# Recent Advances in Treating Insomnia in Older Adults

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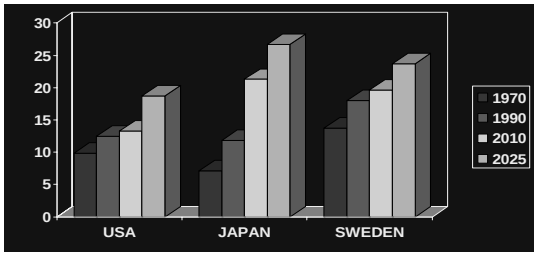
## Presentation Objectives

- Phenomenology and epidemiology of insomnia in older adults.
- Insomnia is frequently co-morbid with, rather than secondary to, medical and psychiatric illnesses, deserving treatment in its own right.
- Cognitive-behavioral therapy for insomnia (CBT-I) is an efficacious and lasting approach to treating insomnia in older adults.

## Estimated Percents of National Populations 65 Years of Age or Older




## Causes of Sleep Disturbance in Aging

- Age-related sleep change
  - Changes in homeostatic sleep drive and circadian rhythm for wakefulness
- Co-morbid medical and psychiatric illnesses
  - E.g.; Pain, Depression, etc.
- Primary sleep disorders
  - OSA, RLS, RBD, Circadian Rhythm Disorders, etc.
- Poor sleep hygiene
  - Learned behaviors, environmental factors, etc.
- Any combination of the above

Vitiello *Clinical Cornerstone* 2000

## Evidence-Based Recommendations for the Assessment and Management of Sleep Disorders in Older Persons

Harrison G Bloom, Imran Ahmed, Cathy A Alessi, Sonia Ancoli-Israel, Daniel J Buysse, Meir H Kryger, Barbara A Phillips, Michael J Thorpy, Michael V Vitiello, and Phyllis C Zee

*Journal of the American Geriatrics Society* 57(5);561-589, 2009

## Evidence-Based Recommendations

- Background and Significance, General Review of Sleep, Recommendations Development, and General Approach to Detecting Sleep Disorders in an Ambulatory Setting.
- Insomnia, Sleep Apnea, Restless Legs Syndrome, Circadian Rhythm Sleep Disorders, Parasomnias, Hypersomnias, and Sleep Disorders in Long-Term Care Settings.
- Evidence and expert-based recommendations.

Bloom et al. *JAGS* 2009

## Insomnia

- Insomnia is a disorder with associated impairment and a unique pathophysiology.
- Insomnia is highly prevalent and typically is co-morbid with other disorders.
- Insomnia has independent effects on QOL, function and co-morbid conditions and merits treatment.
- New developments in pharmacologic and cognitive-behavioral therapies provide a wide range of empirically-supported treatment options.

NIH State-of-the-Science Conference Statement *Sleep* 2005

## Physiologic Arousal in Insomnia

- Increased heart-rate (Stepanski, 1988)
- Increased metabolic rate (Bonnet and Arand, 1995)
- Increased high/low EEG frequency ratio (Bonnet, 1998)
- Increased body temperature (Lushington et al, 2000)
- Increased catecholamines (McClure et al, 2001)
- Increased cortisol (Vgontzas et al, 2001)
- Increased high frequency EEG (Perlis, 2001)
- Increased brain activity during sleep (Nofzinger, 2004)

## Insomnia Diagnostic Criteria (DSM-IV)

- Subjective difficulties initiating/maintaining sleep, or non-restorative sleep > 1 month.
- Insomnia (or daytime fatigue) causes marked distress or significant impairment in social or occupational functioning.

## Insomnia 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

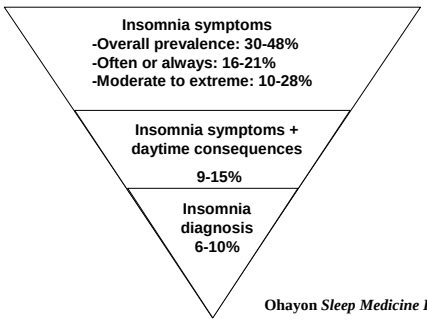
Edinger et al. *Sleep* 2004

## Insomnia Research Diagnostic Criteria

C. At least one of the following forms of daytime impairment related to the 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 et al. *Sleep* 2004

## Insomnia Epidemiology




Ohayon *Sleep Medicine Reviews* 2002

## Prevalence of Insomnia

- 30-50% of the general population have disturbed sleep.
- 6-10% of the general population meet diagnostic criteria for insomnia.
- ~50% of patients under clinical care meet diagnostic criteria for insomnia.

