Anti-Anxiety Agents 2007 Cost Effective Usage

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ASCP Model Curriculum

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Pre- and Post-Lecture Competency Exam

Question 1

All of the following antianxiety treatments are inexpensive (September 2007) except

A. venlafaxine
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
- Costs of medications
- Benzodiazepines
- Buspirone, propranolol, hydroxyzine, and other antianxiety agents
- Dosing of medication and general approach to the pharmacotherapy of each anxiety disorder

Major Teaching Points

- Many patients with anxiety have situational problems that are best managed with psychotherapy
- The cost of anti-anxiety agents varies 1-200 fold without much evidence that the more expensive options are any better or safer
- Knowledge of benzodiazepine pharmacokinetics will enable them to be used optimally
- Underutilized valuable options include buspirone, propranolol, hydroxyzine, and prazosin

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.

Cost-Conscious Treatment

- 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

Antidepressant Monthly Procurement Costs in the VA System – July 2007

citalopram 40 mg	$ 0.60
fluoxetine 20 mg	0.90
sertraline 100 mg	1.80
mirtazapine 30 mg	3.30
paroxetine 20 mg	9.00
bupropion SA 300 mg	26.50

Antidepressant Monthly Procurement Costs in the VA System – July 2007

Nefazodone 400 mg	29.00
Lexapro 20 mg	41.00
Cymbalta 60 mg	64.00
Effexor SA 150 mg	67.00
venlafaxine 150 mg	88.00
bupropion XR 300 mg	104.00

Antianxiety Agents: Monthly Cost in VA

August, 2007

clonazepam 0.25 tid	$ 1
alprazolam 0.5 mg tid	4
oxazepam 15 mg tid	14
lorazepam 1 mg tid	15
buspirone 20 mg bid	4
trazodone 50 mg tid	2
clonidine 0.1 mg tid	2
hydroxyzine 10/10/20 mg	9

Antianxiety Agents: Monthly Cost in VA

August, 2007

gabapentin 300 mg tid	**5**
tiagabine 8 mg/d	**48**
quetiapine 25 mg tid	**38**
risperidone 0.5 mg bid	**64**
pregabalin 150 mg bid	**210**
olanzapine 2.5 mg bid	**218**

Drugs Used as Hypnotics in the VA System (Monthly Procurement Cost, 7/2007)

amitriptyline 10 mg	$ 0.40
doxepin 25 mg	0.50
trazodone 50 mg	0.60
zolpidem 10 mg	0.83
lorazepam 2 mg	2.00
mirtazapine 30 mg	3.30

Drugs Used as Hypnotics in the VA System (Monthly Procurement Cost, 7/2007)

- **quetiapine 50 mg** **13.00**
- **ramelteon (Rozerem) 2 mg** **42.00**
- **eszopiclone (Lunesta) 1, 2, or 3 mg** **44.00**
- **zaleplon (Sonata) 10 mg** **56.00**

Benzodiazepines: Metabolism

- Glucuronidation: lorazepam (Ativan), oxazepam (Serax), temazepam (Restoril), alprazolam (Xanax), triazolam (Halcyon)
- Nitroreduction: clonazepam (Klonopin)
- Demethylation and oxidation: diazepam (Valium), chlordiazepoxide (Librium), chlorazepate (Tranxene)

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

- oxazepam (Serax) 15 mg
- diazepam (Valium) 5 mg
- lorazepam (Ativan) 1 mg
- alprazolam (Xanax) 0.5 mg
- clonazepam (Klonopin) 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**

Other Unlabeled Drugs used for Anxiety

- 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.
- tiagabine (Gabatril)– didn’t separate from placebo in unpublished studies. Also, incr. Sz risk.
- MAOIs
- Antihistamines e.g. hydroxyzine, diphenhydramine
- Clonidine (alpha-2 agonist)
- Prazosin and terazosin (Alpha-1 antagonists)

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.

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:** sertraline, paroxetine
- **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

Prescribing Cost-Effectively for Anxiety

Strategies for PTSD (see www.ipap.org)

- Generic SSRI first-line
- Avoid benzodiazepines due to abuse potential, lack of effect on primary symptoms of PTSD
- If no comorbid depression and prominent insomnia, try trazodone first as hypnotic.
- Consider prazosin: two placebo controlled trials.
- Other options with some evidence are sedating tricyclic, clonidine.
- Options for treatment-resistant case: gabapentin, divalproex, augment SSRI with atypical antipsychotics (most costly)

Prazosin (Minipress)

- Two placebo-controlled studies in PTSD (Raskin 2003, 2007. Especially good for nightmares in combat vets
- 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.

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.

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Answers to Competency Examination

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