

## Understanding Benzodiazepines

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## Steven Juergens MD – Speaker Bureau Participation

- ◆ AstraZeneca – Seroquel (quetiapine)
- ◆ Sanofi Aventis – Ambien CR (zolpidem)
- ◆ Forest – Lexapro (escitalopram) and  
Campral (acamprosate)
- ◆ Bristol-Myers Squibb – Abilify  
(aripiprazole)
- ◆ Wyeth – Effexor XR (venlafaxine)
- ◆ Pfizer – Geodon (ziprasidone)

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## Benzodiazepine Use

11% of population use a benzodiazepine annually

80% for < 4 months

5 % for 4 - 12 months

15% > 12 months ( about 1.6% of population)

Mellenger et al, JAMA 1984;251:375-379

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## Gap Between Treatment Guidelines and Actual Clinical Care

- ◆ 443 patients with panic disorder in Harvard/Brown Anxiety Research Project followed prospective over 10 years to examine their use of psychotropic
- ◆ Only a modest increase in use of SSRIs over 10 years was found
- ◆ Benzodiazepines were the most commonly used medication for panic disorder and SSRI use has remained low
- ◆ Patients using an SSRI did not have a more favorable clinical course than those using a benzodiazepine, nor were there significantly better rates of remission in patients using SSRIs and benzodiazepines concomitantly

Bruce et al, Am J Psychiatry, 2003;160(8):1432-8

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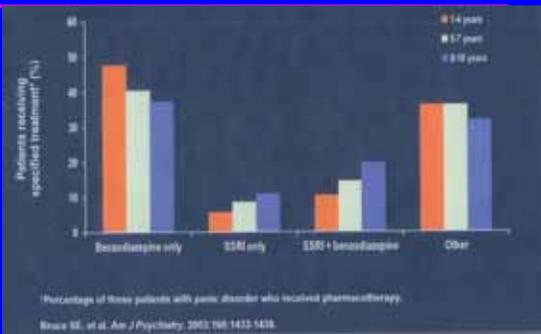
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## Longitudinal Follow-up Study of Patients with Panic Disorder 1989-2001 (N=443)




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## Benzodiazepines

- ◆ Benzodiazepines all work in essentially the same way but vary in:
  - Dosage
  - Rate of onset of action (diazepam and clorazepate most rapid)
  - Duration of action
  - Tendency to accumulate
  - Potency

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## Benzodiazepine Receptor

GABA is the major inhibitory neurotransmitter and it operates in more than a third of CNS synapses

Benzodiazepines enhance synaptic actions of GABA

Benzodiazepine receptor is an allosteric recognition site on the GABA receptors

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## GABA-Benzodiazepine Receptor Complex

- ◆ Pentameric structure composed of 5 distinct glycoprotein subunits that span a lipid bi-layer and form a cylindrical structure with a chloride channel as a center
- ◆ Activation causes an influx of chloride ions and membrane hyperpolarization responsible for neuronal inhibition
- ◆ Benzodiazepines do not activate this process but facilitate the action of GABA by increasing the frequency of ion channel opening
- ◆ Barbiturates and high dose alcohol prolong the opening

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## GABA-Benzodiazepine Receptor Complex

- ◆ Several molecular families of subunits:  $\alpha$  with 6 isoforms,  $\beta$  with 3 isoforms,  $\gamma$  with 3 isoforms,  $\theta$  with 1 isoform and  $\rho$  with 3 isoforms
- ◆ The receptor complex is known to consist of 2  $\alpha$  subunits alternating with 2  $\beta$  subunits and a single  $\gamma$  subunit
- ◆ Each receptor complex has 2 GABA binding sites but only 1 benzodiazepine binding site. The benzodiazepine binding site is at the intersection of the pairing of the  $\alpha$  and  $\gamma$  subunits

Roy-Byrne, J Clin Psychiatry 2005;66(suppl 2):14-20

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## $\alpha 1$ and $\alpha 2$ subunits

- ◆  $\alpha 1$  subunits mediate
  - sedative
  - amnesic
  - possibly ataxic
  - anticonvulsant (to lesser extent)effects of benzodiazepines (expressed throughout the cerebral cortex). Majority of benzodiazepine receptors.
- ◆ Agents (ie zolpidem) that bind specifically to  $\alpha 1$  subunits have no effects in animals in which the  $\alpha 1$  subunit is made to be insensitive
- ◆  $\alpha 2$  subunits involved primarily in antianxiety effects of benzodiazepines (expressed in hippocampus, amygdala, and cortex on initial axonal segments of pyramidal neurons)

Weinberger DR (2001) Anxiety at the frontier of molecular medicine. New England Journal of Medicine 344:1247-1249

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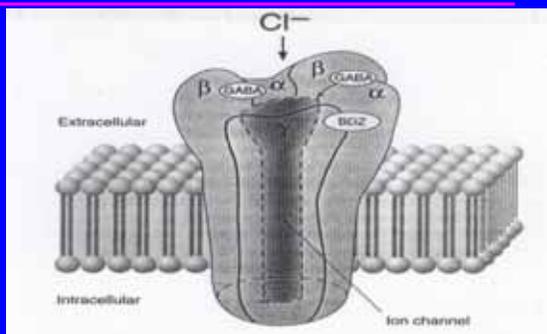
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## Pharmacodynamics of Benzodiazepines



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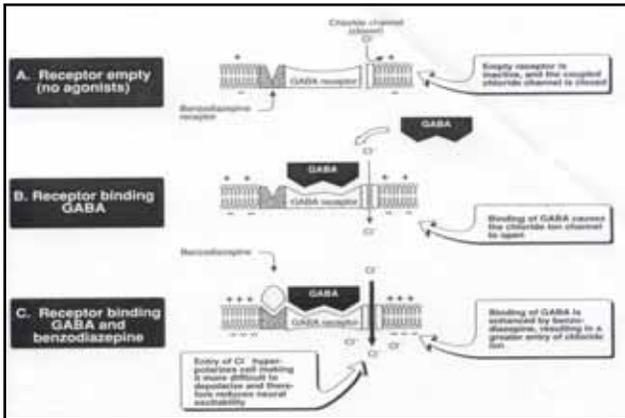
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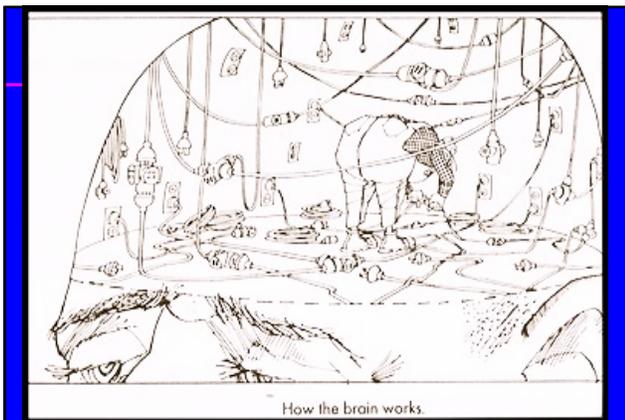
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**Benzodiazepine Agonists, Antagonists and Inverse Agonists**

