

Managing Insomnia and Anxiety In the Elderly

Francisco Fernandez, M.D.
Professor and Chair
USF Health Department of Psychiatry

Insomnia - Objectives

- To review the new research findings of insomnia in the elderly
- To discuss the implications for improving clinical practice

Barriers & Changes In Attitude		
	NIH – 1983	NIH – 2005
Definition	Insomnia is a symptom, not a primary disorder	Insomnia is a disorder, typically comorbid with other disorders
Treatment	Treat the primary disorder	Chronic insomnia exists and merits treatment
	Hypnotics should generally be used only for short-term treatment	Treat insomnia as well as other disorder(s): improvements in insomnia may result in improvements in other disorder(s)
Other	Chronic insomnia occurs in the context of med-psych disorders	Insomnia is associated with significant impairment in function and quality of life

Myth 1: Insomnia is Sleep Deprivation

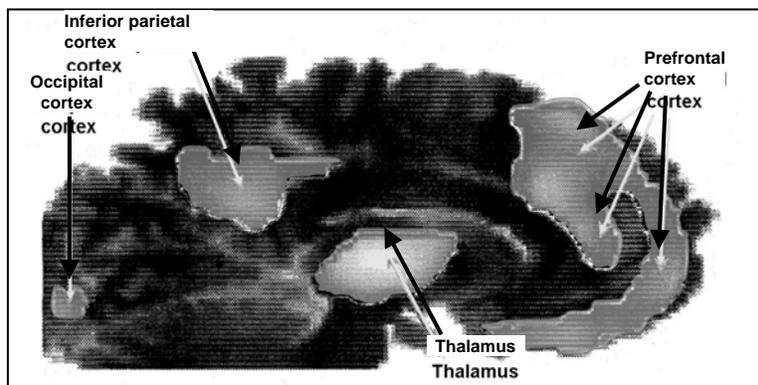
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| <ul style="list-style-type: none"> ■ Sleep deprivation <ul style="list-style-type: none"> – Adequate ability to sleep – Inadequate opportunity | <ul style="list-style-type: none"> ■ Insomnia patients <ul style="list-style-type: none"> – Inadequate ability to sleep – Adequate opportunity |
|--|--|

Myth 2: Insomnia → Symptom

- Unique set of physiologic changes
- Associated with impairment in function and quality of life

Insomnia Is Associated With Decreased Cortical Activity

¹⁸FDG PET Study of Healthy, Sleep-Deprived Adults, Showing Decreased Metabolism in the Thalamus, Prefrontal Cortex, and Inferior Parietal Cortex



FDG, fluorodeoxyglucose; PET, positron emission tomography

Thomas M et al. *J Sleep Res.* 2000;9:335-352.

Insomnia Definition (Research Diagnostic Criteria)

- A. The individual reports one or more of the following sleep-related complaints:
1. Difficulty initiating sleep
 2. Difficulty maintaining sleep
 3. Waking up too early, or
 4. Sleep that is chronically nonrestorative or poor in quality
- B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep

Edinger JD et al. *Sleep*. 2004;27:1567-1596.

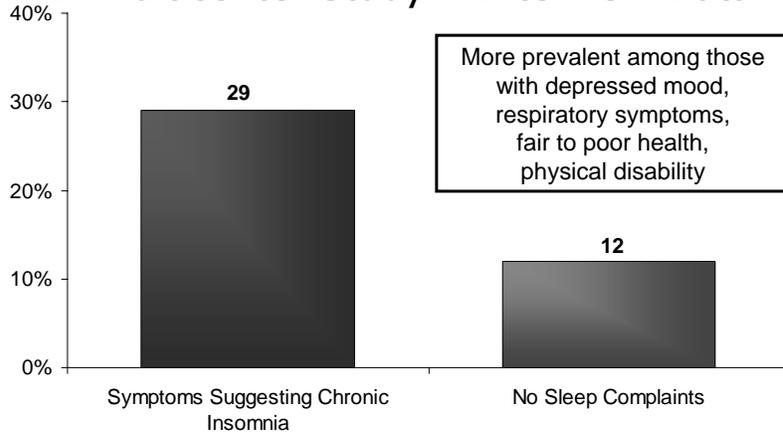
Insomnia Definition (Research Diagnostic Criteria)

- C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the individual:
1. Fatigue/malaise
 2. Attention, concentration, or memory impairment
 3. Social/vocational dysfunction or poor school performance
 4. Mood disturbance/irritability
 5. Daytime sleepiness
 6. Motivation/energy/initiative reduction
 7. Proneness for errors/accident at work or while driving
 8. Tension headaches, and/or GI symptoms in response to sleep loss
 9. Concerns or worries about sleep

Edinger JD et al. *Sleep*. 2004;27:1567-1596.

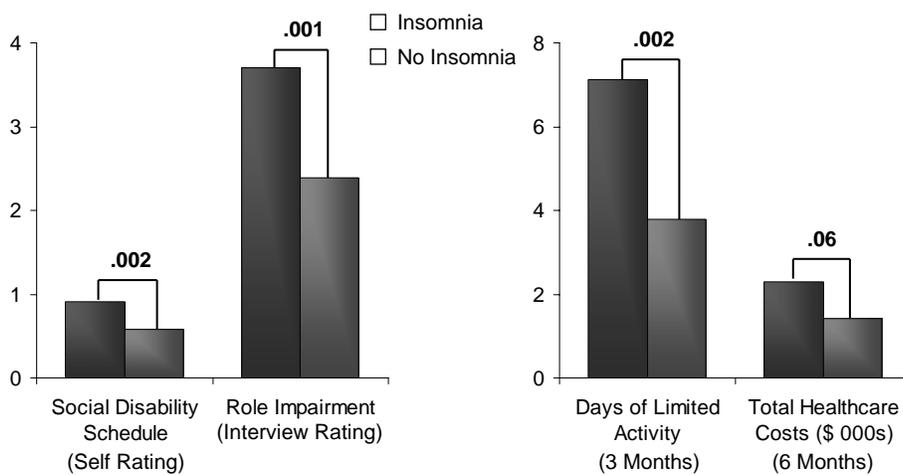
Insomnia Complaints Prevalence within Elderly (n=9,282)

NIA Multicenter Study – Interview Data



Foley DJ et al. *Sleep*. 1995;18:425-432.

