Treatment Of Anxiety Disorders

Unique issues in Geriatrics
including use of Benzodiazepines.

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reduce psychic tension

Valium® (diazepam)
Learning Objectives

- Discuss the differential diagnosis of anxiety disorders in the elderly, including medical and psychiatric causes.
- Confidence in treating anxiety disorders, specifically in using benzodiazepines and other CNS-active medications.
Disorders presenting later in life are more likely to have contributing organic etiological factors, e.g. cerebrovascular disease and less likely to have a genetic loading.

Disorders may present atypically in elderly

Obsessive-compulsive disorders, hysteria, hypochondriasis, and conversion disorder do not come on *de novo* later in life.

Suspect underlying organic disease or other psychiatric disorder.
Epidemiology of Anxiety Disorders in the Elderly

- 6 month and lifetime prevalence
  - Decline from mid-life to old age
  - 19.7% at 6 months
  - 34.1% lifetime

- However, anxiety disorders are still the most prevalent mental health diagnoses in elders as in adults
  - Roughly 10%

- Untreated anxiety leads to higher medical and psychiatric morbidity in geriatric patients
Prevalence in the Elderly

- Prevalent in the elderly
  - Many studies note anxiety symptoms
    - 1-19% in community dwelling elderly
      - GAD 1-14%
      - Phobic disorders 0.7-7%
      - Panic disorder 0.1-1%
  - Anxiety leads to impairment in quality of life
    - Related to disability in some cases
      - Anxiety about existing disability
      - Anxiety can lead to disability
    - Steeper cognitive declines when anxiety untreated in dementia
      - Anxious people cannot focus or pay attention
How Common are Co-morbid Anxiety Disorders in Depressed Older People?

- N = 39 consecutive patients (mean age 78.1 yrs) with Major Depressive Disorder
- 12 (30.8%) had co-morbid Generalized Anxiety Disorder
- 2 (5.1%) had Panic Disorder with Agoraphobia
- 2 (5.1%) had Panic Disorder without Agoraphobia
- 1 (2.6%) had Agoraphobia without a history of panic attacks

Subjects mainly outpatients and community patients. DSM-IV diagnoses based on structured diagnostic interviews using the CIDI-A.
Gen. Anxiety Disorder

- The most common anxiety disorder in late life
- >6 months of worry about a number of life domains that interfere with social or occupational functioning.
- A new onset of GAD among older adults is often related to a depressive disorder or new onset dementia.
- MDD + GAD: worse prognosis overall, requiring 50% more time to respond to treatment and incomplete recovery from the depression.
Specific phobias

- Agoraphobia is the most common of phobias, representing up to 80% of new-onset cases in late life.
- Agoraphobia does not always occur with a concurrent panic disorder but can follow a traumatic event such as medical illness, mugging, or a fall.
- The fear of falling is much more common among older adults than in young patients, occurring in 30-77% of older adults who have fallen, and it is associated with becoming housebound, worsening depression, and the impediment of rehabilitation after a fall.
Panic Disorder

- 12-month prevalence: 0.82%  Lifetime prevalence : 2.45%
- Rare to develop for the first time in the elderly
- Risk of panic disorder decreased with older age and was significantly lower among widowed respondents.
- Physical limitations in daily activities as well as the presence of other psychiatric disorders (major depression, and social phobia) were also significantly associated with panic disorder
- Always look for organic causes in elderly:
  - COPD
  - CHF
  - Medications
  - Withdrawal states- benzodiazepines/ alcohol
OCD

- More likely to appear among older adults who have a co-morbid medical illness or dementia, and to have different clinical presentations than in younger individuals.
- More themes of sins and religion than infections or contamination compared with younger persons; and in those with dementia
- Perseveration about toileting and medication schedules are common themes.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic drugs</td>
<td>Memory impairment, producing secondary anxiety; with acute toxicity, a state similar to a panic attack</td>
</tr>
<tr>
<td>Antidepressants (eg, SSRIs, SNRIs, bupropion, desipramine, nortriptyline)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>β agonists (eg, albuterol, salmeterol, terbutaline)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Anxiety</td>
</tr>
<tr>
<td>OTC sympathomimetic drugs (eg, ephedrine, pseudoephedrine, appetite suppressants)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Thyroid replacement therapy (eg, levothyroxine, liotrix)</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>

SNRIIs = serotonin-norepinephrine reuptake inhibitors.
Anxiety Disorder Due To General Medical Condition