- ◆ Agonists include the benzodiazepines (alprazolam, diazepam) that increase affinity of GABA for its receptor, and augment GABA-mediated inhibition.
- ◆ Antagonists (such as flumazenil) have no intrinsic activity, but block the effects of both agonists and inverse agonists by competitive receptor binding
- ◆ Inverse agonists (such as beta-carboline-3-carboxylic acid ethyl ester [B-CCE]) have opposite action of the benzodiazepines, decreasing GABA-mediated chloride responses, thereby increasing arousal and activation and promoting seizures by increasing neuronal excitability

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## Benzodiazepine Pharmacokinetics

Name	Dose	Onset	T 1/2	Metabolism	Active substances
Clonazepam	0.25	Inter	18-50	Oxidation	Clonazepam
Alprazolam	0.5	Inter	6-20	Oxidation	Alprazolam
Lorazepam	1.0	Inter	10-20	Conjugation	Lorazepam
Diazepam	5.0	Fast	30-100	Oxidation	Diazepam Desmethyldiazepam
Clorazepate	7.5	Fast	30-100	Oxidation	Desmethyldiazepam
Chlordiazepoxide	10.0	Inter	5-100	Oxidation	Chlordiazepoxide Desmethyldiazepam
Oxazepam	15	Slow	5-12	Conjugation	Oxazepam

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## Benzodiazepine Pharmacokinetics

### Metabolism

Glucuronide conjugation - rapid and metabolic products inactive

Little change with aging

lorazepam, oxazepam, and temazepam

Microsomal oxidation - slow and many metabolic products active

Significant changes with aging

Under normal circumstances (i.e. excluding cirrhosis) the metabolic products of alprazolam, triazolam, and midazolam are of little clinical importance

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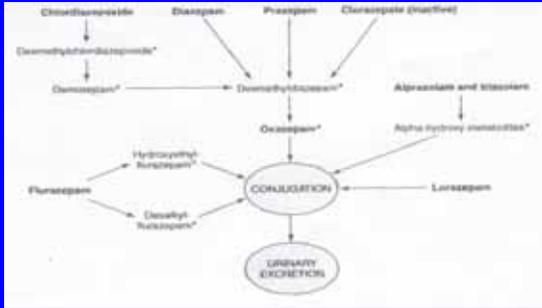
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## Biotransformation of Benzodiazepines




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## Benzodiazepine Pharmacokinetics

Oxidatively transformed drugs have longer half-life and longer duration of action

Diazepam - T<sub>1/2</sub> increases from 20 hours at 20 years to 90 hours at 90 years

Desmethyl diazepam - T<sub>1/2</sub> of 51 hours in young to 151 hours in old

Lorazepam and oxazepam - little change in T<sub>1/2</sub> with age

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## Benzodiazepines

Highly lipophilic and rapidly enter the brain tissue

Rate limiting step orally - rapidity of GI absorption

Gastric emptying slowed by food and anticholinergics

Tablets more rapidly absorbed than capsules.

Most benzodiazepines easily cross the blood brain barrier and placental barrier

IM administration - lorazepam - good

diazepam and chlordiazepoxide - unpredictable with possible precipitation

Intravenous - diazepam, lorazepam or midazolam

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## Common BZP Withdrawal Sx

### Symptoms Common in Anxiety

Anxiety	Headache	Muscle aching
Irritability	Tremor, Shakiness	Fatigue
Sweating	Dizziness	Insomnia
Concentration difficulties		

### Symptoms More Representative of Withdrawal

Nausea, Loss of Appetite  
Observable Depression  
Depersonalization, Derealization  
Increased Sensory Perception (Smell, Light, Taste, Touch)  
Abnormal Perception or Sensation of Movement  
Delirium  
Grand Mal Seizures

Roy-Byrne and Hommer. Am J Med 1988

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## Benzodiazepine Discontinuation

- ◆ **Withdrawal** - “new” time limited symptoms, not part of the original anxiety state, that begin and end depending on the pharmacokinetics of the benzodiazepine
- ◆ **Relapse** - reemergence of the original anxiety state
- ◆ **Rebound** - increase in anxiety above original baseline levels that may be a combination of withdrawal and relapse

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## Benzodiazepine Withdrawal

- ◆ **Pharmacologic Variables:**
  - a) higher daily dose of benzodiazepine (or higher plasma level)
  - b) short benzodiazepine half-life
  - c) longer duration of daily benzodiazepine therapy
  - d) rapid rate of taper (especially the final 50% of the taper)
  - e) high potency

(Rickels et al. J Clin Psychopharm 19(suppl 2):12S-16S 1999)

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## Benzodiazepine Withdrawal

### ◆ Patient Variables:

- a) diagnosis of panic disorder
- b) higher pre-taper levels of anxiety and depression
- c) concomitant alcohol and/or substance dependence or abuse
- d) higher levels of personality psychopathology (e.g. neuroticism, dependency)

(Rickels et al, J Clin Psychopharm 19(suppl 2):12S-16S 1999)

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## Benzodiazepine Withdrawal

- ◆ Non-pharmacologic variables contribute almost as much to withdrawal severity / discontinuation problems as pharmacologic variables
- ◆ Severity of withdrawal experience does not correlate significantly with the inability of the patient to taper off the BZP successfully
- ◆ Personality disordered patients sensitive to minor cues of withdrawal symptoms
  - drop out in early phases of the BZP taper (before severe symptoms occur), never giving taper a chance

(Rickels et al, J Clin Psychopharm 19(suppl 2):12S-16S, 1999)

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## Prognosis with Tapering Benzodiazepines

- ◆ If patients able to taper off BZPs, about 3/4 will be off BZPs 3 years later
- ◆ If taper attempt is unsuccessful, but intake reduced by 50%, only 39% are without a BZP 3 years later
- ◆ If patients refused a taper program, all but 14% used BZPs daily
- ◆ Patients who remained off BZPs for 3 years had a significantly lower level of anxiety and depression compared with patients continuing on BZPs over the 3 years

(Rickels et al, Am J Psych 148:757-761 1991)

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## **Benzodiazepines: Severity of Withdrawal**