Functional Impairment and Health Services Cost for Elderly Patients with and without Insomnia



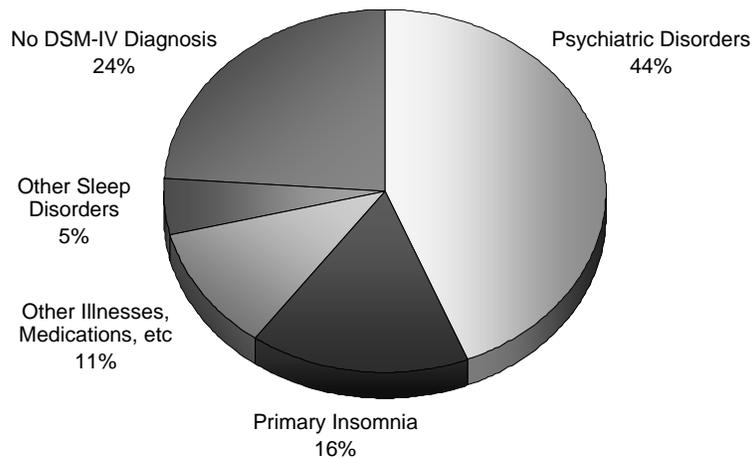
Simon GE, VonKorff M. *Am J Psychiatry*. 1997;154:1417-1423.

Myth 3: Hypnotic Use is Responsible for Falls in the Elderly

- The relationship between insomnia, hypnotic use, falls, and hip fractures was examined in older people
- 34,163 nursing home residents (76% women), aged 65 and older and with 150-210 days follow-up
- Results
 - Insomnia is associated with increased risk of future falls
 - Hypnotic use was not independently associated with falls
- Conclusion
 - In elderly nursing home residents, insomnia, but not hypnotic use, is associated with a greater risk of subsequent falls

Avidan AY et al. *J Am Geriatr Soc.* 2005;53:955-962.

Primary vs Comorbid Insomnia



Ohayon MM. *Sleep Med Rev.* 2002;6:97-111.

Medical Disorders Comorbid with Insomnia

Think about pain, breathing difficulty, and impaired mobility

- Arthritis and other chronic pain syndromes
- Congestive heart failure
- Cerebrovascular disease
- Chronic pulmonary disease
- Renal failure
- Parkinson's disease
- Dementia
- Gastroesophageal reflux

Medications and Substances Associated with Insomnia

- Alcohol
 - Acute use
 - Withdrawal
- Caffeine
- Nicotine
- Antidepressants
 - SSRI
 - SNRI, atypical
- Corticosteroids
- Decongestants
 - Phenylpropanolamine
 - Pseudoephedrine
- β agonists, theophylline derivatives
- β antagonists
- Statins
- Stimulants
- Dopamine agonists

SSRI = Selective Serotonin Reuptake Inhibitor.
SNRI = Serotonin and Norepinephrine Reuptake Inhibitor.
Schweitzer, PPSM.

Any drug that crosses the blood brain barrier and affects a neurotransmitter system may be associated with insomnia

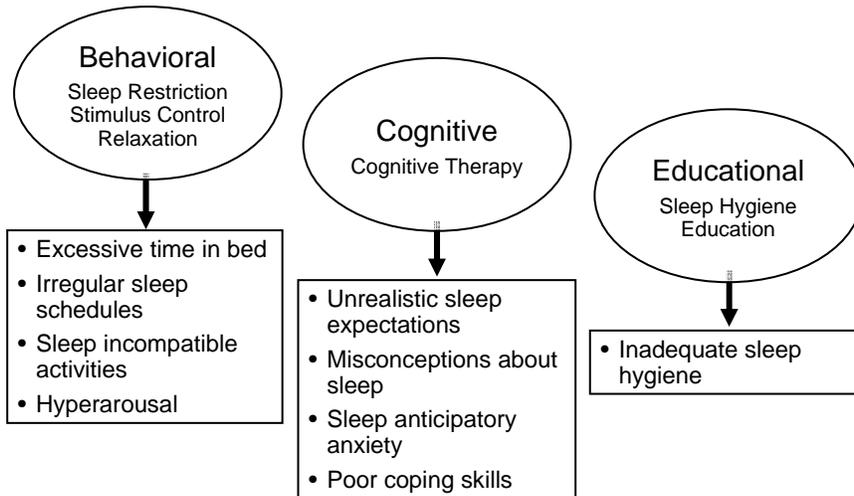
Treatment

- Cognitive and behavioral therapies
- Pharmacologic therapies
- Future directions

Barriers to Use of Behavioral Insomnia Therapies

- Lack of awareness
- Limited number of Providers with expertise
- Time requirements
- Misconceptions about patient acceptance
- Restricted insurance reimbursement

Psychologic/Behavioral Treatments (Treatment Targets)



Sleep Hygiene Education

- Caffeine: sources and effects
- Nicotine
- Role of exercise
- Light bedtime snack (milk, peanut butter)
- Alcohol, tobacco, and other substances
- Environment: light, noise, temperature

Sleep Restriction Therapy Rules

- Cut bedtime to actual amount patient reports sleeping, but not <4 hours/night
- Prohibit sleep outside of these hours
- Have patient report daily the amount of sleep obtained
- Compute sleep efficiency (SE); based on moving average of 5 nights, when SE is >85%, increase bedtime by 15 minutes
- With the elderly, SE cutoff is 80%.
Allow a 30-minute nap

Spielman AJ et al. *Sleep*. 1987;10:45-56.

Stimulus Control Therapy Rules

- Go to bed only when sleepy
- Use the bed only for sleeping – do not read, watch TV, or eat in bed
- If unable to sleep, move to another room. Stay up until really sleepy. The goal is to associate the bed with falling asleep quickly
- Repeat tactic immediately above as often as necessary
- Awaken at the same time every morning regardless of total sleep time
- Do not nap

Bootzin RR, Epstein DR. *Stimulus Control*. In: Lichstein KL, Morin CM, eds. *Treatment of late-life insomnia*. Thousand Oaks, Calif: Sage; 2000:167-184.

