine: increase with fluoxetine & fluvoxamine
- Phenobarbital: Decrease [SSRI]
- Theophylline & cimetidine: increase [SSRI]
### Neurotransmitters, Receptors and Their Clinical Relevance

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<td>Nausea</td>
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</tr>
<tr>
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<td>Nervousness</td>
<td>Vomiting</td>
<td>Headache</td>
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<td></td>
<td>Insomnia</td>
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<td></td>
<td>Sexual Dysfunction</td>
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Adapted from: Richelson, 1994; Dubovsky, 1995

- **Sleep and anxiety improves**
- **Nausea improves**
### Effects of Antidepressants On Sleep

<table>
<thead>
<tr>
<th>Medicine</th>
<th>REM Time</th>
<th>REM Latency</th>
<th>Sleep Efficiency</th>
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</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>↓</td>
<td>↑</td>
<td>↓ or ↑</td>
</tr>
<tr>
<td>MAOIs</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SSRIs</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SNRIs</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>–↑</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>–↑</td>
<td>↑</td>
<td>↑</td>
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# Efficacy of Mirtazapine versus SSRIs and SNRI

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>VS. Fluoxetine</th>
<th>VS. Citalopram</th>
<th>VS. Paroxetine</th>
<th>VS. Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD-17 ≥ 21</td>
<td>HAMD-17 ≥ 22</td>
<td>HAMD-17 ≥ 18</td>
<td>HAMD-17 ≥ 25, with melancholic features</td>
<td></td>
</tr>
<tr>
<td>Patient Population at Start</td>
<td>in-+- out-patients</td>
<td>in-+- out-patients</td>
<td>in-+- out-patients</td>
<td>in-patients</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Overall Efficacy</td>
<td>M ≥ F</td>
<td>M ≥ C</td>
<td>M ≥ P</td>
<td>M = V</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>M &gt; F</td>
<td>M &gt; C</td>
<td>M &gt; P</td>
<td>M = V</td>
</tr>
</tbody>
</table>
Mirtazapine and Sleep

- Mirtazapine significantly improves the total sleep architecture by:
  - Increasing sleep stages 3 and 4
  - Increasing REM latency
  - Increasing sleep efficiency in total
  - ...by blocking 5 HT₂ postsynaptic receptor
  - ...initial and long effect on sleep improvement
Anticholinergic Drugs & Cognitive Impairment

- Serum anticholinergic activity (SAA) associated with frank delirium
  - N=201 community subjects: SAA & MMSE
  - 180 (89.6%) had SAA 0.50-5.70 pmol/mL
  - SAA >2.80 (90th Percentile) were 13x more likely to have MMSE <24 (10th Percentile)
  - Largest & first analysis of SAA to link to cognitive performance in community sample.

Confirms that SAA found in most older community samples & correlated with cognitive impairment

Sedative-hypnotic (SH) use of OTC meds: effects on cognition

- N=1627, age >65, 1987-1989, 10 year cohort
- Data: sleep meds, depressive S/S, sleep complaints & MMSE
- Age 73.4 to 80.5 yrs,
- 8.17% took sleep aid

Prescription sedative-hypnotics 1.8% to 3.1%, mostly benzodiazepines
OTC diphenhydramine 0.4-7.6%

Associated with cognitive impairment without dementia

### Common Drugs Potentially Worsening Cognition

<table>
<thead>
<tr>
<th></th>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anticholinergic</td>
<td>Lomotil, ditropan, detrol</td>
</tr>
<tr>
<td>2</td>
<td>Antidepressants</td>
<td>Elavil, sinequan, prozac, lithium</td>
</tr>
<tr>
<td>3</td>
<td>Antipsychotic</td>
<td>Haldol, stelazine, mellaril</td>
</tr>
<tr>
<td>4</td>
<td>Antihypertensives</td>
<td>Betablockers, alpha-antagonists, calcium channel</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>Cipro, flagyl, keflex</td>
</tr>
<tr>
<td>6</td>
<td>Anticonvulsants</td>
<td>Dilantin, tegretol, Velproic acid</td>
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<tr>
<td>7</td>
<td>Antiemetics</td>
<td>Antivert, phenergan, gravol</td>
</tr>
<tr>
<td>8</td>
<td>Antiparkinsonian</td>
<td>Cogentin, artane, sinemet, parlodel</td>
</tr>
<tr>
<td>9</td>
<td>Antihistamines</td>
<td>Benadryl, cough &amp; cold preparations (OTC)</td>
</tr>
<tr>
<td>10</td>
<td>Narcotics</td>
<td>Codeine, demerol, talwin</td>
</tr>
<tr>
<td>11</td>
<td>H₂ Receptor Antagonists</td>
<td>Cimetidine, ranitidine</td>
</tr>
<tr>
<td>12</td>
<td>NSAIDs</td>
<td>Motrin, naprosyn, indocid</td>
</tr>
<tr>
<td>13</td>
<td>Benzodiazepines</td>
<td>Valium, dalmene, ativan, halcion</td>
</tr>
</tbody>
</table>

AHCPR Clinical Practice Guidelines # 19 publication #97-0702
Washington – Dept. of Health and Wellness Services Nov 1956
Bezodiazepine Use in Elderly:

- The prevalence of benzodiazepine therapy for older people in Ontario has steadily declined between 1993 and 1998. There is a trend of dispensing relatively more short-acting than long-acting benzodiazepines and of replacing benzodiazepines with antidepressants in older people without a remarkable increase in barbiturate consumption. These findings suggest that, without undue regulation, physicians are making progress in the prescribing of benzodiazepine therapy on the basis of current knowledge available.

CONCLUSION:
Benzodiazepine use in Ontario for the elderly is decreasing.

Tu K, Mamdani MM, Hux JE, Tu JB
Antidepressant response in elderly

- Minor health / medical issues increase the severity of depression.

- BUT they do not interfere crucially with the efficacy of antidepressant

- Depression is similar in old age but recovery is slightly slower compared with younger individuals.

- Late-onset depression is associated with a positive outcome.

Importance of Mental Health

• Mental health is fundamental to health