Most severe - quickly eliminated, high potency BZPs (alprazolam, lorazepam, triazolam)

Intermediate severity - quickly eliminated, low potency BZPs (oxazepam) or slowly eliminated high potency BZPs (clonazepam)

Mildest severity - slowly eliminated, low potency BZPs (diazepam, clorazepate, chlordiazepoxide)

Wolf and Griffiths: Drug and Alcohol Dependence 1991

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## **Benzodiazepine Detoxification**

Gradual taper of primary sedative drug with more rapid taper first 50% of dose and more slowly for each successive 25%

Clonazepam taper for short-acting benzodiazepines

Transfer to long-acting barbiturate (diazepam 10mg = phenobarb 30 mg) and then reduce by phenobarb 30 mg per day

Carbamazepine 200-800mg daily (or valproic acid 250 mg tid) + BZP for 1-2 weeks and then taper BZP over 4 weeks; continue anticonvulsant alone for 2-4 weeks

Cognitive behavioral therapy significantly increases success rate

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## **Components of Memory**

Acquisition: Information enters via sensory route

Retention (short - term memory): The information is of interest and draws attention

Consolidation: Information of interest is transferred to long - term memory

Retrieval: Consolidation in reverse; the obtaining of a memory from long - term storage

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### Benzodiazepines and Memory

◆ **Types**

Short term memory

Semantic memory - information that is independent of context learned i.e. use / memory of words

Episodic memory - sequence of events

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### Benzodiazepines and Memory

Impair consolidation of memory and episodic memory

Anterograde amnesia (memory loss after drug has been taken) with IV administration and short half - life, high potency BZPs

Do not affect recall of information learned before drug taken

Elderly most sensitive

With discontinuation, middle-aged and elderly report improved memory and testing improves

Amnesic effects enhanced by alcohol

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### Psychomotor Performance and BZPs

Impaired cognitive and neuromotor functioning with acute and chronic dosing, though results more inconsistent with long term use

Decreased psychomotor speed

Impaired coordination - ataxia

Decreased sustained attention

Increased effects with:

Increased age

Increased dose

Peak levels

Alcohol

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### Cognitive Effects of Long-Term Use of Benzodiazepines

- ◆ Meta analysis of 13 research studies between 1980 and 2000 employing neuropsychological tests in long term users of benzodiazepines
- ◆ Duration of use was from 1 – 34 years (mean 9.9 yrs) with average dose equivalency of 17.2 mg/day of diazepam
- ◆ Long term benzodiazepine users were consistently more impaired than controls across all cognitive categories examined
- ◆ Significant limitations of data present

Barker et al, CNS Drugs 2004;18:37-48

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### Cognitive Effects of Long-Term Use of Benzodiazepines

**Figure 1. Cognitive Functions in Patients Taking Benzodiazepines Long Term\***

Mean Weighted Effect Sizes (95% 95% Confidence Intervals)

Cognitive Function	Mean Weighted Effect Size	95% CI
Attention	-0.15	-0.25 to -0.05
Psychomotor Speed	-0.15	-0.25 to -0.05
Memory	-0.15	-0.25 to -0.05
Executive Function	-0.15	-0.25 to -0.05
Verbal Ability	-0.15	-0.25 to -0.05
Visual Spatial Ability	-0.15	-0.25 to -0.05
Learning	-0.15	-0.25 to -0.05
Working Memory	-0.15	-0.25 to -0.05
Problem Solving	-0.15	-0.25 to -0.05
Reaction Time	-0.15	-0.25 to -0.05
Speed of Processing	-0.15	-0.25 to -0.05
Fluency	-0.15	-0.25 to -0.05
Complexity	-0.15	-0.25 to -0.05
Interference	-0.15	-0.25 to -0.05
Stimulus Response	-0.15	-0.25 to -0.05
Motor Control	-0.15	-0.25 to -0.05
Working Memory	-0.15	-0.25 to -0.05
Problem Solving	-0.15	-0.25 to -0.05
Reaction Time	-0.15	-0.25 to -0.05
Speed of Processing	-0.15	-0.25 to -0.05
Fluency	-0.15	-0.25 to -0.05
Complexity	-0.15	-0.25 to -0.05
Interference	-0.15	-0.25 to -0.05
Stimulus Response	-0.15	-0.25 to -0.05
Motor Control	-0.15	-0.25 to -0.05

\*Significant with p-values less than 0.05. A negative effect size indicates a negative effect on the cognitive function, and a positive effect size indicates a positive effect on the cognitive function.

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### Persistence of Cognitive Effects after Withdrawal from Long-Term Benzodiazepine Use

- ◆ Barker et al meta-analysis of same (12/13) studies. Average post-withdrawal follow-up assessment at 3 months
- ◆ Improvement in all areas of cognitive function
- ◆ Improvement never rises to the level of cognitive performance of non-benzodiazepine-using controls
- ◆ Potential of permanent cognitive defects or may take months to improve. Data not conclusive.

Barker et al, Arch Clin Neuropsychol 2004;19:107-113

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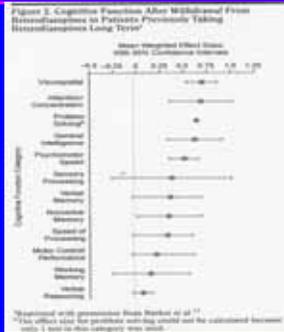
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### Persistence of Cognitive Effects after Withdrawal from Long-Term Benzodiazepine Use



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### Benzodiazepines and Driving

- ◆ Benzodiazepines impair skills of importance to driving.
- ◆ There is epidemiologic evidence of an increased risk of crash involvement in younger and older benzodiazepine users
- ◆ In older users, the annual rate of involvement in injurious crashes is up to 1.5 to 2 times higher than nonusers and increases as a function of the prescribed dose
- ◆ Long half life benzodiazepines are implicated most often

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## Falls and Benzodiazepines

- ◆ In older people use of long and short-half life BZPs increase the risk for falls and femur fracture  
(Herings et al, Arch Int Med, 1995; Leipzig et al, J Am Ger Soc, 1999)
- ◆ Risk of falling leading to femur fracture is dose dependent, irrespective of half-life or type of use (intermittent or continuous)
- ◆ High relative risk among patients:
  - prescribed benzodiazepines for the first time
  - continually exposed whose dose was increased
  - concomitantly using several benzodiazepines  
(Herings et al, Arch Int Med, 1995)
- ◆ Short half-life BZPs have significant psychomotor effects in first few hours after administration in older patients:
  - increased falls if get out of bed for any reason

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## Depression and Anxiety in Chronic Benzodiazepine Users