Relaxation

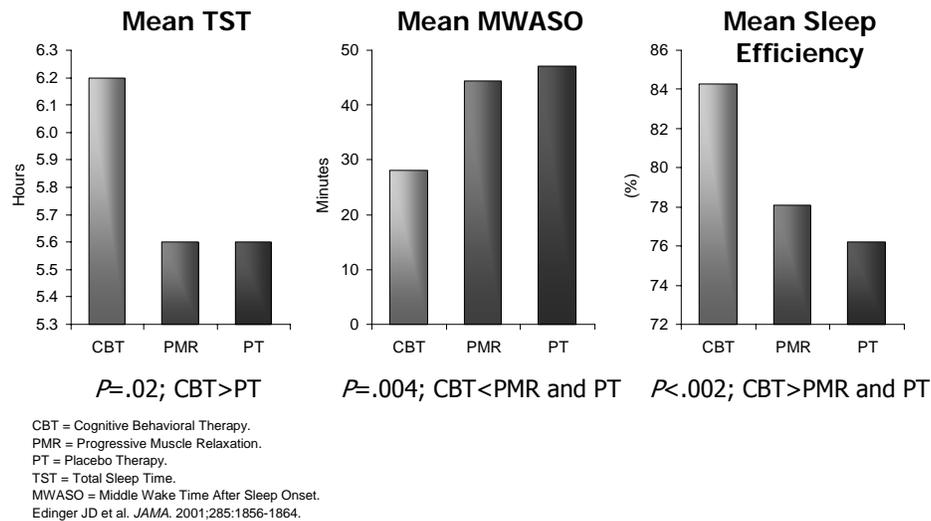
- Quiet self-inquiry
- Relaxation response (Benson, 1975)
 - Quiet environment
 - Object to dwell upon (monotonous stimulation)
 - Passive attitude
 - Comfortable position

Lichstein KL et al. 2000.

Cognitive Therapy

- Identify dysfunctional attitudes and beliefs about sleep
- Explore the validity of self-statements about sleep
- Replace dysfunctional attitudes and beliefs about sleep with more appropriate self-statements
- Worry time
 - Remove thoughts and general cognitive activation away from bedtime and moves them to a better period of the day
 - Write down thoughts (brainstorm)
 - Order priorities for attention
 - Develop problem-solving strategies
 - Regular practice is important (be proactive)

Cognitive Behavioral Therapy vs Relaxation Therapy for Primary Sleep-maintenance Insomnia



U.S. Food and Drug Administration



FDA Public Health Advisory March 22, 2004

Subject: WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS

Today the Food and Drug Administration (FDA) asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for the emergence of agitation, irritability, insomnia, and other symptoms inclusive of worsening depression or the emergence of suicidality.

The drugs that are the focus of this new Warning are:

**Fluoxetine (Prozac); Sertraline (Zoloft); Paroxetine (Paxil);
 Fluvoxamine (Luvox); Citalopram (Celexa); Escitalopram (Lexapro);
 Bupropion (Wellbutrin); Venlafaxine (Effexor); Nefazodone (Serzone);
 and Mirtazapine (Remeron).**

New Advisory Oct 9th – on Coumadin

- Food and Drug Administration (FDA) requested that Bristol-Myers Squibb strengthen its US label for warfarin (*Coumadin*) to include a black-box warning about the risk for major or fatal bleeding.
- The new black box notes that warfarin can cause major or fatal bleeding.
 - Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR).
 - Risk factors for bleeding are listed as: high intensity of anticoagulation (INR greater than 4.0), age 65 or over, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy.
- Regular monitoring of INR should be performed on all treated patients.
- The FDA Medwatch announcement also notes that warfarin prescriptions will also be issued with a new patient medication guide warning about potentially serious bleeding with the drug.

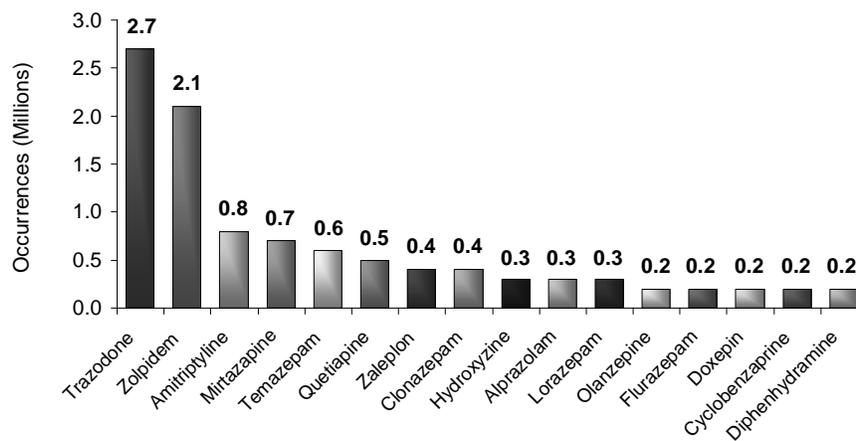
Hot off The MEDWATCH Press O2

- Food and Drug Administration (FDA) requested that nature include a black-box warning about the risk of oxygen used for respiration.
- The new black box notes that oxygen can cause major or fatal problems in humans.
 - While atmospheric oxygen and other gases are generally non-toxic, they can have a hazardous effect on your health.
 - This is more likely to occur if oxygen is enriched in your environment.
 - Risk factors include being a breathing human being with normal senses which generally can't detect changes in atmospheric concentrations.
- Apart from the hazards of oxygen enrichment of the air already described, the following misuses of oxygen are particularly dangerous and must be strictly forbidden:
 - Inflating vehicle tires, rubber boats etc.
 - Cooling or freshening the air in confined spaces.
 - Cooling the person.
 - Dusting benches, machinery and clothing.
 - **This list is by no means complete**

Goal for Today

No Clinician Left Behind

Drugs Most Commonly Used for Insomnia in 2002



Walsh JK. *Sleep*. 2004;27:1441-1442.

