Anti-Anxiety Agents Cost Effective Usage

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ASCP Model Curriculum

Pre- and Post-Lecture Competency Exam

Question 1

All of the following antianxiety treatments are inexpensive (December 2009) except

A. Venlafaxine SA
B. sertraline
C. citalopram
D. buspirone
E. clonazepam

Question 2

True or False

A patient is taking 3 mg of clonazepam per day in divided doses. This is the equivalent of 12 mg per day of lorazepam.

Question 3

All of the following are absorbed reasonably quickly and would be suitable for use as a “prn” except

A. clonazepam
B. alprazolam
C. oxazepam
D. diazepam
E. lorazepam

Question 4

Benzodiazepines have evidence supporting a role in the treatment of the primary symptoms of all of the following except

A. Panic Disorder
B. Social Anxiety Disorder.
C. Generalized Anxiety Disorder
D. PTSD

Question 5

Which of the following is correct about buspirone?

A. Impairs motor coordination in driving tests
B. No abuse potential
C. Impairs cognition
D. Has muscle relaxant properties

Lecture Outline

- Introduction to anxiety
- Benzodiazepines
- Buspirone, propranolol, hydroxyzine, and other antianxiety agents
- Dosing of medication and general approach to the pharmacotherapy of each anxiety disorder
- Clinical approach to insomnia
- Costs of medications

Major Teaching Points

- Many patients with anxiety have situational problems that are best managed with psychotherapy
- Knowledge of benzodiazepine pharmacokinetics will enable them to be used optimally
- Underutilized valuable options include buspirone, propranolol, hydroxyzine, and prazosin
- Insomnia is usually a symptom, not a disease
- The cost of anti-anxiety agents varies 1-200 fold without much evidence that the more expensive options are any better or safer

Antianxiety Agents: The Menu I.
Benzodiazepines – generic and (old) brand names and daily dose equivalence. Hypnotics listed separately.

- Alprazolam 0.5 mg — Xanax
- Chlordiazepoxide 25 mg — Librium
- Clonazepam 0.25 mg — Klonopin
- Diazepam 5 mg — Valium
- Lorazepam 1 mg — Ativan
- Oxazepam 15 mg — Serax
- Clorazepate 7.5 mg — Tranxene

Hypnotics

- Flurazepam 15 mg — Dalmane
- Temazepam 7.5 mg — Restoril
- Triazolam 0.125 mg — Halcion

Other Medications FDA-Approved For or Commonly Used For Anxiety or Insomnia: The Menu II.
Generic and (old) brand names. Hypnotics (H)

Buspirone	Buspar
Propranolol	Inderal
Clonidine	Catapres
Prazosin	Minipress
Hydroxyzine	Atarax, Vistaril
Trazodone	Desyrel
Zolpidem (H)	Ambien
Zaleplon (H)	Sonata
Eszopiclone (H)	Lunesta
Ramelteon (H)	Rozerem
Chloral hydrate	Noctec
Quetiapine	Seroquel

Antidepressants for anxiety disorders

- Widely used
- Details about antidepressant dosage and properties are provided in the antidepressants crash course lecture.
- Usage in specific anxiety disorders will be discussed.

The problem of anxiety

- 25% lifetime prevalence of any anxiety disorder (Nat. Comorbidity Survey 1994)
- Many more have situational anxiety related to “normal” fears and use of medication for short term relief can be appealing. (Pomerantz JM, 2007)
- Disabling nature of anxiety has been increasingly recognized over the past 20 years. Now seen as brain disorders.

Role of Medication in Anxiety

- Due to stigmatization, patients often seek a quick, private remedy.
- Self-medication with alcohol and drugs of abuse are common, and reinforced by social acceptance – and even psychiatric clinicians.
- The culture of inpatient psychiatric care often encourages “taking a PRN” – and discourages reliance on cognitive coping strategies.
- Yet, if patients become aware of the option of cognitive, relaxation, and other non-pharmacological remedies, they often are very receptive.

PRNs for Anxiety

PRN = pro re nata = as the event is born

- The anxious agitated, potentially out-of-control manic or psychotic patient can benefit from a benzodiazepine PRN.
- Intramuscular lorazepam (e.g. 2 mg) is as effective as haloperidol 5 mg but the combination is probably > effective.
- May be used in the ER even in substance-using patients
- Use of benzodiazepines PRN for milder degrees of anxiety can reinforce drug-seeking behavior and undermine clinicians' efforts to encourage the patient to face the causes of their distress and find better coping strategies.
- Patients with borderline personality are challenging. Their perception of a need for external control of their anxiety may be difficult to redirect until a therapeutic alliance has developed.

Ansari A, Osser D. Chapter 3. In: Principles of Inpatient Psychiatry, ed by Ovsiew and Munich. Wolters Kluwer 2009.