- ◆ Significant anxiety and depressive psychopathology remains in many long-term benzodiazepine users
- ◆ If withdrawn successfully from long term benzodiazepine treatment:
  - lower levels of anxiety and depression compared to pre-taper baseline implying benzodiazepines may worsen depression and anxiety long-term.  
(Schweizer et al, Arch Gen Psychiatry, 1990; Rickels et al, J Clin Psychopharm 1999)
- ◆ Depression and inter-dose anxiety have been noted to emerge with benzodiazepine therapy
- ◆ Deterioration in mood and social behavior in subjects on benzodiazepines noted by raters but not subjects themselves  
(Griffiths et al, Arch Gen Psychiatry, 1983)

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## Suicide/Death and Benzodiazepines

- ◆ Though safer than barbiturates, there can be completed suicides with overdoses of benzodiazepines alone, though most often combined with alcohol or other drugs

(Drummer and Ranson, Am J Forensic Med and Path, 1996, Ekkedahl et al, Acta Scan Psych, 1994; Serfaty & Masterton, Br J Psych, 1993)

- ◆ In opiate addicts, deaths linked to use of buprenorphine/heroin and benzodiazepines, most likely related to respiratory depression

(Reynaud M et al, Addiction, 1998)

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## Benzodiazepines and Respiratory Function

- ◆ Benzodiazepine use is risk factor for pulmonary aspiration in neurologically impaired long-term care patients

(Pick et al, J Am er Soc, 1996)

- ◆ Aspiration, as well as respiratory depression may be a cause of death in benzodiazepine overdoses

(Drummer and Ranson, Am J Forensic Med Path, 1996)

- ◆ Benzodiazepines contraindicated in patients with sleep apnea or significant respiratory disease because of risk of respiratory depression

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## Victimization and Benzodiazepines

- ◆ Robbery and sexual assault (including 'date-rape') have been associated with the involuntary and voluntary use of benzodiazepines, often with use of other drugs or alcohol

(Boussairi et al, Clin Tox, 1996, Calhoun et al, J Psychoactive Drugs, 1996)

- ◆ Flunitrazepam (Rohypnol):

- rapid onset, intermediate acting, highly potent (10 times more potent than diazepam) hypnotic BZP
- never been marketed in the United States but has been smuggled in the country
- noted for abuse/alleged use to facilitate 'date rape'
- not clear it poses greater public health risk than other benzodiazepines

(Woods, J Clin Pharm, 1998) (Simmons and Cupp, Ann Pharmacotherapy, 1998)

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## Benzodiazepines and Pregnancy

- ◆ A syndrome of dysmorphic features, growth aberrations, and abnormalities of the central nervous system reported in infants exposed to benzodiazepines during pregnancy (Laegreid et al, J Peds, 1989; Laegreid et al, Dev Med Child Neurol;1990)
- ◆ Lower birth weight in babies with maternal use of benzodiazepines has been reported. (Laegreid et al, Neuropediatrics, 1992)
- ◆ However these findings have not been confirmed by others and alternative causes for these abnormalities have been suggested. (Dolovich et al, 1998)
- ◆ Sedation and withdrawal has been shown in infants of mothers taking benzodiazepines up to term (Bergman et al, Lancet, 1992; Laegreid et al, Neuropediatrics,1992)

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## Benzodiazepines Use in Pregnancy and Major Malformations or Oral Cleft

- ◆ Meta-analysis of studies from 1966 to present, 23 studies included with first trimester exposure
- ◆ Analysis of cohort studies showed fetal exposure to benzodiazepines was not associated with major malformations
- ◆ Analysis of case-control studies showed a small association between exposure to benzodiazepines and development of major malformations or oral cleft alone
- ◆ Recommended level 2 ultrasonography should be used to rule out visible forms of cleft lip (Dolovich et al, BMLJ; 1998, 317:839-843)

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## Reinforcement and Benzodiazepines

- ◆ Benzodiazepines are reinforcers in:
  - subjects with histories of drug abuse
  - subjects with histories of moderate social alcohol drinking
  - subjects with a history of low frequency “recreational” drug use that does not meet the diagnostic criteria for abuse and dependence
  - abstinent alcoholics and children of alcoholics have reinforcing responses to benzodiazepines
  - anxious and insomniac subjects
- ◆ Not reinforcing in normal subjects without histories of moderate drinking, anxiety or insomnia

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## Benzodiazepines and the Alcoholic



(Librium) “During the rehabilitation period...strengthens the physician patient relationship...Librium therapy helps reduce the patients need for alcohol by affording a constructive approach to his underlying personality disorders”

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## Rates of Benzodiazepine Abuse

Clinical and descriptive data regarding benzodiazepine addiction are surprisingly inadequate.

<u>Population</u>	<u>Prevalence (%)</u>
General Population	Unknown
Alcohol Abusers	30-75
Opiate Abusers	Up to 80
Inpatient Drug Abusers	
Isolated BZP Abusers	12
Poly Drug Dependent	80

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## Patterns of Benzodiazepine Abuse

### Inappropriate chronic use by patients

- Older
- Lower daily doses
- More withdrawal symptoms

### Polydrug abuse

- Younger
- Higher daily doses
- More escalation of dose

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## Benzodiazepines - Uses

- ◆ Psychiatric disorders - mainly anxiety, panic and agitation
- ◆ Anticonvulsant
- ◆ Muscle relaxant properties
- ◆ Alcohol withdrawal

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## Chronic Benzodiazepine Use

- ◆ Use reevaluated at regular intervals :
  - diagnosis correct?
  - distress and disability warrant use?
  - benzodiazepine providing a positive therapeutic response, with appropriate doses?
  - any other drug or alcohol addiction?
  - evidence of any BZP-induced adverse effects?
  - family member / significant other confirm effectiveness of BZP use and lack of impairment or addiction?

DuPont RL (1990). A practical approach to benzodiazepine discontinuation. Journal of Psychiatric Research 24:81-90.