NIH State-of-the-Science Conference Statement *Sleep* 2005

## Risk Factors for Insomnia

- Female
- Age
- Medical illness, especially chronic pain, respiratory and neurological disorders
- Psychiatric illness, especially depression
- Lower socioeconomic status
- Race (African-American > White)
- Widowed, divorced
- Work schedules

Buysse *Primary Psychiatry* 2005

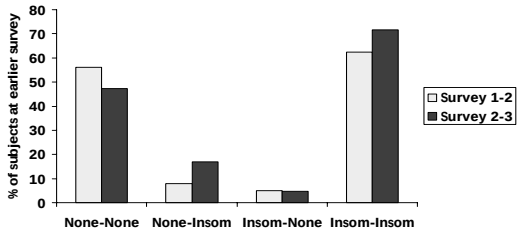
## Consequences of Insomnia

- Decreased quality of life.
- Impaired vigilance, concentration and memory.
- Increased incidence of medical and psychiatric disorders.
- Increased risk of falls and fractures.
- Increased healthcare utilization.
- Increased absenteeism and decreased job performance.

Buysse *Primary Psychiatry* 2005

## Insomnia is Typically Chronic

(N = 2319; Survey 2 = 3.6 yrs post baseline; Survey 3 = 10.26 yrs post baseline)




Buysse et al. *Sleep* 2004

## Insomnia - a Disorder not a Symptom

- Relative consistency of insomnia symptoms and consequences across co-morbid disorders.
- Course of insomnia does not consistently co-vary with the co-morbid disorder.
- Insomnia responds to different types of treatment than the co-morbid disorder.
- Insomnia responds to the same types of treatment across different co-morbid disorders.
- Insomnia poses common risk for development of and poor outcome in different disorders.

Harvey *Clinical Psychology Reviews* 2001

## Insomnia – Secondary or Co-Morbid

- Most insomnias occur in association with other conditions and were historically termed "secondary."
- Limited understanding of insomnia's mechanistic pathways precludes drawing conclusions about the nature of these associations or direction of causality.
- The term "secondary insomnia" may promote under-treatment.
- "Co-morbid insomnia" may be more appropriate.

NIH State-of-the-Science Conference Statement *Sleep* 2005

## Sleep Disturbance Co-Morbid with Illness

- **Both acute and chronic illnesses increase in prevalence with age.**
- **Sleep may be adversely affected:**
  - **By an illness per se.**
  - **By consequences of and treatments for an illness:**
    - **Surgery/pain**
    - **Bed-rest/inactivity**
    - **Medications (Rx, OTC, other)**
      - **Dangers of polypharmacy in older adults**

## Prevalence of Sleep Complaints

**Vitiello, et al. Prevalence of Chronic Sleep Complaints and Their Relationships to Medical Conditions in the VITAL Study Cohort of 77,000 Older Adults. *Sleep* 27, A120, 2004.**

| | SOD | SMD | EMA | NRS | EDS |
|---|---|---|---|---|---|
| Total | 17.6 | 33.1 | 26.6 | 26.0 | 13.3 |
| Men | 13.7 | 27.8 | 26.6 | 23.7 | 13.1 |
| Women | 21.2* | 37.9* | 26.6 | 28.1* | 13.4 |

## Prevalence of Chronic Illnesses in Older Adults

| | | | |
|---|---|---|---|
| Chronic pain/OA | 48.4 | Diabetes | 7.0 |
| Indigestion/GERD | 21.4 | Rheumatoid A. | 3.9 |
| BPH* | 16.8 | COPD | 3.7 |
| Depression | 16.7 | Stroke | 2.5 |
| Headache/Migraine | 15.5 | Heart Failure | 1.8 |
| Cancer | 14.5 | Kidney Disease | 1.0 |
| CAD | 9.2 | Cirrhosis/Liver Dis. | 0.5 |