Pharmacologic Treatments

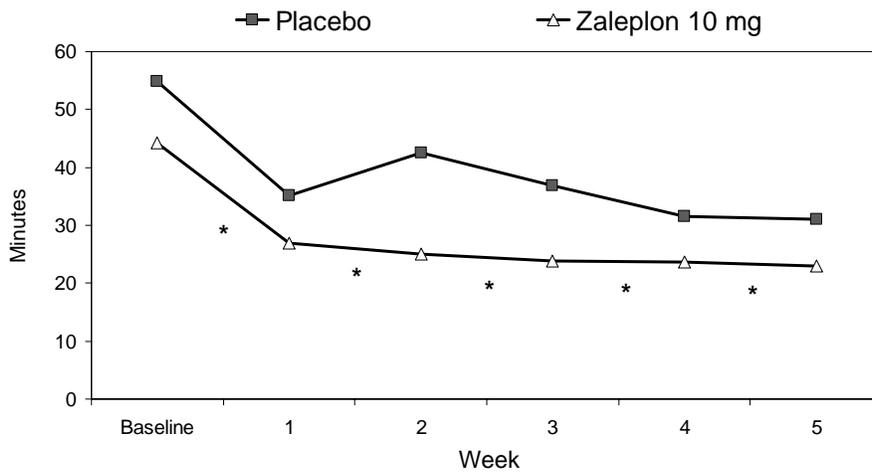
- FDA-approved drugs
 - Benzodiazepine receptor agonists
 - Melatonin receptor agonist
- Drugs used off-label (not FDA approved for insomnia)
 - Sedating antidepressants
 - Antipsychotics
- Self medication
 - Alcohol
 - H1 antihistamines (OTC sleep aids)
 - Herbal remedies

Drugs Indicated for Insomnia

Generic	Brand	T _{1/2} (Hours)	Dose (mg)	Drug Class
Flurazepam	Dalmane	48-120	15-30	BZD
Temazepam	Restoril	8-20	15-30	BZD
Triazolam	Halcion	2-6	0.125-0.25	BZD
Estazolam	Prosom	8-24	1-2	BZD
Quazepam	Doral	48-120	7.5-15	BZD
Zolpidem	Ambien	1.5-2.4	5-10	non-BZD
Zaleplon	Sonata	1	5-20	non-BZD
Eszopiclone	Lunesta	5-7	1-3	non-BZD
Zolpidem Ext. Rel.	Ambien CR	1.5-2.4*	6.25-12.5	non-BZD
Ramelteon	Rozerem	1.5-5	8	MT agonist

* Modified formulation.

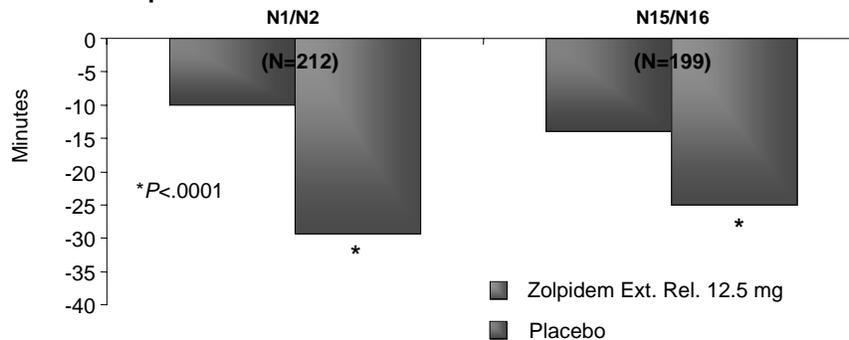
Sleep Onset (LPS)



* $P < .031$ or better vs Placebo.
Walsh JK et al. *Sleep Med.* 2000;1:41-49.

Sleep Maintenance (WASO)

- Decrease in wake time after sleep onset (adults with primary insomnia)
- Cumulative analysis of WASO from hour 1 through hour 6 postdose



Roth T et al. *Sleep Med.* 2006;7:397-406.

Adverse Events

BzRA & Other Hypnotic Agents

■ Determinants

- C_{max} , $T_{1/2}$

■ AEs

- Somnolence
- Ataxia
- Amnesia
- Dizziness
- Taste
- Nausea

■ Discontinuation effects

- Rebound insomnia, withdrawal syndrome

■ Dependence liability

- Dose escalation, self-administration outside therapeutic context

BzRA = Benzodiazepine Receptor Agonist.

BzRA Discontinuation Effects

■ Recurrence

- Return of original symptom(s)
- At basal level of severity

■ Rebound insomnia

- Single symptom
- Exacerbation relative to baseline
- 1 to 2 night duration

■ Withdrawal syndrome

- Complex of symptoms
- Longer duration

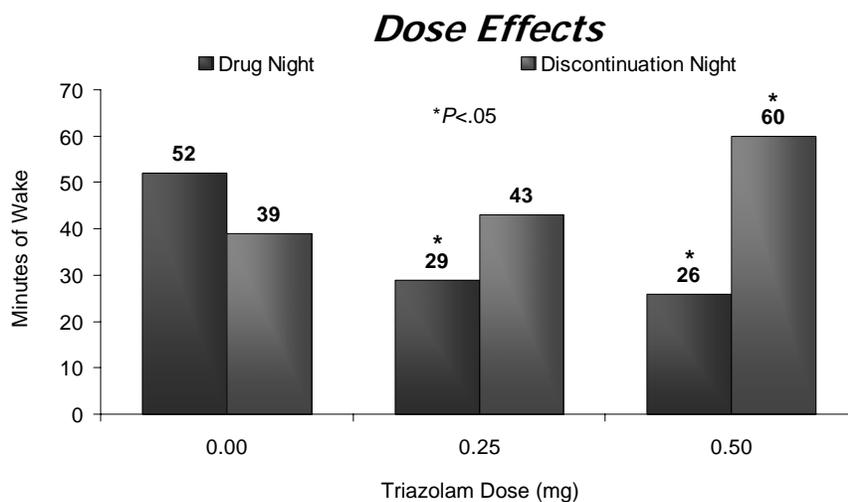
BzRA = Benzodiazepine Receptor Agonist.