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### Zaleplon, Zolpidem and Eszopiclone

Generic Name	Classification	Adult Dose	Elderly Dose	T ½	T max
Zaleplon	pyrazolopyrimidine	10 mg, 20 mg	5 mg	1 hr	1 hr
Zolpidem tartrate	imadazopyridine	10 mg	5 mg	2.5 hr, 2.9 hr in elderly	1.6 hr
Eszopiclone	Pyrolopyrazine derivative of cyclopyrrolone class	2 mg, 3 mg	1 mg	6 hr, 9 hr in elderly	1.0 hr
Zolpidem tartrate extended release	imadazopyridine	12.5 mg	6.25 mg	2.8 hr, 2.9 hr in elderly	1.5 hr, 2.0 hr in elderly

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### Zaleplon, Zolpidem and Eszopiclone

- ◆ Zolpidem and Zaleplon
  - actions are mediated at the alpha-1 benzodiazepine receptor subtype
  - CYP3A4 has been reported to play an important role in metabolism of zolpidem and zaleplon
- ◆ Eszopiclone - [(S)-zopiclone] is the active enantiomer of racemic zopiclone [(R,S) zopiclone]
  - Exact MOA unknown, but believed to be due to its interaction with an allosteric modulation of the GABA-A receptor complex
  - Active metabolite has low potency
  - Unpleasant taste (34%) with 3 mg dose

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### Zolpidem, Zaleplon and Eszopiclone

- ◆ Like BZPs, zolpidem, zaleplon and eszopiclone classified as Schedule IV controlled substances by DEA
- ◆ Zaleplon, zolpidem and eszopiclone decrease sleep latency with little effect on sleep stages
  - BZPs decrease sleep latency, prolong the first two stages of sleep and shorten stages 3 and 4 (deep sleep) and REM sleep

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### Ramelteon

- ◆ Selective MT1/MT2 receptor agonist
- ◆ Negligible affinity for GABA-A receptor complex
- ◆ 1/2 Life = 1-2.6 hours
- ◆ More than 17 times more potent than melatonin
- ◆ No known abuse liability
- ◆ Metabolized by CYP 1A2 with minimal involvement of CYP 2C9 and 3A4
- ◆ Should not be used with fluvoxamine
- ◆ 8 mg dosage strength
- ◆ Not scheduled as a controlled substance by FDA

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### Abuse Potential of Zolpidem, Zaleplon and Eszopiclone

- ◆ Evidence is mixed regarding abuse potential of the zaleplon, zolpidem and zopiclone.
- ◆ Some studies showing comparable drug liking, reinforcing effects and decrements on performance tests depending on dose and time tested compared to benzodiazepines and some showing less abuse potential compared to benzodiazepines
- ◆ There are case reports of abuse and withdrawal from zolpidem and zopiclone
- ◆ Based on prescription numbers, reported dependence for zopiclone and zolpidem is “remarkably lower” than that of benzodiazepines used for insomnia

Hajak et al, Addiction, 2003 Oct;98(10):1371-8

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### Barbiturate and Barbiturate-Like Drugs

- ◆ Except for the anticonvulsant actions of phenobarbital and its congeners, the barbiturates and other barbiturate-like sedative-hypnotics (with the partial exception of meprobamate) have similar properties
- ◆ The withdrawal syndrome following chronic use can be severe and life threatening
- ◆ Low therapeutic index and low degree of selectivity
  - therapeutic effect of sedation / anxiolysis accompanied by CNS depression

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### Barbiturate and Barbiturate-Like Drugs

- ◆ Other disadvantages compared to the benzodiazepines :
  - induce hepatic enzymes (more drug interactions) i.e. oral contraceptives
  - produce more tolerance, impairment and toxicity
  - greater liability for development of abuse and dependence
  - more dangerous in overdose; acute intoxication produces respiratory depression and hypotension

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### Barbiturates

- ◆ Pentobarbital, secobarbital, and butobarbital are used as sedatives and butalbital is marketed in combination with analgesic agents
  - classified as short to intermediate acting barbiturates
    - » half-life of these drugs (from 15-80 hours)
    - » will accumulate during repetitive administration
- ◆ Phenobarbital - long acting barbiturate (half-life 80-120 hours) used predominately for treatment of seizure disorders, abuse is relatively uncommon
- ◆ Ultra-short-acting agents (thiopental or methohexital) are employed as anesthetics

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## Glutethemide

- ◆ Pharmacology is like the barbiturates but it also exhibits pronounced anticholinergic activity
- ◆ Erratically absorbed
- ◆ In acute intoxication the symptoms are similar to barbiturate poisoning with somewhat less severe respiratory depression
  - Antimuscarinic actions cause xerostomia, ileus, urinary bladder atony, long-lasting mydriasis and hyperpyrexia, which can persist for hours after the patient has regained consciousness
  - In some cases there can be tonic muscle spasms, twitching and even convulsions

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## Chloral Hydrate

- ◆ Rapidly reduced to the active compound, trichloroethanol, largely by hepatic alcohol dehydrogenase.
- ◆ Trichloroethanol conjugated with glucuronic acid and excreted mostly into the urine.
- ◆ The plasma half-life is 4 to 12 hours.
- ◆ Trichloroethanol exerts barbiturate-like effects on GABA A receptor channel.
- ◆ Chloral hydrate is irritating to the skin and mucous membranes
  - causes unpleasant taste, epigastric distress, nausea, and occasional vomiting, especially if the drug is insufficiently diluted or taken on an empty stomach

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## Chloral Hydrate

- ◆ Chloral hydrate and alcohol in combination is the “Mickey Finn”
- ◆ Overdose effects resemble acute barbiturate intoxication, although may have icterus.
- ◆ Chronic users may exhibit sudden acute intoxication, which can be fatal; this results either from an overdose or from a failure of the detoxification mechanism secondary to hepatic damage

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## Meprobamate

- ◆ Important aspect of intoxication with meprobamate is formation of gastric bezoars consisting of undissolved meprobamate tablets - treatment may require endoscopy and mechanical removal of the bezoar
- ◆ Carisprodol (SOMA) - Skeletal muscle relaxant whose active metabolite is meprobamate, also has abuse potential and is a 'street drug'

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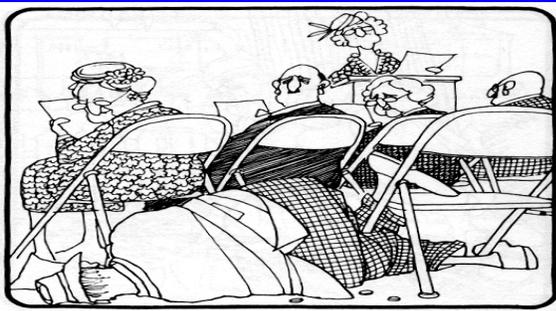
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Sid Baldwin continues to be nagged by a short attention span.

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## Additional Slides for Your Perusal

I thought you might use these to study.

Good luck!

