Anti-Anxiety Agents

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ASCP Model Curriculum 8th Edition

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Pre- and Post-Lecture Competency Exam

Question 1

All of the following antianxiety treatments are inexpensive except

A. pregabalin
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

- Very brief 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
- Very brief material on 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 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

Medications 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
Doxepin (H)	Silenor
Chloral hydrate	Noctec
Quetiapine	Seroquel
Suvorexant (H)	Belsomra

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)**

Benzodiazepines Absorption and Half-Life

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

Benzo-diazepine	Absorption (hours)	Distribution	Half-Life (hr)
oxazepam	Slower (3) (5 in older pts)	Intermediate	5-15
diazepam	Fastest (0.5-2)	Fast (2.5 hr)	20-100 (200 – elderly)
lorazepam	Intermediate (2)	Intermediate	10-20
alprazolam alprazolam XR	Intermed. (1-2) Slowest (10)	Intermediate Intermediate	6-27 11-16
clonazepam	Intermed. (1-2)	intermediate	30-50

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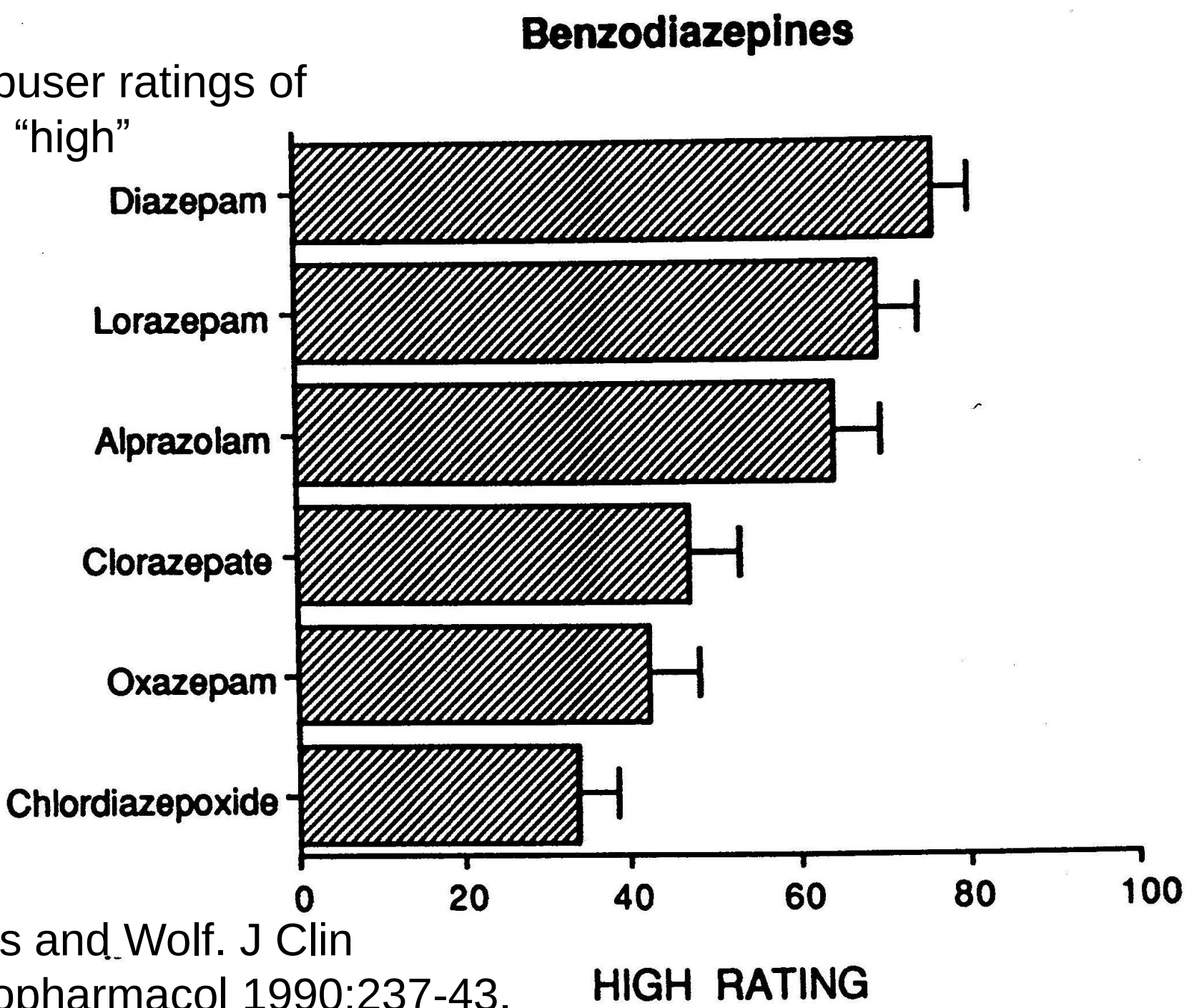
ative “high”