- Again more likely in the elderly
  - The elderly have more medical problems
- This is a partial list of common conditions
  - **Lung disease**-Asthma, COPD, PE
  - Cardiovascular-CHF, arrhythmia, MI
  - **Endocrine**-hypoPTH, thyroid, hyperadrenalism
  - **Immunologic**- RA, SLE, TA
  - **GI disease**-Crohn’s, UC
  - **Neurological illness**-CVA, MS, MG, Neurosyphilis, postconcussive syndrome, seizures, TIAs, vertigo
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrhythmias</td>
<td>Palpitations, shortness of breath, anxiety</td>
</tr>
<tr>
<td>Delirium</td>
<td>Moderately severe anxiety and agitation, especially if the patient is in unfamiliar surroundings</td>
</tr>
<tr>
<td>Dementia</td>
<td>Anxiety, often with periodic panic attacks</td>
</tr>
<tr>
<td>Depression</td>
<td>Anxiety and agitation</td>
</tr>
<tr>
<td>Drug withdrawal (eg, alcohol, sedatives, hypnotics)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Agitation, anxiety, palpitations, eating disorders, confusion</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>Moderately severe generalized anxiety, which is usually intermittent and less severe than that in other mental disorders</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Intermittent anxiety with substantial physical manifestations</td>
</tr>
<tr>
<td>MI</td>
<td>Shortness of breath, anxiety</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Shortness of breath, anxiety</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>Shortness of breath, anxiety</td>
</tr>
<tr>
<td>Somatization disorder</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>
Common Indications for BZDs

- Anxiety (generalized, panic)
- Insomnia
- Alcohol and sedative withdrawal
- Adjunct to mood-stabilizers for mania
- Adjuncts to antipsychotics for acute psychosis
- Sedation for brief procedures
- Ongoing sedation
- Anesthesia induction
Less Common Indications for BZDs

- Nausea/ vomiting secondary to chemotherapy
- Adjunctive use with antidepressants for phantom limb pain
- Catatonia
- Terminal restlessness during death
- Seizures
- Myoclonus
- Akathisia
- Periodic limb movements of sleep
- REM sleep behavior disorder (clonazepam)
- Tinnitus (alprazolam)
History of Benzodiazepines

- Landmark drugs in the development of “mood-altering” chemicals.
- Replaced barbiturates which had many side-effects.
- Librium was synthesized by Dr. Leo Sternbach during his postdoctoral studies in Poland.
- Dr. Sternbach tested the compound many years later at Hoffmann-La Roche Labs in NJ and it was found to have enormous potential as an anxiolytic, sedative and hypnotic.
- Librium was also potent as an anticonvulsant and had muscle-relaxant properties.
- In 1960 after clinical trials, Librium became available to geriatric patients. Interest in the drug diminished due to ataxia and slurred speech side-effects.
<table>
<thead>
<tr>
<th>Benzodiazipine</th>
<th>Dosage (mg)</th>
<th>Half-life*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>1</td>
<td>6-10</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>25</td>
<td>5-100+</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>.5</td>
<td>18-50</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>15</td>
<td>30-200</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>10</td>
<td>30-100+</td>
</tr>
<tr>
<td>Estazolam (Prosom)</td>
<td>4</td>
<td>20-120</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>30</td>
<td>1-120</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>2</td>
<td>10-20</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>30</td>
<td>3-21</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>30</td>
<td>20-120</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>30</td>
<td>10-12</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>1</td>
<td>2-3</td>
</tr>
</tbody>
</table>

*includes metabolites
Benzos: Patterns of Use

- 45% of Use <30 days
- 80% of Use <4 months
- 15% of Use >12 months (7-18% Europe)
- Women, twice the rate as men
- <40% of Anxiety Diagnosis Treated
- >40% of Panic Disorder Treated
- 13% of NH patients have significant anxiety
Beer’s Criteria 2003

- Potentially inappropriate at doses of short-acting BZDs greater than:
  - Lorazepam 3mg/day
  - Oxazepam 60mg/day
  - Alprazolam 2mg/day
  - Temazepam 15mg/day
  - Triazolam 0.25mg/day

- “Total daily doses should rarely exceed the suggested maximums”
Beer’s Criteria 2003

- Long-acting benzodiazepines
  - Chlordiazepoxide (Librium)
  - Chlordiazepoxide/amitryptiline (Limbitrol)
  - Diazepam (Valium)
  - Quazepam (Doral)
  - Halazepam (Paxipam)
  - Chlorazepate (Tranxene)