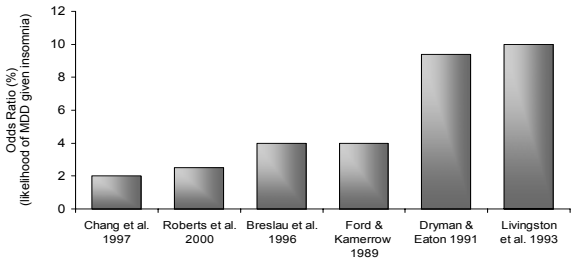
**Vitiello et al. *Sleep 2004***

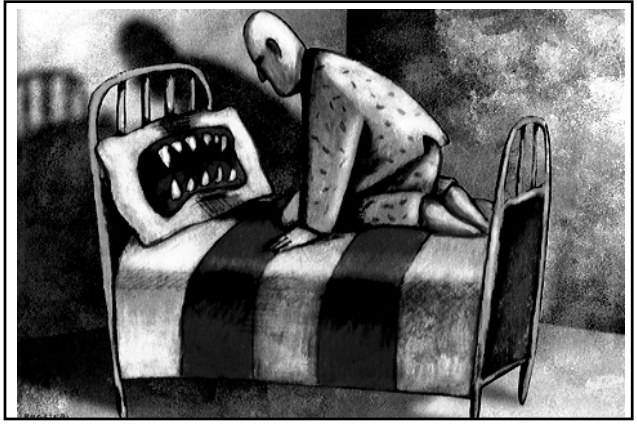
## Associations of Chronic Illnesses and Sleep Complaints

- **Most illnesses were associated with both nighttime (ORs of 1.0 - 1.7) and daytime sleep-related complaints (ORs of 1.1 - 2.8).**
  - **Depression (ORs of 1.7 - 2.8) had the strongest associations.**
  - **Chronic Pain/OA (ORs of 1.6 - 1.9) had the second strongest associations.**
  - **Similar patterns were observed for medical burden and were comparable for men and women.**

**Vitiello et al. *Sleep 2004***

## Insomnia Is a Risk Factor for Major Depressive Disorder (MDD)



## Pharmacological Treatment Approaches

- Hypnotics – Benzodiazepines
- Hypnotics – Benzodiazepines Receptor Agonists
  - Zaleplon (*Sonata*)
  - Zolpidem (*Ambien, Ambien-CR**)
  - Eszopiclone (*Lunesta**)
- Melatonin agonists
  - Ramelteon (*Rozerem**)
- Others agents currently available or in development:
  - OTC - Melatonin, valerian, anti-histamines, etc.
  - Prescription - Anti-depressants, anti-psychotics, etc.
  - In development - 5HT, GABA and Hypocretin/Orexin.

## Caveats Concerning Drug Treatment

- The BZRAs are efficacious:
  - Good safety profiles but not without side-effects:
    - Residual daytime sedation, cognitive and psychomotor impairment, dependence, and rebound insomnia.
  - Reasonably demonstrated intermediate-term safety and efficacy.
  - Long-term safety and efficacy remain to be demonstrated.
- Melatonin agonists appear to be safe and fairly efficacious for sleep onset difficulties, but are relatively new and lack extensive data.

NIH State-of-the-Science Conference Statement *Sleep* 2005

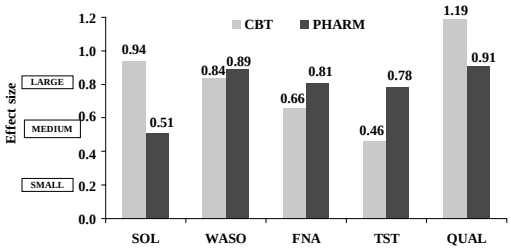
## Chronic Insomnia Treatment Strategy

- First - Useful in almost all cases - a careful review and optimizing of a patient's sleep hygiene practices.
- Second - Use of more formal cognitive-behavioral interventions as appropriate.
- Third - Judicious use of appropriate hypnotics in association with cognitive- behavioral techniques or alone may be helpful.