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## Benzodiazepine Structure

- ◆ The core structure of benzodiazepines consists of a benzene ring fused to a seven-membered 1,4 diazepine ring thus their name
- ◆ Almost all also have a 5-aryl substituent ring
- ◆ They differ from one another in the chemical nature of the substituent groups at positions 1,2,3, and 4 (of the diazepine ring), position 7 (of the benzene ring), and position 2' (of the 5-aryl substituent ring)

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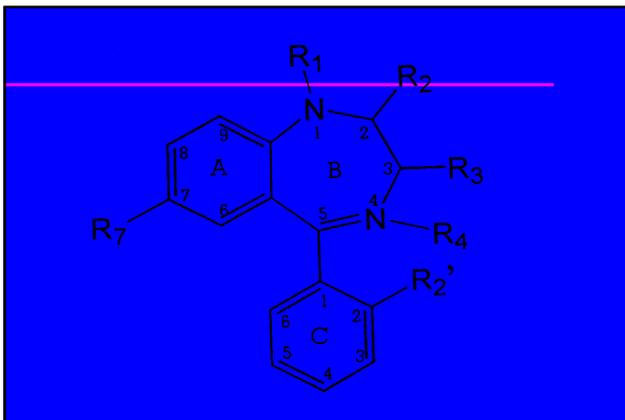
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## Absorption of Benzodiazepines

- ◆ Highly lipophilic and rapidly enter the brain tissue
- ◆ Rate limiting step in oral dosing - rapidity of absorption from the GI tract.
- ◆ Gastric emptying slowed by anticholinergic agents and food.
- ◆ Tablets are more rapidly absorbed than capsules.
- ◆ Rapidly absorbed benzodiazepines (diazepam) produce more euphoria / more reinforcing
- ◆ Slower absorbed drugs (oxazepam, temazepam) have longer latency period, will produce a lower peak, perceived as less intense and more gradual.
- ◆ May be modified by gastric acid to affect absorption (ie clorazepate is prodrug modified by acid hydrolysis in the stomach to form desmethyldiazepam, then absorbed with a fast onset of action).
- ◆ Only lorazepam available for sublingual administration but absorption rate not different from oral administration

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## Benzodiazepine Absorption

- ◆ Chlordiazepoxide, diazepam, lorazepam and midazolam are formulated to be administered IM
- ◆ Chlordiazepoxide may precipitate locally and is slowly and poorly absorbed
- ◆ Diazepam is absorbed in a variable and unpredictable manner
- ◆ There is little experience with midazolam except for preanaesthetic use
- ◆ The rates of absorption and peak plasma levels with IM lorazepam and midazolam are higher than for oral administration

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## Five Types of Benzodiazepines

- 2-keto compounds (clorazepate, chlordiazepoxide, diazepam, halazepam, prazepam, flurazepam). Metabolized to desmethyldiazepam. Oxidized in the liver before conjugated and tend to have long half-lives as desmethyldiazepam has a 30-200 hour half-life, with the length increasing with age
- 3-hydroxy compounds (lorazepam, oxazepam, temazepam). Active compounds with shorter half-lives, rapidly metabolized by direct conjugation with a glucuronide radical and do not generate active metabolites. Age, drug interactions or liver function does not affect the metabolism.

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## Five Types of Benzodiazepines

- Triazolo (alprazolam, triazolam, estazolam) and
- imidazo (midazolam) compounds have short half lives, transformed into hydroxylated compounds prior to conjugation, but these hydroxylated intermediates, although quite active, are conjugated rapidly and do not accumulate
- 7-nitro compounds (clonazepam) which are active, have long half-lives, no active metabolites, and are metabolized by nitroreduction.

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## Drug Interactions

- ◆ BZPs have additive CNS effects with other sedative drugs
- ◆ The metabolism of BZPs (except the 3 hydroxy compounds) is mainly catalysed by CYP3A3/4 isoenzyme - impaired in old age and significant hepatic dysfunction
- ◆ Diazepam, at high concentrations, is catalysed by CYP3A3/4 and at low concentrations CYP2C19 is mainly involved
- ◆ Specific SSRIs, nefazodone, the antifungotics ketoconazole and itraconazole, macrolide antibiotics such as erythromycin, cimetidine, omeprazole, ritonavir, grapefruit juice may all inhibit CYP3A4 and increase BZP levels
- ◆ Re the SSRIs, paroxetine and citalopram unlikely to cause interactions with benzodiazepines and sertraline inhibits these enzymes only mildly to moderately at usual therapeutic doses so the potential for interaction is low

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## Endogenous Benzodiazepines and “Endozepines”

- ◆ Endogenous benzodiazepines such as diazepam and nordiazepam as well as other benzodiazepine-like compounds termed ‘endozepines’, which are not halogenated, have been found in human blood and brain
- ◆ They are present in only trace amounts but are increased in patients with cirrhosis and may be a factor in hepatic encephalopathy
- ◆ The source is unknown but they are in vegetables and medicinal plants, such as in camomile or may be synthesised by intestinal bacteria

Baraldi M, Avallone R, Corsi L et al (2000) Endogenous benzodiazepines. *Therapie* 55:143-146

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## Barbiturates, Alcohol and Toxicity

- ◆ Barbiturates also are positive modulators of GABA<sub>A</sub> receptors
  - bind to undefined site on the GABA complex
  - interact with GABA in a concentration dependent manner distinct from benzodiazepines
- ◆ Alcohol also potentiates GABA on receptors with the  $\gamma 2$  subunit, increasing the flow of chloride ions, causing sedation and psychomotor problems.
- ◆ At higher concentrations (>250 mg/dl) alcohol has a direct action on the receptor causing a prolonged opening of the chloride channel that is GABA independent.
- ◆ This prolonged opening is also true for barbiturates but not benzodiazepines.
- ◆ This explains why alcohol and barbiturates are much more toxic in overdose - the chloride influx may result in paralysis of the neurons responsible for respiratory drive. for respiratory drive. (Nutt, Br J Psychiatry 1999)

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## Tolerance Testing

- High or erratic dose, illicit source, polysubstance or alcohol plus benzodiazepine use.
- In 24-hour medically monitored setting
- 200 mg pentobarbital PO Q 2h - hold for intoxication, slurred speech, ataxia, somnolence.
- After 24-48 hrs, calculate 24 hr stabilizing dose
- Give stabilizing dose for 24 hrs divided
- Switch to phenobarbital (30mg = 100mg pentobarbital)
- Initiate gradual taper

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## Patterns of Problematic Benzodiazepine Use

- ◆ The “recreational” abuser:
  - uses benzodiazepines to become intoxicated in an intermittent or chronic pattern of high doses
  - pattern often one of poly-drug abuse.
  - source of the drug is often illicit
  - incidence is relatively rare relative to the rate of widespread legitimate medical use, but similar to abuse of other illicit substances such as opioids or cocaine.