Rebound Insomnia and Withdrawal

- Epidemiologic data
 - 4% to 9% of patients treated chronically with hypnotics in clinical practice experience rebound insomnia
- This was no more common with prescription hypnotics than OTC meds

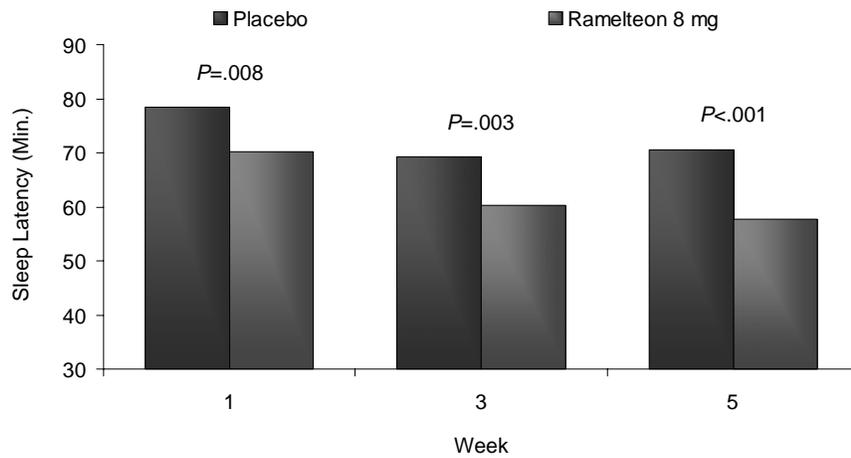
OTC = Over-the-Counter.
Balter MB, Uhlenhuth EH. *J Clin Psychiatry*. 1992;53(suppl):34-39.

Triazolam Rebound



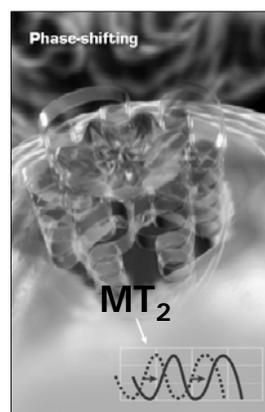
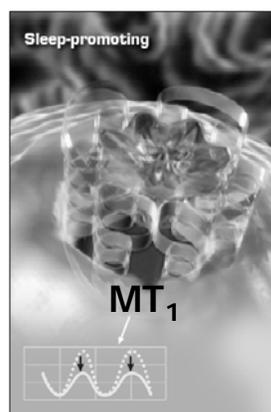
Roehrs T et al. *Br J Pharmacol*. 1986;22:143-147.

Ramelteon (Onset)



Roth T et al. Sleep Med. 2006 Jun;7(4):312-8.

New Agents With Unique Action



Ramelteon (Rozerem)

- Selective melatonin MT1/MT2 receptor agonist
 - Promotes sleep without sedation
 - Indicated for the treatment of insomnia that is characterized by difficulty with sleep onset
 - Polysomnography data
 - Reduction in sleep latency, increase in total sleep time
 - No change in number of nighttime awakenings
 - No rebound insomnia or withdrawal effects
 - No behavioral impairment
 - No abuse potential
 - No restriction on duration of use

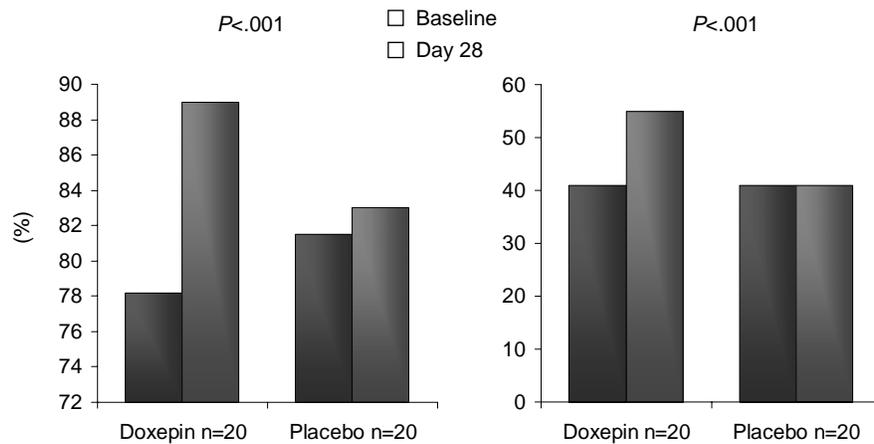
Antidepressants for Insomnia

- Not FDA-approved for use as hypnotics
- Patients with psychoactive substance use disorder history
- Patients with insomnia related to depression, anxiety
- Treatment failures with BzRA
- Suspected sleep apnea
- Fibromyalgia
- Primary insomnia (second-line agents)

Doxepin (25-50mg) in Primary Insomnia

Sleep Efficiency

Subjective Sleep Quality



Hajak G et al. *J Clin Psychiatry*. 2001;62:453-463.

Doxepin Side Effects

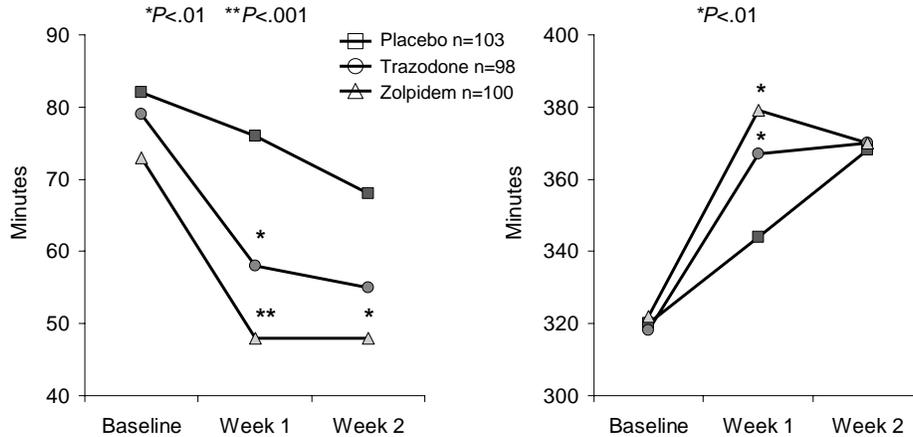
- 3 of 20 patients dropped out of a 4-week study of doxepin 25 mg HS
- Reasons
 - Increased liver enzymes
 - Exanthema
 - Leukopenia

Hajak G et al. *J Clin Psychiatry*. 2001;62:453-463.

Trazodone and Zolpidem Treatment of Primary Insomnia

Subjective Sleep Latency

Subjective Sleep Duration



Walsh, *Hum Psychopharmacol*, 1998.