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sychopharmacol 1990:237-43.

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” though probably not safer.
- 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 divided doses, where it has efficacy.
- Maximum dose 60. Alcoholics with anxiety usually need 50-60 mg daily (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**

Prescribing for Anxiety Disorders, OCD, PTSD

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 effective in women)
- **Generalized anxiety disorder**: paroxetine, escitalopram, venlafaxine, duloxetine, buspirone

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 (Uhlenhuth2000)

Dosing Strategies for **OCD**

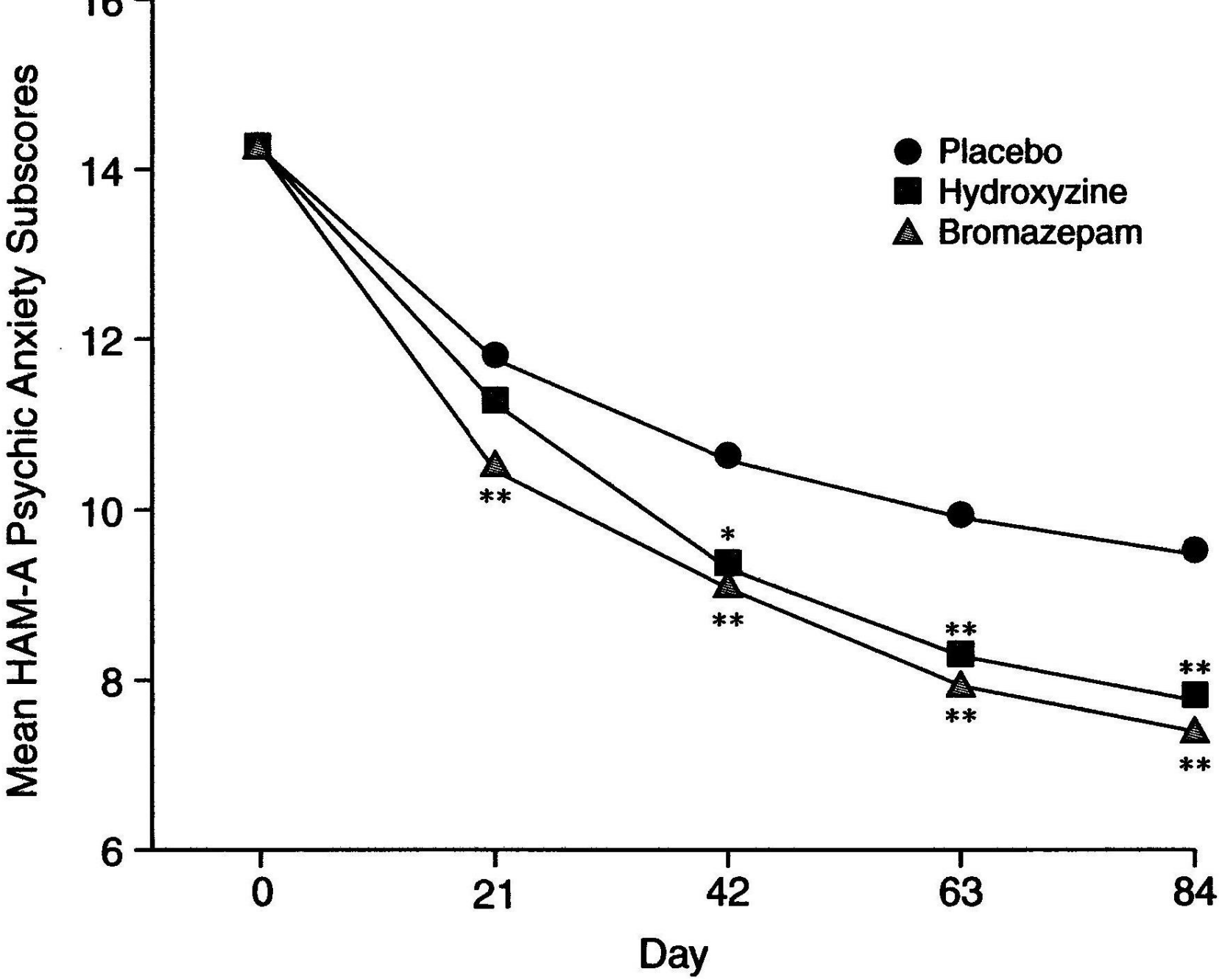
- Higher doses of SSRI usually needed, if 4-10 weeks at moderate dose unsatisfactory
- If still unsatisfactory response, switch to another SSRI or clomipramine. If response unsatisfactory consider going over PDR maximum by up to 100% (Ninan, 2006)
- Augment with CBT (some question the methodology in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