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## Patterns of Problematic Benzodiazepine Use

- ◆ The chronic quasi-therapeutic user:
  - often older
  - may or may not have a history of alcohol or drug abuse or may have a chronic pain problem
  - motive for use is “symptom” treatment
  - many may report unsuccessful efforts to cut down use and use to relieve or avoid withdrawal
  - incidence of this quasi-therapeutic use unknown but estimated to be relatively prevalent to the rate of prescription of benzodiazepines usually therapeutic doses are used
  - source of the drug is usually licit though may involve deception to obtain the drug (e.g. multiple physicians)

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### Benzodiazepines: Addiction Liability

- ◆ Benzodiazepines are less reinforcing and have a lower abuse potential than several barbiturates (amobarbital, pentobarbital, secobarbital ) and older generation sedative/hypnotics (glutethimide, meprobamate, methaqualone).
- ◆ Benzodiazepines vary in abuse liability based on differential subjective effects.
  - Diazepam, lorazepam, triazolam, flunitrazepam and alprazolam have relatively high abuse liability, while oxazepam, halazepam, clorazepate, prazepam and chlordiazepoxide do not.
  - The speed of onset of pleasurable effects is an important factor in addiction potential

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### Benzodiazepine Addiction

- ◆ Clinical and descriptive data regarding benzodiazepine addiction are surprisingly inadequate.
- ◆ Reports document populations of benzodiazepine-addicted patients, largely from hospitals and addiction treatment centers (Busto et al, J Clin Psychopharm 1996, Finlayson & Davis, Mayo Clin Proc, 1994)
- ◆ A high prevalence (40% or more) of benzodiazepine dependence in outpatient users of benzodiazepines has been noted in a Dutch study (Kan et al, Acta Psych Scand, 1997)
- ◆ Survey data give evidence of large number of persons engaged in long-term use of benzodiazepines, and a significant amount of abuse/non-medical use, but difficult to translate that into estimates of addiction (Griffiths and Weerts, Psychopharm, 1997)

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### Benzodiazepines and Addiction

- ◆ 194 pts with long-term BZP use in a German university clinic
  - ◆ Daily intake began immediately after the first Rx in 80%
  - ◆ 34% reported daily dose of 30 mg diazepam per day
  - ◆ 70% had additional abuse of alcohol and/or other drugs
  - ◆ BZPs were the first substances abused in 49%
  - ◆ 30% had dx of organic brain syndrome at some point
  - ◆ During use of BZPs, patients somatic complaints, depressed mood and anxiety increased and after detoxification symptoms improved in 80%
- Luderer et al, Psychiatr Prax:2/6; (231-234), 1995

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## Buprenorphine and Benzodiazepines

- ◆ Benzodiazepine use with buprenorphine is a “relative contraindication”
  - 20 deaths, all but one had benzodiazepines (Taequi et al J Anal Toxicol, 1998 Oct;22:430-44)
  - 2 series of 39 and 78 deaths in buprenorphine patients (Kintz, Forensic Sci Int. 2001 Sep 15;121:65-69)
    - » None buprenorphine alone
    - » 79.5% in one series and 76.9% in the other also had benzodiazepines
  - 13 deaths in buprenorphine patients (Kintz, Clin Biochem. 2002 Oct;35:513-6)
    - ◆ None had buprenorphine alone
    - ◆ Benzodiazepines in 9 cases
    - ◆ All were large dose illicit use, ½ IV illicit use

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## Benzodiazepines – Psychiatric Uses

- ◆ Generalized Anxiety Disorder
- ◆ Adjustment Disorder with Anxiety
- ◆ Anxiety in the Medically Ill
- ◆ Panic Disorder
- ◆ Social Phobia
- ◆ Premenstrual Dysphoric Disorder
- ◆ Obsessive Compulsive Disorder - primary rx and augmentation
- ◆ Schizophrenia and Other Psychosis – augmentation / agitation
- ◆ Depressive Disorders - augmentation
- ◆ Bipolar Disorder - augmentation
- ◆ Movement Disorders - Akathesia, Catatonia/Rigidity
- ◆ Insomnia and Other Sleep Disorders
- ◆ Alcohol Withdrawal

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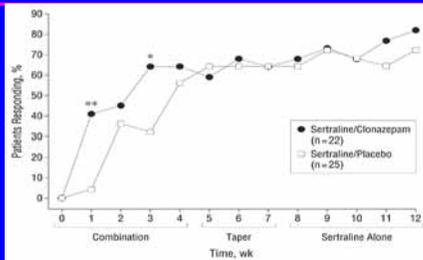
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## Early Coadministration of Clonazepam with Sertraline for Panic Disorder



- ◆ 50 pts with panic disorder randomized to double-blind trial. All received sertraline for 12 weeks with target dose of 100 mg and randomized to receiving either clonazepam 0.5 mg tid or placebo for 4 weeks then tapered over 3 weeks
- ◆ Goddard et al, Arch Gen Psychiatry, 2001;58:681-86

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### Barbiturates and Alcohol and the GABA Receptor

1. Barbiturates exert their effect by enhancing GABA receptor binding and prolonging the opening of Cl channels.
2. In higher doses, barbiturates may act directly on the chloride channel without GABA.
3. At higher concentrations (>250 mg/dl) alcohol has a direct action on the receptor causing a prolonged opening of the chloride channel that is GABA independent.

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### Zaleplon and Zolpidem

- ◆ Zolpidem (Ambien and Ambien CR), an imidazopyridine, and Zaleplon (Sonata), a pyrazolopyrimidine, are non-benzodiazepine hypnotics with rapid onset (within 1 hour), short duration of action, and short half-lives (zolpidem: 2.4 hours and zaleplon: 1 hour)
- ◆ Their actions are mediated at the omega-1 benzodiazepine receptor subtype
- ◆ Both have a dosage range of 5 to 20 mg with 5 mg being the starting dose in the elderly or the medically ill
- ◆ Both seem relatively safe in the elderly, especially compared to longer acting benzodiazepine hypnotics
- ◆ Both extensively metabolized in the liver, eliminated by renal excretion and have no active metabolites
- ◆ Both potentiate psychomotor impairment with alcohol

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### Eszopiclone

- ◆ Nonbenzodiazepine hypnotic, pyrrolopyrazine derivative derivative of the cyclopyrrolone class, binds to GABA receptors but exact mechanism of action unknown
- ◆ Dose: 1-3 mg
- ◆ Little withdrawal and may not lose effectiveness over 6 months of use.
- ◆ High fat and heavy meal may reduce effect of eszopiclone on sleep onset
- ◆ Subjects 65 years and older had an increase of 41% in total exposure and slightly prolonged elimination of eszopiclone with  $T_{1/2}$  of 9 hours
- ◆ If there is severe liver impairment, the exposure was increased 2-fold and  $t_{1/2}$  was not changed
- ◆ Unpleasant taste (34%) with 3 mg dose