Quetiapine

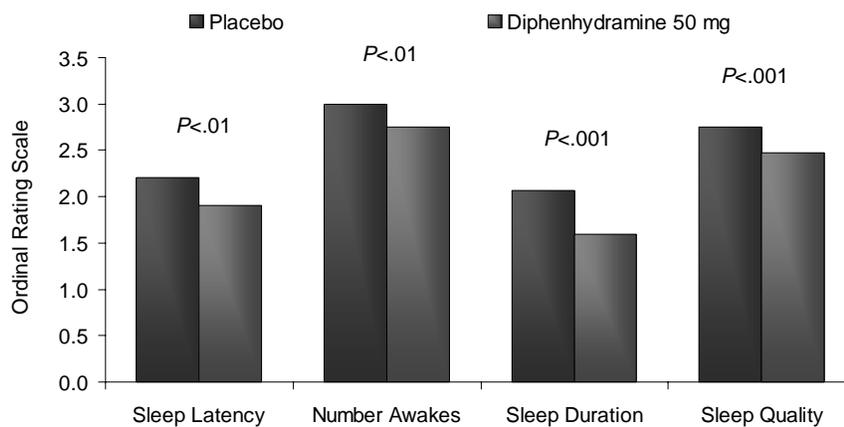
- Mechanism: Antagonist for dopamine D2, 5-HT2, muscarinic cholinergic, alpha1, H1 receptors
- Half-life: 6 hours; metabolized by CYP3A4
- Dose: 50-200 mg QHS
- Sleep effects
 - Subjectively sedating
 - No PSG studies in literature
- Adverse effects
 - Extrapyramidal effects, tardive dyskinesia, neuroleptic malignant syndrome
 - Sedation
 - Hypotension, dizziness
 - Weight gain, metabolic syndrome
 - Possible QTc prolongation
- Potential indications: Insomnia in patients with severe anxiety, bipolar disorders, psychotic disorders

Diphenhydramine

- Mechanism of action
 - Blockade of H1 receptors (basal forebrain, preoptic area of hypothalamus)
 - Blockade of cholinergic, serotonergic, adrenergic receptors
- Dose: 25-100 mg
- Elimination half-life: 3.4-5.0 hours
- Common adverse events:
 - Sedation, dizziness, incoordination, nervousness, anticholinergic effects

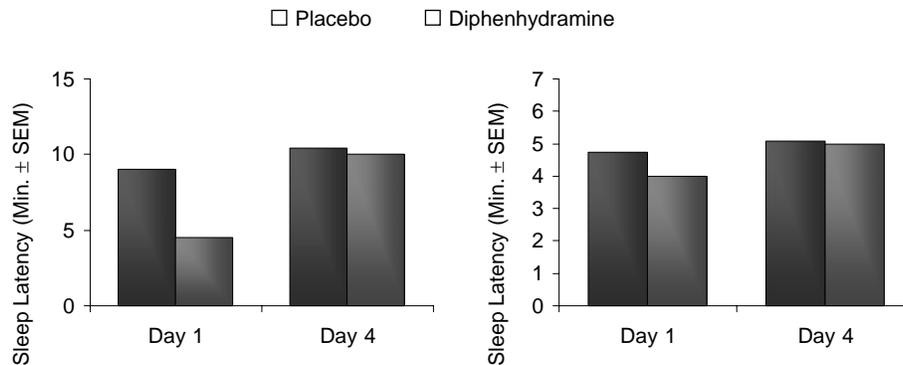
Physicians' Desk Reference® 57th ed. Medical Economics Co., Inc. Montvale, NJ: 2003.

Diphenhydramine in Insomnia



Rickels K et al. *J Clin Pharmacol.* 1983;23:234-242.

Tolerance to Antihistamines



- Daily administration
- After 4 days, antihistamine loses sedative effect
- Diphenhydramine is frequently a component of OTC sleep aids
- Not suitable for repeated use

Richardson GS et al. *J Clin Psychopharmacol.* 2002;22:511-515.

Major Conclusions from the 2005 NIH State-of-the-Science Insomnia Conference

- BzRAs are efficacious in the short-term management of insomnia
 - Frequency and severity of AEs are much lower for the newer BzRAs
 - With the exception of eszopiclone, the benefits of these agents for long-term use have not been studied using randomized control trials
- All antidepressants have potentially significant adverse effects, raising concerns about the risk-benefit ratio
- Barbiturates & antipsychotics have significant risks, use in the treatment of chronic insomnia not recommended
- Antihistamines (H1 receptor antagonists)
 - No systematic evidence for efficacy
 - Significant concerns about risks

Leshner A et al. State-of-the-Science Conference Statement June 15, 2005.

Alternate Agents

- Gaboxadol
 - Selective extrasynaptic GABA_A agonist
 - Effective across all primary outcome measures
 - First agent demonstrating an increase in SWS
- Tiagabine
 - Available anticonvulsant
 - GABA reuptake inhibitor that increases GABA via inhibition of GAT-1 GABA_A transporter
 - Increases SWS
 - Useful in substance abusers with sleep problems

Combining Pharmacologic Treatment with CBT

Research Findings

- Pharmacologic treatment provides immediate benefit
- CBT takes longer to help, but the gains are maintained for up to 2 years later

CBT = Cognitive Behavior Therapy.

New Neural Therapeutic Targets

- Direct GABA agonists
- GABA reuptake inhibitors
- Shorter-acting antihistamines (H1)
- Hypocretin antagonists
- Serotonin 5-HT_{2A} receptor antagonists
- CRH antagonists

CRH = Corticotrophin-releasing Hormone.