## Cognitive-Behavioral Therapy for Insomnia (CBT-I)

- Cognitive-Behavioral Therapy for Insomnia (CBT-I):
  - Sleep Hygiene
  - Sleep Logging
  - Stimulus Control Therapy (SCT)*
  - Sleep Restriction Therapy (SRT)*
- CBT-I may also include:
  - Relaxation Techniques
  - Cognitive Restructuring

## Relative Efficacy of Cognitive-Behavioral and Pharmacological Therapies




Morin et al. 1994; Murtagh and Greenwood 1995; Nowell et al. 1997; Smith et al. 2002

## Cognitive-Behavioral Therapy for Insomnia (CBT-I)

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## Sleep Education

- Accurate, fact-based information about sleep, for example:
  - What is normal sleep for a given age.
  - What are the consequences of mild sleep loss.
- Addresses erroneous assumptions, misperceptions and dysfunctional beliefs about sleep.

## Sleep Hygiene

- The behavioral and environmental factors, typically under the individual's control, that can maximize or compromise sleep quality.
  - Sleep/Wake Principles.
  - Environmental Principles.
  - Diet and Drug Use Principles.
  - General Principles.

## Sleep/Wake Principles

- Maintain habitual bed and rise times.
  - In particular, get up at the same time each day.
- Restrict time in bed.
  - Stay in bed only as long as you are asleep.
- Explore the usefulness of napping.
  - Remember that daytime naps may decrease nighttime sleep need.
    - Although two recent studies suggest this may not be the case in healthy older adults: Monk et al, Sleep, 2001; Campbell et al, JAGS, 2005

## Environmental Principles

- Ensure the bedroom is sufficiently dark.
- Minimize disturbing noise.
- Ensure bedding, temperature and airflow are consistent with good quality sleep.
- Ensure a nightlight does not illuminate the eyes while in bed.
- Eliminate or place bedroom clocks so that they can not be viewed from bed.

## Diet and Drug Use Principles

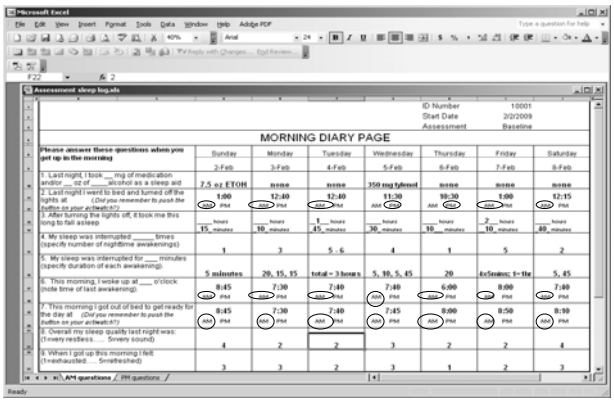
- Avoid rich food late in the evening.
- Explore the usefulness of a light bedtime snack.
  - Try snacking on foods that promote sleep:
    - E.g., milk, bananas, turkey, cheese, peanut butter.
- Avoid caffeine, alcohol and tobacco.
- Be aware that OTC and prescription medications may adversely affect sleep.

## General Principles

- Know what normal, age appropriate, sleep patterns should be.
- Explore if bedroom habits disrupt sleep.
- Develop relaxing bedtime rituals.
- Schedule a regular "worry time".
- Exercise regularly and moderately.
- Spend time outdoors in natural sunlight.
- Avoid bright light during the night.

## Cognitive-Behavioral Therapy for Insomnia (CBT-I)

- **Cognitive-Behavioral Therapy for Insomnia (CBT-I):**
  - **Sleep Hygiene**
  - **Sleep Logging**
  - **Stimulus Control Therapy (SCT)***
  - **Sleep Restriction Therapy (SRT)***
- **CBT-I may also include:**
  - **Cognitive Restructuring**
  - **Relaxation Techniques**