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### Abuse Potential of Zaleplon

- ◆ Zaleplon at high doses (25, 50 and 75 mg), triazolam (0.25, 0.5, and 0.75 mg) and placebo were compared for abuse potential and behavioral effects
- ◆ Zaleplon and triazolam produced comparable dose-dependent decrements on several performance tasks
- ◆ Subject rated measures that reflect abuse potential (e.g. drug liking, good effects and monetary street value) suggested that zaleplon and triazolam were comparable

(Rush CR, Frey JM, Griffiths RR (1999) Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. Psychopharmacology 145:39-51)

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### Abuse and Dependence Potential for Zolpidem and Zopiclone

- ◆ Medline search from 1966 to 2002
- ◆ 36 cases for zolpidem and 22 cases for zopiclone abuse/dependence
- ◆ In extreme cases dose increases reached a factor of 30 – 120 above recommended doses
- ◆ Majority of patients had a history of former drug or alcohol abuse and/or other psychiatric conditions
- ◆ Based on prescription numbers, reported dependence similar for both drugs and “remarkably lower” than that of benzodiazepines used for insomnia

Hajak et al. Addiction. 2003 Oct;98(10):1371-8

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### Eszopiclone

- ◆ Eszopiclone [(S)-zopiclone] is the active enantiomer of racemic zopiclone [(R,S) zopiclone]
- ◆ Virtually all sedative/hypnotic activity of racemic zopiclone is attributable to the (S)-isomer
- ◆ Exact MOA unknown, but believed to be due to its interaction with an allosteric modulation of the GABA-A receptor complex

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## Behavioral Pharmacology of Zolpidem

- ◆ Literature suggests that zolpidem similar to benzodiazepines in terms of its reinforcing effects, abuse potential, subject-rated effects (in individuals with and without a histories of drug or ethanol abuse)
- ◆ Some evidence to suggest that the tolerance and dependence-producing effects may be less than those of benzodiazepines, though paucity of appropriate studies of the question

Rush CR (1998) Pharm, Biochem and Behav 61:253-269

- ◆ There are isolated cases of abuse and withdrawal symptoms reported with zolpidem  
(Cavallaro et al, 1993; Gericke and Ludolph, 1994)

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## Psychomotor Effects of Zaleplon and Zolpidem

- ◆ Zaleplon 10 mg - no decrements in psychomotor performance, memory or learning compared with placebo after 1.25 hours though zolpidem 10 mg and triazolam 0.25 mg did (Troy et al, 2000, J Clin Psychopharm 20:328-337)
- ◆ Zolpidem (compared with temazepam and triazolam) produces similar impairment of learning, recall, and performance as well as estimates of drug effects  
(Rush & Griffiths, 1996)
- ◆ Zolpidem 15 mg impaired coordinative, reactive and cognitive skills at 1 and 3.5 hours more clearly than diazepam 15 mg, oxazepam 30 mg, and ethanol  
(Mattila et al, 1998)
- ◆ Zolpidem appears to induce minimal next-day effects  
(Darcourt et al, 1999)

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## Buspirone (Buspar)

- ◆ Azapirone class - 5HT 1A partial agonist
- ◆ Does not bind to the BZP - GABA receptor complex
- ◆ T 1/2 is 2 - 8 hours
- ◆ As efficacious as benzodiazepines for GAD
- ◆ "Lag time" of 1 - 2 weeks
- ◆ No muscle relaxant or anticonvulsant properties
- ◆ Less sedation or psychomotor effects compared to BZPs
- ◆ Abuse potential low and no withdrawal symptoms
- ◆ Prior use of BZPs may reduce effectiveness
- ◆ Dose : 5 - 10 mg tid

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## Bupirone

- ◆ In anxious alcoholics who received weekly relapse prevention therapy in addition to bupirone found bupirone superior to placebo in:
  - the reduction of anxiety
  - the retention in treatment
  - the reduction of drinking days in follow-up
  - delayed return to heavy drinking(Kranzler et al 1994 Arch Gen Psychiatry 51:720-731)
- ◆ In patients with GAD who had recent history of benzodiazepine treatment:
  - greater discontinuation rates
  - more adverse events
  - less efficacycompared to patients treated with bupirone who had no previous benzodiazepine treatment  
(DeMartino et al J Clin Psychiatry 61:91-94)

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## Bupirone in the Rx of Anxiety

### Advantage

- No sedation
- No withdrawal
- No interaction with alcohol
- No impaired cognition
- No psychomotor effects
- Well tolerated
- Safe in overdose

### Disadvantage

- No sedation
- Gradual onset of effects
- Titration of dose
- Multiple daily dosing
- Lower acceptance by recent BZP users
- Efficacy questions

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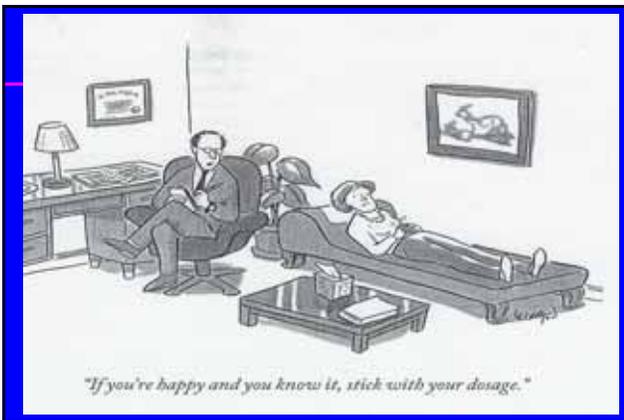
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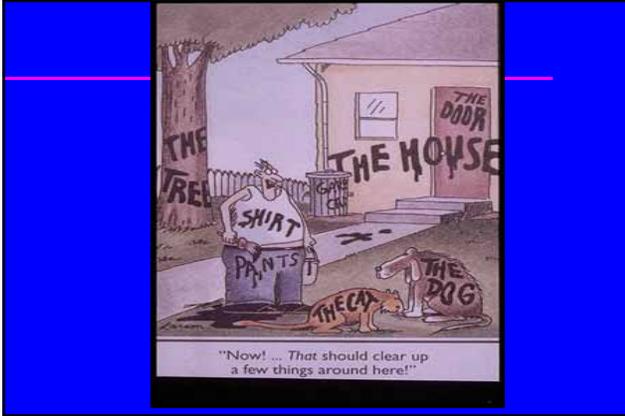
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