Dosing Strategies for **Social Anxiety and 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 alternatives (e.g., Muehlbacher, 2005)
- Alcohol dependency more common in social anxiety disorder and must be diagnosed, treated.

Hydroxyzine – effective for GAD in 5 RCTs
(Guaiana et al. Cochrane Review 2010 (12))

- Antihistamine (H_1) with less affinity for muscarinic, serotonergic, DA and alpha$_1$ receptors than others
- More effective than placebo, odds ratio 0.30.
- No abuse potential or withdrawal syndrome
- Less cognitive impairment than benzodiazepines
- Similar sedation to benzodiazepines
- Usual dose 10-12.5 mg bid and 25 mg hs
- An interesting alternative but would like to see replication in a US center. Best study-Llorca 2002:



Llorca P-M et al. J Clin Psychiatry 2002;63:1020-7 **p<.01

[a]Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety

Pregabalin for GAD

- 8 controlled trials in GAD, most are positive.
- Better for sleep compared with venlafaxine or placebo (Kasper et al, 2009)
- Largest effect size of any medication class for GAD – 0.5 (hydroxyzine 0.45, SNRIs 0.42, benzodiazepines 0.38, SSRIs, 0.36, buspirone 0.17); Hidalgo et al, 2007)
- Largest cost: $333-$666 monthly at VA.
- Twice not approved by US FDA but approved in Europe for GAD. Manufacturer will not disclose reasons why FDA did not approve it.

Bupropion XL for GAD
(Bystritsky et al, 2008)

- One very small but interesting controlled trial in comparison with FDA-approved escitalopram. 24 adults for 12 weeks. Results measured by Ham-A and CGI-I. Funded by Glaxo.
- Dose of bupropion 150, then 300 after 2 weeks (90%).
- Dose escitalopram 10 mg, then 20 after 2 weeks (92%)
- Excluded patients with depression or other Axis I
- Bupropion (BUP): 91% female: escitalopram (ESC): 38%
- Result: BUP Ham-A went from 26 to 5 (100% responders); ESC from 26 to 11 (62% responders). $p < 0.01$ for the change difference. No difference in depression ratings.
- Thus BUP is an interesting and unexpected option for GAD.