Microsoft Excel

Assessment sleep log.xls

ID Number 10001
Start Date 2/2/2009
Assessment Baseline

MORNING DIARY PAGE

| Please answer these questions when you get up in the morning | Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|---|
| | 2-Feb | 3-Feb | 4-Feb | 5-Feb | 6-Feb | 7-Feb | 8-Feb |
| 1. Last night I took ___ mg of medication and/or ___ oz of ____alcohol as a sleep aid | 7.5 oz ETOH | none | none | 350 mg tylenol | none | none | none |
| 2. Last night I went to bed and turned off the lights at (Did you remember to push the button on your actiwatch?) | 1:00 AM PM | 12:40 AM PM | 12:40 AM PM | 11:30 AM PM | 10:30 AM PM | 1:00 AM PM | 12:15 AM PM |
| 3. After turning the lights off, it took me this long to fall asleep | ___ hours 15 minutes | ___ hours 10 minutes | 1 hours 45 minutes | ___ hours 30 minutes | ___ hours 10 minutes | 2 hours 10 minutes | ___ hours 40 minutes |
| 4. My sleep was interrupted _____ times (specify number of nighttime awakenings) | 1 | 3 | 5 - 6 | 4 | 1 | 5 | 2 |
| 5. My sleep was interrupted for ___ minutes (specify duration of each awakening). | 5 minutes | 20, 15, 15 | total ~ 3 hours | 5, 10, 5, 45 | 20 | 4x5mins; 1~1hr | 5, 45 |
| 6. This morning, I woke up at ___ o'clock (note time of last awakening). | 8:45 AM PM | 7:30 AM PM | 7:40 AM PM | 7:40 AM PM | 6:00 AM PM | 8:00 AM PM | 7:40 AM PM |
| 7. This morning I got out of bed to get ready for the day at (Did you remember to push the button on your actiwatch?) | 8:45 AM PM | 7:30 AM PM | 7:40 AM PM | 7:45 AM PM | 8:00 AM PM | 8:50 AM PM | 8:10 AM PM |
| 8. Overall my sleep quality last night was: (1=very restless ..... 5=very sound) | 4 | 2 | 2 | 3 | 2 | 2 | 4 |
| 9. When I got up this morning I felt: (1=exhausted..... 5=refreshed) | 3 | 3 | 2 | 3 | 1 | 2 | 3 |

AM questions / PM questions

Ready

## Stimulus Control Therapy

- **Develop a pre-bed ritual and ensure the bedroom is comfortable.**
- **Maintain a consistent rise time.**
- **Go to bed only when sleepy.**
- **If unable to fall asleep, leave the bedroom and return only when sleepy.**
- **Use the bedroom only for sleep and sex and avoid activities such as watching television or working while in bed.**
- **No daytime naps.**

**Bootzin et al. *Progress in Behavior Modification* 1978**

## Sleep Restriction Therapy

- **Determine average time asleep.**
- **Set time in bed = time asleep.**
- **Maintain a consistent wake-up time.**
- **No daytime naps.**
- **If time asleep $\geq$ 90% (85%) of time in bed then increase time in bed (~15 minutes).**
- **If time asleep < 80% of time in bed then decrease time in bed (~15 minutes).**

**Spielman et al. *Sleep* 1987**

## Cognitive Behavioral Therapy

- **CBT-I compared with pharmacotherapy for late-life insomnia:**
  - **CBT and pharmacotherapy were both effective and comparable in the short term.**
  - **CBT was rated more effective than drug therapy by subjects, significant others and clinicians.**
  - **Sleep improvements were better sustained by CBT over a two year follow-up period.**
    - **Morin, et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA* 281(11):991-9, 1999.**

## Cognitive Behavioral Therapy

- **CBT-I out of the lab and into practice:**
  - **CBT-I was successful in improving sleep in a large group insomniacs in a general medical practice.**
  - **CBT-I was delivered in group settings by trained health practitioners (community nurses).**
  - **Follow-up data was similar to more controlled laboratory-based trails.**
    - **Espie, et al. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. *Behav Res Ther.*; 39(1):45-60, 2001.**

## Cognitive Behavioral Therapy

- CBT-I can successfully improve the sleep of chronic hypnotic users, resulting in discontinuation of drug use at a significant health care cost savings:
  - Cost of training: £155, vs. Cost savings: £3400/yr.
    - Morgan et al. Psychological treatment for insomnia in the management of long-term hypnotic drug use: a pragmatic randomized controlled trial. *Br J Gen Pract.* 53(497):923-8, 2003.

## Cognitive Behavioral Therapy

- Efficacy of a brief, two session, "primary practice friendly" CBT-I protocol has been demonstrated.
  - Edinger and Sampson. A primary care "friendly" cognitive behavioral insomnia therapy. *Sleep.* 26(2):177-82, 2003.
- Efficacy of a single session plus brief 2-week booster protocol has been demonstrated.
  - Germain et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med.* 2(4):403-6, 2006.