Benzodiazepines: Metabolism

- Glucuronidation: lorazepam, oxazepam, temazepam, alprazolam, triazolam
- Nitroreduction: clonazepam
- Demethylation and oxidation: diazepam, chlordiazepoxide, clorazepate

Some Drug Interactions with Benzodiazepines

- **Cytochrome inhibitors: metoprolol, propranolol, disulfiram, omeprazole, erythromycin, fluoxetine. Biggest effect (100-300%) with fluvoxamine on desmethyldiazepam (2C19 substrate).**
- **Anticholinergics: additive cognitive impairment especially in the elderly**
- **Additive CNS depression with other sedatives**
- **Clozapine added to ongoing BZ may rarely give severe sedation, delirium, respiratory depression/death. Monitor VS, warn patient. (Grohman et al, 1989)**

Benzodiazepine Dose Equivalencies

Chlordiazepoxide	25 mg
oxazepam	15 mg
Clorazepate	7.5 mg
diazepam	5 mg
lorazepam	1 mg
alprazolam	0.5 mg
clonazepam	0.25 mg

Benzodiazepines Absorption and Half-Life

adapted from Gelenberg AJ et al, 1991; Rosenbaum JF et al, 2005; and 2004 PDR

Benzo-diazepine	Absorption	Distribution	Half-Life (hr)
oxazepam	Slower	Intermediate	5-15
diazepam	Fastest	Fast (2.5 hr)	20-100 (200 – elderly)
lorazepam	Intermediate	Intermediate	10-20
alprazolam alprazolam XR	Intermediate Slower	Intermediate Intermediate	6-27 11-16
clonazepam	Intermediate	intermediate	30-50

Benzodiazepine Withdrawal Syndrome

- Anxiety
- Agitation
- Tremulousness
- Insomnia
- Dizziness
- Headaches
- Seizures (rare, case reports – Janicak 06)
- Exacerbation of psychosis

Benzodiazepine Side Effects

- **Dependence, addiction, abuse – by far most common in alcoholics and other drug abusers**
- **Elderly – watch for increased fall risk with long half-life drugs**
- **Memory impairment**
- **Impaired motor coordination, auto driving in simulated driving tests**
- **Disinhibition/violence – more uncommon than presumed, but may require antipsychotic**
- **Depression: clonazepam (5.5%) vs alprazolam (0.7%) [Cohen and Rosenbaum, 1997]**

Pregnancy Risk with Benzodiazepines

- Pregnancy risks “D” level due to oral cleft, except clonazepam C
- Most recent studies show they are fairly safe but old studies suggested cleft palate

Buspirone - Properties

- 5HT1A agonist – but benefits probably due to adaptation over several weeks to this effect
- No sedating, muscle-relaxant, or anticonvulsant effects
- Cytochrome P450 3A4 substrate
- No abuse potential
- Does not suppress respiration so is useful for anxiety in COPD patients
- No impairment of cognition or motor coordination

Buspirone - prescribing

- Initial dose 5 mg bid or tid. Increase every 2-3 days by 5-10 mg to reach dose of 30-40 in two divided doses.
- Maximum dose 60. Alcoholics with anxiety usually need 50-60 (Krantzler ’94)
- Has some efficacy in **depression** at 40 mg/d (Schweizer ’98). As effective as bupropion for SSRI augmentation (STAR*D)
- Side effects: headache, insomnia, jitteriness, and nausea.

Propranolol – for performance anxiety (off label use)

- **Propranolol 10 – 40 mg 30 minutes prior to the event. Try test doses before**
- **Side effects: hypotension, bradycardia, dizziness, asthma, fatigue. Evidence contradicts idea that betablockers mask hypoglycemia symptoms. (Chalon, 1999)**
- **Half-life 3-6 hours**
- **Hold if BP < 90/60 or P < 55**
- **Lipophilic so crosses into brain**
- **Alternatives: metoprolol 50 mg (more beta-1 selective)**
- **Not useful for social phobia, generalized type**

Hydroxyzine – an effective treatment for GAD in 3 randomized, placebo-controlled studies

- Antihistamine (H_1) with less affinity for muscarinic, serotonergic, DA and alpha$_1$ receptors than others
- No abuse potential or withdrawal syndrome
- Less cognitive impairment than benzodiazepines
- Less sedating than benzodiazepines but > placebo
- Efficacy seemed to gradually increase over 3 mo.
- Usual dose 10-12.5 mg bid and 20-25 mg hs
- An interesting alternative but would like to see replication in a US center. See Llorca 2002.