- Inc. risk of falls/fractures. Use short-acting agents
Beer’s Criteria 2003

- Flurazepam (Dalmane)
- Singled out by Beer’s
- “This benzodiazepine hypnotic has an extremely long half-life (often days) producing prolonged sedation and increasing incidence of falls and fracture. Medium or short-acting benzodiazepines are preferable.”
(Potentially) Inappropriate Medications for Older Adults

<table>
<thead>
<tr>
<th>Diazepam</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptiline, Doxepin</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Meprobomate, barbiturates</td>
<td>Carisoprodol, Methocarbamol</td>
</tr>
<tr>
<td>Meperidine, Propoxyphene</td>
<td>Morphine</td>
</tr>
<tr>
<td>Diphenhydramine for sleep</td>
<td>Trazadone, Imidazopyridine</td>
</tr>
<tr>
<td>NSAID for arthritis</td>
<td>Acetaminophen, Tylenol Arthritis</td>
</tr>
<tr>
<td>NSAID for gout</td>
<td>Celecoxib, Rofecoxib</td>
</tr>
</tbody>
</table>
Drugs NOT Indicated in Anxiety Disorders

- Barbiturates
- Meprobamate (Miltown)
- Antihistamines
- Antiepileptics/mood stabilizers
- Chloral hydrate
- Neuroleptics/Antipsychotics
Pharmacokinetics: Benzodiazepines

- **Absorption:** rapid absorption, except clorazepate
- **Onset of action:** increase lipid solubility → faster onset
- **Duration of action:** single dose with increased lipid solubility → faster redistribution to fat tissues → shorter duration of action.
- **Chronic use:** in equilibrium with fat tissues
- **Half life:** In part, determines duration of action
- **Metabolism:** lorazepam, oxazepam, temazepam not metabolized by liver
Phase 1 metabolism (oxidation, reduction, hydrolysis etc.) is reduced in the elderly and in patients taking drugs that inhibit hepatic metabolism or have liver disease.
Benzodiazepine Course Timeline

Fig. 7  Schematic
BZD: Interactions

- CNS Depressants
- p450 2C9
  - Diazepam, TCAs, Warfarin, phenytoin. (Luvox inhibits)
- p450 3A4
  - triazolam, midazolam, alprazolam, CBZ, quinidine, erythromycin (Luvox, Serzone inhibit)
- Disulfiram & Cimetidine ↑BZD levels
Common Adverse Effects

- Drowsiness
- Fatigue
- Weakness
- Ataxia
- Severity increases with dose
- Also increases in most frail elderly patients.
- Synergistic effects with opiates/ alcohol/ etc.
Adverse Motor Effects

- Increased fall risk up to 4x risk of non-BZD pts.
- Most falls occur within first 7 days of use
- Risk factors: excessive dose, rapid rate of dose increase, $t^{1/2} > 24$ hours.
- In those with $t^{1/2} > 24$ hours = 45% inc. in MVA with injury in first 7 days of use.
  - Dec. reaction time, tracking, hand-eye coordination, judgment
- Impairs motor recovery after stroke.
Adverse Cognitive Effects

- Amnesia (anterograde) i.e. pre-colonoscopy
- Impairs information acquisition
- Impairment of consolidation and storage of memory
- Most marked in heavy alcohol drinkers
- Chronic use shows impairment in attention and visuospatial impairments
- May mimic dementia, albeit reversible with BZD discontinuation.
Dose and Titration

- Start at the lowest end of therapeutic dose range.
- Will see anxiolytic, muscle relaxant, and anticonvulsant effects after the first dose.
- Effects may increase until steady state (4.3 x half-life)
- Should be time-limited, i.e. under 4 months then dose reduction attempted
- Levels can be done for Xanax (target 20-40 ng/mL for panic attacks)
- Evaluated at least every 6 months to look for cognitive impairment, falls, MMSE.
Switching Agents

- BZD → Buspirone
  - Add Buspirone to BZD, titrate Buspirone up to 20mg po TID if tolerated while on BZD
  - Both meds co-administered for 4 weeks.
  - Taper BZD at 10-25% per week after 4 weeks.
  - If unable to tolerate BZD taper, could benefit from Neurontin 300-900mg/day, Melatonin 2mg qHS for insomnia, propranolol for autonomic sx, Tegretol 200-800mg/day.
Contraindications to BZDs