## Cognitive Behavioral Therapy

- CBT-I improves the sleep of AD caregivers.
  - McCurry, Logsdon, Vitiello and Teri. Successful behavioral treatment of sleep disturbance in caregivers of dementia patients. *J Gerontol.* 53B(2): P122-P129, 1998.
- CBT-I improves the sleep quality of community-dwelling AD patients.
  - McCurry, Gibbons, Logsdon, Vitiello and Teri. Nighttime Insomnia Treatment and Education for Alzheimer's Disease (NITE-AD): A Randomized Controlled Trial. *JAGS.* 53(5): 793-802, 2005.
  - McCurry, Vitiello, Gibbons, Logsdon and Teri. Factors associated with caregiver perceptions of sleep disturbances in persons with dementia. *Am J Geriatr Psychiatry*. 14 (2): 112-120, 2006.

## Cognitive Behavioral Therapy

- CBT-I improves sleep of insomniacs with co-morbid chronic illnesses (OA, COPD, CVD).
  - Rybarczyk, et al. A placebo-controlled test of cognitive-behavioral therapy for co-morbid insomnia in older adults. *J Consult Clin Psychol.* 73(6):1164-74, 2005.
- CBT-I improves sleep and decreases pain in older adults with insomnia and co-morbid osteoarthritis.
  - Vitiello, et al. Sleep as Analgesic: Improving Sleep and Pain in Older Insomniacs with Co-Morbid Osteoarthritis. *Sleep* 30: A103, 2007.

## CBT-I Improves both Sleep and Pain in Older Adults with Co-morbid Osteoarthritis and Insomnia

Michael V. Vitiello, Bruce D. Rybarczyk,
Michael Von Korff and Edward J. Stepanski

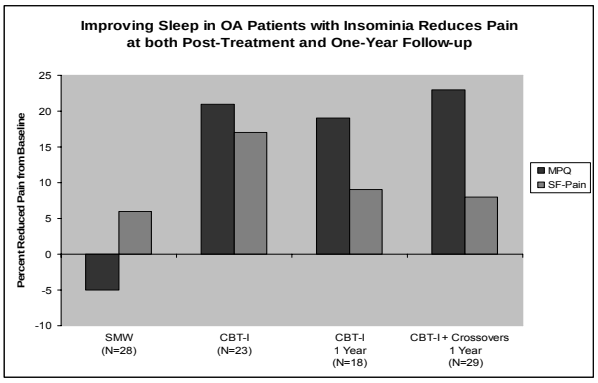
Journal of Clinical Sleep Medicine
(accepted pending revision)

## Study Design

- Subjects meeting diagnostic criteria for co-morbid OA and chronic insomnia were randomized to either:
  - Standard CBT-I (Eight 2-hour sessions).
  - Stress Management and Wellness (SMW) intervention.
- Neither intervention specifically mentioned pain management; although SMW contained components typically included in behavioral pain interventions.
  - Problem-solving, goal setting, cognitive approaches to reducing stress and anxiety, interpersonal skills training, and exercise enhancement

| | SMW (N=28) | | | CBT-I (N=23) | | |
|---|---|---|---|---|---|---|
| | Pre | Post | p | Pre | Post | p |
| TST | 342 (84) | 370 (71) | .059 | 351 (60) | 372 (59) | .069 |
| SE | 70.2 (14.1) | 75.2 (14.0) | .069 | 71.0 (12.3) | 84.0 (8.1) | .000 |
| SLAT | 36.9 (27.1) | 33.4 (31.0) | .360 | 40.4 (21.4) | 23.5 (22.0) | .014 |
| WASO | 67 (45) | 55 (41) | .134 | 62 (47) | 25 (21) | .000 |
| MPQ | 11.1 (9.6) | 11.6 (10.8) | .704 | 10.1 (9.6) | 8.0 (7.1) | .221 |
| SF-36P | 50.3 (21.4) | 53.1 (25.0) | .371 | 56.4 (19.7) | 66.1 (24.3) | .010 |