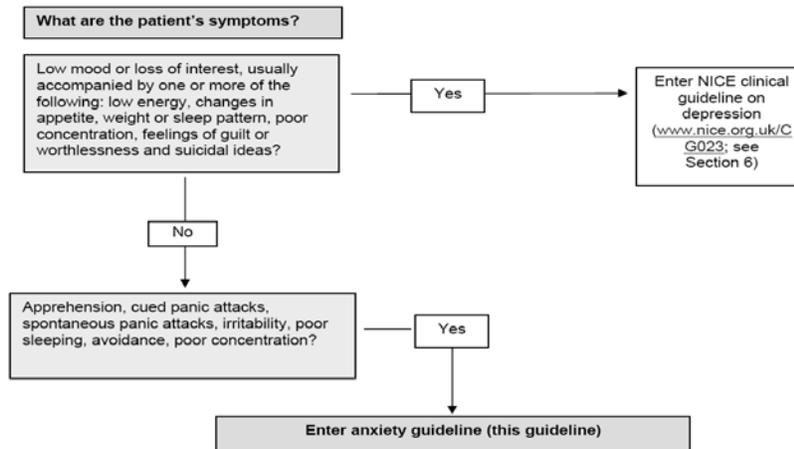
Summary

1. Insomnia is a disorder
2. Insomnia occurs in 10% of the population with clearly identified risk factors
3. Insomnia is associated with significant morbidities
4. Insomnia typically co-exists with other medical, psychiatric, and sleep disorders
5. There are safe and effective behavioral and pharmacologic treatments for insomnia

Anxiety in the Elderly

Removing Barriers and Promoting Change

Triaging Symptoms



MAD

- For patients with Mixed Anxiety and Depression, treat the Depression before treating the Anxiety disorder.

Assessment

- 2 questions: mood and interest (Whooley)
- DSM or ICD based tool (e.g. PHQ9, BDI, HADS etc)
- High risk groups: variable evidence
 - Postnatal, **elderly**, chronically physically ill/disabled
 - Social isolation
 - Post myocardial infarction, diabetics, COPD, post-procedure

PHQ-2

Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things ?	0	1	2	3
Feeling down, depressed, or hopeless?	0	1	2	3

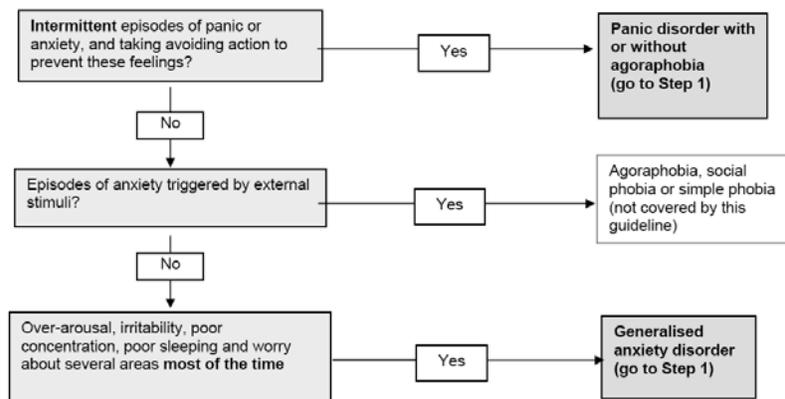
PHQ -2

- The PHQ-2 screens for depression
- Positive result:
 - score 3 or more
 - What does a positive score mean?
 - What to do with a positive scoring patient?
- Negative result:
 - score less than 3
 - What does a negative score mean?
 - What to do with a negative scoring patient?

Questionnaires

- There are two easy to use tools
 - HAD
 - Beck's
- All assess symptom severity

Anxiety Disorders



Panic Disorder

- Interventions are equally effective
- Allowing patient to select/state preference of intervention increases effectiveness of intervention

GAD

- Benzodiazepines should not be used beyond 2 – 4 weeks
- Interventions that are effective are
 - Psychological therapy
 - CBT
 - Medication
 - SSRIs

Clinical Management

- Try one intervention
 - If no improvement.....
- Try another from a different intervention type
 - If no improvement....
- Refer to psychiatrist

CBT

- CBT is not routinely available to primary care services
- Accessed through secondary care services
 - Waiting times in excess of 3 months

The DAWN Report

APRIL 2004

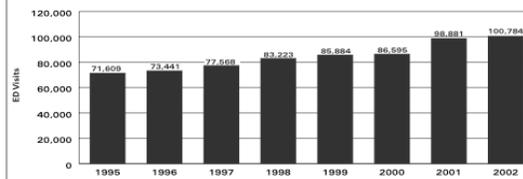
Benzodiazepines in Drug Abuse-Related Emergency Department Visits: 1995-2002

In Brief

Benzodiazepines are psychotherapeutic sedatives used to treat anxiety, insomnia, and seizures. Examples of some common brands include Valium®, Xanax®, Librium®, and Ativan®.

- In 2002, over 100,000 drug abuse-related emergency department (ED) visits involved benzodiazepines.
- Drug abuse-related ED visits involving benzodiazepines increased 41 percent from 1995 to 2002.
- Alprazolam and clonazepam were the benzodiazepines most frequently reported in drug abuse-related ED visits in 2002. However, a third of total benzodiazepine mentions were reported only as "benzodiazepine," with no specific drug name.
- Most benzodiazepine-related ED visits (78%) involved more than one drug.
- Alcohol was the substance most frequently reported with benzodiazepines in drug abuse-related ED visits.

FIGURE 1
Trends in benzodiazepine-involved ED visits: 1995-2002



Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (3/2003 update).

“Emerging research suggests that optimum benzodiazepine therapy consists of judicious, circumspect, and critically monitored use of benzodiazepines in terms of target symptoms and diagnoses”

Rickels et al

Dosage Conversion Table for Benzodiazepines

Benzodiazepines	Dosages (mg)	Half-life*
Alprazolam (Xanax)	1	6-10
Chlordiazepoxide (Librium)	25	5-100+
Clonazepam (Klonopin)	.5	18-50
Clorazepate (Tranxene)	15	30-200
Diazepam (Valium)	10	30-100+
Estazolam (Prosom)	4	20-120
Flurazepam (Dalmene)	30	1-120
Midazolam (Versed)	n/a	
Lorazepam (Ativan)	2	10-20
Oxazepam (Serax)	30	3-21
Quazepam (Doral)	30	20-120
Temazepam (Restoril)	30	10-12
Triazolam (Halcion)	1	2-3
Zolpidem (Ambien)	20	2.5
Zaleplon (Sonata)	20	1

Adapted from Giannini AJ. Drugs of abuse. 2d ed. Los Angeles: Practice Management Information Corp., 1997:121-5.