Prescribing Cost-Effectively for Anxiety

Strategies for PTSD (see algorithm by Bajor L, Ticlea A, Osser DN. Harvard Rev Psychiat 2011:19(5):240-58)

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, nefazodone, phenelzine.
- Augmentation with quetiapine has some evidence

Other Products used Unlabeled for Anxiety

- Prazosin and terazosin (Alpha-1 antagonists) – will discuss prazosin in detail.
- Clonidine (alpha-2 agonist): uncontrolled evidence
- Anticonvulsants e.g., gabapentin, valproate, lamotrigine, topiramate
- MAOIs
- Quetiapine (Seroquel XR): effective for GAD but FDA rejected the indication due to side effects

Prazosin for PTSD Nightmares

- Four placebo-controlled studies in PTSD (Raskind 2003, 2007, 2013: Taylor 2008) Three in veterans and soldiers and one in civilian trauma cases (mostly women)
- Dosage in men: begin with 1 mg hs to avoid first dose orthostasis or syncope
- After 2 days, increase to 2 mg hs. After 5 more days, increase to 4 mg hs if tolerated. If still no response after 7 days, increase to 6 mg hs.
- After another week, increase to 10 mg hs, then 15 and then 20 mg at hs with weekly increases. May give additional daytime dose up to 5 mg
- In women, max dose is 10 mg hs and 2 mg in day

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 for hypnotic use in terms of pharmacokinetic properties
- 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, though it causes rebound insomnia after even one dose.

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 – but cause some attentional impairment. (Conen et al, 2011)
- 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
- Quetiapine. This is not a good choice for off-label, non-proven uses.

Quetiapine for insomnia

- Mysliwiec, 2011: 692 soldiers, mean age 27, were treated with quetiapine: 9% for an FDA-approved indication; 60% - sleep; 19% - anxiety.
- Patients gained mean of 6.3 lb
- Quetiapine weight gain not dose-related.(Simon, 2009)
- July 19, 2011: New product label warning on QTc prolongation. “Should be avoided” with 12 other meds. Sept. 1: have to add citalopram to the list.
- Wine et al, 2009 reviewed data on quetiapine for sleep. Conclusion: benefits do not justify risks.

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 should not have much use.

*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

Antianxiety Agents: Monthly Cost in VA

April, 2013

gabapentin 300 mg tid	**5**
hydroxyzine 25 mg bid	**2**
risperidone 0.5 mg bid	**1**
quetiapine 25 mg tid	**7**
buspirone 20 mg bid	**3**
pregabalin 150 mg bid	**333-666 (CVS)**

Drugs Used as Hypnotics
(Monthly VA Procurement Costs, Sept. 11, 2014)

amitriptyline 10 mg	$ 0.41
trazodone 50 mg	1
zolpidem 10 mg	1
hydroxyzine 25 mg	1
lorazepam 2 mg	2
prazosin 5 mg	2
doxepin 10 mg	3
quetiapine 50 mg	3

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

- **zaleplon (Sonata) 10 mg $ 74**
- **eszopiclone (Lunesta) 1, 2, or 3 mg 106**
- **ramelteon (Rozerem) 2 mg 107**
- **Suvorexant (Belsomra) 10 or 20 mg ??**

Antidepressant Monthly Procurement Costs in the U.S. Dept. of Veterans Affairs– Aug. 6, 2014

- fluoxetine 20 mg $ 0.45
- citalopram 40 mg 1
- nortriptyline 100 mg 2
- mirtazapine 30 mg 2
- paroxetine 20 mg 2
- escitalopram 10 mg 3
- sertraline 100 mg 4
- bupropion SA 150 bid 6

Antidepressant Monthly Procurement Costs in the VA – Continued

- bupropion XR 300 mg $ 8*
- venlafaxine IR 150 mg 6
- venlafaxine SA 150 mg 44
- nefazodone 400 mg 45
- duloxetine 60 mg 106

*some generics have had problems

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