Prescribing Cost-Effectively for Anxiety

Labeled indications. Labeling is probably not very important within the SSRI/SNRI class

- **Panic**: fluoxetine, sertraline, venlafaxine, paroxetine
- **OCD**: fluoxetine, fluvoxamine, sertraline, paroxetine
- **Social anxiety**: sertraline, paroxetine, venlafaxine
- **PTSD:** paroxetine, sertraline (only in females?)
- **Generalized anxiety**: paroxetine, escitalopram, venlafaxine, buspirone
- **Bulimia**: fluoxetine

Prescribing Cost-Effectively for Anxiety

Dosing Strategies for **Panic Disorder**

- Start low and increase SSRI slowly
- Concomitant clonazepam (but not alprazolam) at the beginning may help (Goddard 2001)
- Only unprecipitated panic attacks respond well to SSRIs (Uhlenhuth 2000)

Prescribing Cost-Effectively for Anxiety

Dosing Strategies for **OCD**

- Higher doses of SSRI usually needed, if 4-10 weeks at moderate dose unsatisfactory
- If still unsatisfactory response, switch to another SSRI or clomipramine. If response unsatisfactory consider going over PDR maximum by up to 100% (Ninan, 2006)
- Augment with CBT (some question the methodology in the supporting literature)
- Augment with antipsychotic. Haloperidol if tics, atypicals if not – but evidence base weak

Prescribing Cost-Effectively for Anxiety

Dosing Strategies for **Social Anxiety, Generalized Anxiety Disorders**

- Do NOT need to start low, go slow
- Sexual side effects of SSRIs/SNRIs problematic for many of these patients. Gabapentin, mirtazapine and nefazodone may be options (e.g. Muehlbacher, 2005)
- Alcohol dependency more common in social anxiety and must be diagnosed, treated. It will not improve with an SSRI.

Prescribing Cost-Effectively for Anxiety

Strategies for PTSD

First, try to treat insomnia if that is a prominent symptom and no comorbid depression

- Consider prazosin if prominent nightmares/disturbed awakenings. Trazodone may be helpful for difficulty falling asleep.
- Avoid benzodiazepines due to abuse potential, lack of effect on primary symptoms of PTSD
- If no prominent insomnia or if the above fails, try a general symptom treatment – an SSRI. For second trial, another SSRI, SNRI, or mirtazapine.
- Other options with some evidence are clonidine, topiramate, lamotrigine, phenelzine.
- May try augmentation with atypical antipsychotic

Other Products used Unlabeled for Anxiety

- Prazosin and terazosin (Alpha-1 antagonists) – will discuss prazosin in detail.
- Clonidine (alpha-2 agonist
- Anticonvulsants e.g. gabapentin, valproate, lamotrigine, topiramate
- pregabalin (Lyrica) – got “non-approvable” letter from FDA in 2004 for GAD but approved in Europe in 2006. Dizziness (30%), weight gain, sedation
- tiagabine (Gabatril)– didn’t separate from placebo (Pollack, 2008). Also, incr. Sz risk.
- MAOIs
- Quetiapine (Seroquel XR): effective for GAD but FDA rejected the indication due to LT side effects

Prazosin for PTSD

- Three placebo-controlled studies in PTSD (Raskin 2003, 2007: Taylor 2008) Two in combat vets and one in civilian trauma cases
- Begin with 1 mg hs to avoid first dose orthostasis or syncope
- After 3 days, increase to 2 mg hs. After 4 more days, increase to 4 mg hs. If still no response after 7 days, increase to 6 mg hs.
- After another 7 days, increase to 4 mg at 3:00 pm & 6 mg at hs.
- In women with civilian trauma, start 1 mg hs and increase by 1 mg weekly. Usual dose 3-4 mg

Clinical Approach to Insomnia - I

- Diagnose the causes of the insomnia. Although “primary insomnia”, the condition treated in most of the studies of hypnotics, exists, it is rarely the main cause of insomnia seen in psychiatric practice.
- Often the causes are multfactorial
- Insomnia is a symptom of most psychiatric disorders (psychotic, mood, and anxiety disorders) and usually the treatment will be directed to those disorders.
- Medical causes are frequent and include pain conditions, restless leg syndrome, and obstructive sleep apnea
- Caffeine use late in the day is a common contributing factor
- Nicotine and other addictions can awaken patients
- Many medications have stimulating side effects, like SSRIs, SNRIs, bupropion, aripiprazole

Clinical Approach to Insomnia – 2

- **Conditioned insomnia** is worth a whole slide
- It is a common component of chronic sleep problems
- Symptoms are preoccupation with watching the clock, worrying about whether one will be able to sleep, and inability to redirect one's focus to more restful thoughts
- Usually there was some original cause of the insomnia that has passed, but left the patient traumatized and worried that he/she will not sleep
- Treatment is with cognitive behavioral approaches