*Includes metabolites - in hours

Therapeutic Uses

- Sedative-hypnotic
- Anxiolytic
- Panic disorder
- Generalized anxiety disorder
- Muscle relaxants
- Anticonvulsants
- Alcohol withdrawal
- Premenstrual syndrome
- Psychoses
- Adjunct in mania of bipolar disorder

Other Agents

- Barbiturates - pentobarbital, phenobarbital, secobarbital, butalbital (Fiorinal)
- Azapirone: buspirone (2-10 mg TID - max 60 mg/d)
 - slow onset of action (1-3 wks)
 - not abused, no withdrawal
 - effective for anxiety disorders-not for acute
 - does not block benzo withdrawal
 - not sedating, anticonvulsant or mm relaxing
 - no resp dep/ cognitive/psychomotor impair

Anxiety

- BzRA good for immediate symptom relief faster than SSRI's for panic. long-acting, low potency preferred (clonazepam or chlordiazepoxide)
- BzRA best used for exacerbations of anxiety- short term vs continuous use

Adverse Effects

- Diminished psychomotor performance
- Impaired reaction time
- Loss of coordination, decreased attention
- Ataxia
- Falls
- Excessive daytime drowsiness
- Confusion
- Amnesia
- Increase of existing depressed mood
- Overdose rarely lethal

REINFORCING EFFECTS

- Increased with rapid drug effect - alprazolam
- Subjective effects - high - diazepam, lorazepam, triazolam, flunitrazepam, and alprazolam.
- Speed of onset of pleasurable effects - eg GHB
- Increased reinforcement in those with history of drug abuse

Tolerance

- Time-dependent decrease in effect.
- Neurochemical basis unclear
- Varying rates for different behavioral effects:
 1. sedative and psychomotor effects
 2. diminish first (e.g. few weeks)
 3. memory and anxiety effects persist
 4. despite chronic use.
- Varying rates with different BzRA.
- If no history of addiction, rarely see dose escalation or overuse
- Cross-tolerance with ETOH and other sed-hyp

Dependence

- Negative reinforcement of withdrawal - major deterrent to discontinuing use.
- Difficult to distinguish between wd & rebound anxiety upon discontinuing drug.
 1. Withdrawal-time-limited (not part of original anxiety state)
 2. Relapse-reemergence of original anxiety
 3. Rebound - increased anxiety > baseline
- Also see insomnia, fatigue, headache, muscle twitching, tremor, sweating, dizziness, tinnitus, difficulty concentrating, nausea, depression, abnormal perception of movement, irritability

Dependence/Withdrawal, cont.

- Rarely -seizures, delirium, confusion, psychosis.
- Triggering of depression, mania, OCD.
- 90% of long-term users (>8mo-1yr) experience significant withdrawal
- Insignificant withdrawal if used less than 2 wks
 1. Mild-moderate if used >8 weeks
- Slow taper (>30days) with +/- carbamazepine, valproic acid, trazodone, imipramine.
- CBT effective in discontinuing BzRA and controlling panic/anxiety.

Predictors of severe withdrawal

- High-potency-quickly eliminated (e.g. alprazolam, lorazepam, triazolam)
- Higher daily dose
- More rapid rate of taper (esp last 50%)
- Diagnosis of panic disorder (not GAD)
- High pretaper levels of anxiety and depression
- ETOH or other substance dependence/abuse
- Personality pathology -e.g. neurotic or dependent
- Not motivated to discontinue use

Pharmacology

Drug Interactions:

- additive with other CNS depressants
- utilizes cytochrome P450-levels increased by
 - SSRI's - (less with paroxetine/Paxil, citalopram/Celexa, and sertraline/Zoloft)
 - ketoconazole, itraconazole
 - antibiotics - erythromycin
 - cimetidine, omeprazole
 - ritonavir
 - grapefruit juice

NB - C-P450 impaired in elderly or liver failure- increases effects

Benzodiazepine Abuse

- Two patterns of abuse -
 - 1.recreational abuse (nonmedical use to get high)
 - 2.quasi-therapeutic use - long-term drug taking inconsistent with accepted medical practice - multiple MD's
- 467 internet sites to access scheduled Rx websites

Detoxification

- Traditional Taper Method - using another BzRA (usually longer acting) as substitute and taper
- Anticonvulsants
 1. Carbamazepine (Tegretol)
 2. Gabapentin (Neurontin)
 3. Valproic acid (Depakote)

Tolerance Testing

- High or erratic dose, illicit source, polysubstance or alcohol plus benzo use.
- In 24-hour medically monitored setting
 1. 200 mg pentobarbital PO Q 2h - hold for intoxication, slurred speech, ataxia, somnolence.
 2. After 24-48 hrs, calculate 24 hr stabilizing dose
 3. Give stabilizing dose for 24 hrs divided
 4. Switch to phenobarbital (30mg = 100mg pentobarbital)
 5. Initiate gradual taper

Additional Measures

Carbamazepine - decreased subjective symptoms

- 200 mg TID
- In conjunction with phenobarbital or cdp taper
- GI upset, neutropenia, thrombocytopenia, low sodium.

Valproic acid - attenuates withdrawal - GABA

- 250 mg TID
- In conjunction with taper
- Continue for 2-3 wks or more after taper
- Need to check LFT's prior to starting
- GI upset, bone marrow suppression, pancreatitis

Additional Measures, cont

- Gabapentin - 200-300 mg TID - edema, fatigue
- Tiagapine (Gabitril) - gaba-ergic -
- Propranolol - diminish adrenergic s/s (60-120 mg/d)
- Clonidine - not effective
- Buspirone - not effective
- Trazadone - decreases anxiety-improve sleep - helpful
- CBT - improves rate of successful discontinuation and rate of abstinence from BzRA

Taper Method

- Slow, gradual decrease in dosage (e.g. .5 mg Alprazolam every 3-5 days or as slow as .25mg every 7-14 days or 10% of starting dose per wk)
- Last doses are hardest to eliminate - (?5% per wk)
- Varies from patient to patient
- Ambulatory setting - reliable follow-up
- Best with therapeutic-dose benzo dependence - (no other drugs/ETOH)
- Supportive therapy
- Limited Rx - withdrawal agreement

Summary

- Anxiety disorders are common in the elderly & may lead to excessive disability and decline in function
- Evaluation should include risk factor assessment, and home assessment
- Exercise and specific therapies can improve outcomes
- Medication management is essential
 - Needs more study in geriatric medicine