- History of alcohol or substance abuse
- ? Family history of substance abuse
- Untreated obstructive sleep apnea
- Brain injury/mental retardation due to rare “paradoxical agitation”
- ???? Dementia
FDA Indications for Other Agents useful in treatment of Anxiety

- **SSRIs**
  - Citalopram: None
  - Escitalopram: GAD
  - Sertraline: OCD; PD; PTSD; SAD
  - Paroxetine: OCD; PD; SAD; PTSD; GAD
  - Fluoxetine: OCD; PD
  - Fluvoxamine: OCD

- **Venlafaxine**
  - GAD; SAD

- **Duloxetine**
  - GAD

- **Buspirone**
  - GAD

- **Mirtazapine**
  - None
Serotonin Selective Reuptake Inhibitors

- Fluoxetine (Prozac), 20-80 mg/d
  - Initiate with 5-10 mg/d

- Sertraline (Zoloft), 50-200 mg/d
  - Initiate with 25-50 mg/d

- Paroxetine (Paxil), 20-50 mg/d
  - Initiate with 10mg/d

- Fluvoxamine (Luvox), 50-300 mg/d
  - Initiate with 25 mg/d

- Citalopram (Celexa)
  - Initiate with 10-20 mg/d

Start low to minimize anxiety

Adjunctive BZD, beta blocker
SSRI Considerations

- 10-12% rate of SIADH in the elderly
- Paroxetine - most anticholinergic SSRI
- Citalopram - warning on QT prolongation
- Fluvoxamine - potent cytP450 3A4 inhibitor
- Fluoxetine – best studied in ESRD patients
- Sertraline - best studied in post-MI patients
Combining Antidepressants with Benzodiazepines

- Provides rapid anxiolysis during antidepressant lag
- Decreases early anxiety associated with initiation of antidepressant
- Treats residual anxiety with antidepressant treatment
- Prevents and treats depression on benzodiazepines
End-Point (LVCF) Analysis of Panic Disorder Severity Scale Scores for Each Group

* Together the Clonazepam groups differ from the Placebo group at p< .05
† Clonazepam groups differ from each other at p<.05

Pollack, et al 2001
Beta Blockers

- Decrease autonomic arousal
- May be useful as adjunct for somatic symptoms of panic and GAD but not as primary treatment
- Useful for non-generalized social phobia, performance anxiety subtype
- Propranolol 10-60 mg/d; Atenolol 50-150 mg/d
Anticonvulsants

- Valproate and gabapentin effective for non-ictal panic
- Gabapentin effective for social phobia
- Gabapentin (600-5400 mg/d) used as alternative to benzodiazepines
- Valproate, Carbamazepine, Gabapentin, Topiramate and Lamotrigine for PTSD
Strategies for Refractory Anxiety Disorder

- Maximize dose
- Combine antidepressant and benzodiazepine
- Administer cognitive-behavioral therapy
- Attend to psychosocial issues
## Strategies for Refractory Anxiety Disorders

<table>
<thead>
<tr>
<th>Augmentation</th>
<th>Combined SSRI/TCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anticonvulsants</td>
<td>- Combined SSRI/TCA</td>
</tr>
<tr>
<td>- Gabapentin</td>
<td>- Alternative antidepressant</td>
</tr>
<tr>
<td>- Valproate</td>
<td>- Clomipramine</td>
</tr>
<tr>
<td>- Topiramate</td>
<td>- MAOI</td>
</tr>
<tr>
<td>- Beta blocker</td>
<td>- Other</td>
</tr>
<tr>
<td>- Buspirone</td>
<td>- Inositol</td>
</tr>
<tr>
<td>- Clonidine/Guanfacine</td>
<td>- Kava-kava</td>
</tr>
<tr>
<td>- Pindolol</td>
<td>- Atypical neuroleptics</td>
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<tr>
<td>- Dopaminergic agonists</td>
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<tr>
<td>(e.g., Ropinirole)</td>
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<tr>
<td>for social phobia</td>
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<tr>
<td>- Cyproheptadine</td>
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</tbody>
</table>
Discontinuation of Tx

- Withdrawal/rebound more common with Bzd than other anxiolytic treatment
- Relapse: a significant problem across treatments. Many patients require maintenance therapy
- Bzd abuse is rare in non-predisposed individuals
- Clinical decision: balance comfort/compliance/comorbidity during maintenance treatment with discontinuation-associated difficulties