Clinical Approach to Insomnia – 3

- For general use, trazodone (25-150 mg) is a reasonable first-line hypnotic. It is the most widely prescribed medication used as a hypnotic in the US
- Trazodone is “in many ways an ideal hypnotic agent” due to its sleep-promoting actions at 5-HT2A, alpha-1, and H1 (Stahl SM CNS Spectr 2009:14(10):536-546
- Lorazepam is perhaps the best benzodiazepine in terms of pharmacokinetic properties as a hypnotic
- Zolpidem is now an inexpensive generic and is a reasonable hypnotic for many patients who could benefit from benzodiazepine receptor action with relatively minimal addiction risk the minimal risks

Clinical Approach to Insomnia – 4

- Generic agents with antihistaminic action can be effective such as low dose doxepin (10 mg) (Scharf et al. J Clin Psychiatry 2008) and hydroxyzine.
- Sedating agents associated with weight gain such as mirtazapine should generally be avoided unless this side effect would be acceptable
- Prazosin is a good choice for PTSD as we have noted
- One should avoid using quetiapine because of weight gain and other metabolic side effects (which are not dose-related (Simon V et al. J Clin Psychiatry 2009)
- Furthermore, the risk of sudden cardiac death with antipsychotics makes them a poor choice for off-label, non-proven uses (Ray et al. NEJM 2009)

Hypnotics: A Cost-effectiveness Note

What is the role of eszoplicone (Lunesta)?

- Zopliclone (racemic version of eszopiclone, approved in Europe) impairs driving in the elderly more than temazepam*
- CBT is more effective than zopiclone for primary insomnia*
- Lunesta is an expensive brand product
- Looks like it doesn't have much of a role.

*Tim RM et al. J Clin Psychopharmacol 2009;29:432-8.

**JAMA 2006;295(24):2851-8

Cost-Conscious Treatment

- The last slide provides a segue to the final slides of this lecture
- Physicians have a responsibility know what the medications cost
- After appropriate clinical evaluation and determination of the most evidence-supported treatment, costs should be taken into consideration.

Culture change required?

General Issues on Prices of Drugs

- Depends partly on where the patient gets the medication
- Price differences vary, but usually the ranking by price is similar
- Generics are usually but not always cheaper
- Dosage regimen affects cost
- Pill strength can be important

Prescribing Cost-Effectively for Anxiety

Use generics first line unless there is a good reason not to.

- citalopram, sertraline, fluoxetine
- prazosin, hydroxyzine
- generic benzodiazepines like lorazepam

Antianxiety Agents: Monthly Cost in VA

December, 2009

gabapentin 300 mg tid	**5**
risperidone 0.5 mg bid	**16**
quetiapine 25 mg tid	**40**
tiagabine 8 mg/d	**77**
pregabalin 150 mg bid	**144**
olanzapine 2.5 mg bid	**237**

--the latter often used irrationally on inpatient units as a "PRN"

Drugs Used as Hypnotics in the VA System
(Monthly Procurement Cost, September 2009)

amitriptyline 10 mg	$ 0.42
trazodone 50 mg	0.53
lorazepam 2 mg	0.78
doxepin 25 mg	1.87
zolpidem 10 mg	2.13
mirtazapine 30 mg	2.55

Drugs Used as Hypnotics in the VA System (Monthly Procurement Cost, September 2009)

- **zaleplon (Sonata) 10 mg 13.00**
- **quetiapine 50 mg 14.00**
- **eszopiclone (Lunesta) 1, 2, or 3 mg 50.00**
- **ramelteon (Rozerem) 2 mg 60.00**

Antidepressant Monthly Procurement Costs in the VA System – September 2009

fluoxetine 20 mg	$ 0.72
citalopram 40 mg	1.74
nortriptyline 100 mg	1.86
mirtazapine 30 mg	2.55
sertraline 100 mg	2.70
paroxetine 20 mg	4.38
bupropion SA 150 bid	14.00

Antidepressant Monthly Procurement Costs in the VA System – September 2009

- **Venlafaxine 150 mg 12.00**
- **Nefazodone 400 mg 27.00**
- **Escitalopram 20 mg 53.00**
- **Duloxetine 60 mg 72.00**
- **Venlafaxine SA 150 m 77.00**
- **Bupropion XR 300 mg 130.00**

Summary/Conclusions

- Antianxiety medications as “PRN’s” for all kinds of situational stresses are overused.
- Polypharmacy is common and in many cases unnecessary
- Knowledge of benzodiazepine pharmacokinetics will improve the ability to use them appropriately
- When using medication for anxiety disorders, inexpensive but effective options are widely available.

Pre- and Post-Lecture Competency Exam

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B. No abuse potential
C. Impairs cognition
D. Has muscle relaxant properties

Answers to Competency Examination

- Question 1 – A
- 2 – True
- 3 – C
- 4 – D
- 5 – B