| | CBT-I (N=19) | | | CBT-I+CO (N=29) | | |
|---|---|---|---|---|---|---|
| | Pre | One-Year | p | Pre | One Year | p |
| TST | 361 (51) | 393 (48) | .034 | 364 (48) | 390 (56) | .16 |
| SE | 74.3 (9.3) | 82.8 (6.9) | .001 | 74.9 (10.0) | 82.8 (9.3) | .000 |
| SLAT | 35.4 (17.9) | 24.0 (17.7) | .006 | 34.3 (22.6) | 23.6 (17.8) | .001 |
| WASO | 48.1 (29.0) | 28.7 (20.7) | .015 | 48.9 (30.2) | 29.6 (24.6) | .001 |
| MPQ | 9.1 (8.5) | 7.4 (7.7) | .129 | 9.7 (7.6) | 7.3 (6.7) | .029 |
| SF-36P | 58.5 (19.8) | 64.2 (23.4) | .081 | 59.1 (20.4) | 63.8 (23.5) | .114 |




Vitiello et al. *Sleep* 2007

## Conclusions

- **CBT-I improved both immediate and long-term self-reported sleep quality in this sample of older OA patients with co-morbid insomnia.**
- **CBT-I, without specifically addressing pain management, reduced both immediate and long-term reported pain in these OA patients.**
- **Improving sleep quality in older OA patients with co-morbid insomnia is "analgesic" and has implications for pain management programs.**

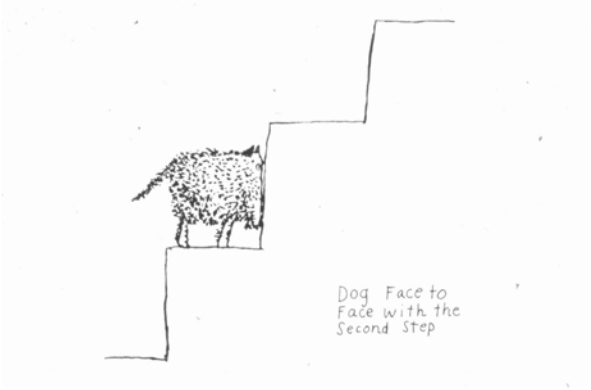
## Implications

- **The relationships among insomnia, pain and aging are complex and not fully understood.**
- **The relationship between sleep and pain is clearly not unidirectional.**
  - **Sleep disruption is not necessarily a result of illness/pain.**
  - **Improving sleep may actually improve illness/pain.**

## AG031126 Cognitive Behavioral Therapy for Arthritis Pain and Insomnia in Older Adults

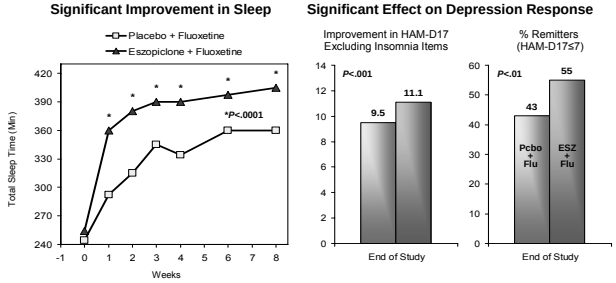
**(Michael V. Vitiello, Susan McCurry and Michael Von Korff, Co-PIs)**

- **375 older GHC patients with co-morbid insomnia and osteoarthritis.**
- **Randomized to three groups, CBT-Pain, CBT-Pain/Insomnia, and an attention control.**
- **Sleep, pain, cognition and affect assessed pre and post-treatment and at 9 and 18 month follow-ups.**
- **Long-term changes in health care utilization and related costs will also be assessed.**




## Treatment of Insomnia Co-morbid with Depression Improves Both Sleep and Depression Outcomes

**(Fluoxetine + Eszopiclone versus Fluoxetine + Placebo, N=545)**




**Fava et al. *Biol Psychiatry* 2006**

## Treatment of Insomnia Co-morbid with Depression Improves Both Sleep and Depression Outcomes

**(Escitalopram + CBT-I versus Escitalopram + Control (Quasi-desensitization), N = 30)**

- **EsCIT + CBT-I resulted in a higher rate of remission from insomnia (50.0%) than EsCIT + CTRL (7.7%).**
- **EsCIT + CBT-I resulted in a higher rate of remission from depression (61.5%) than EsCIT + CTRL (33.3%).**

**Manber et al. *Sleep* 2008**

## Treatment of Insomnia Co-morbid with GAD Improves Both Sleep and GAD Outcomes

**(Escitalopram + Eszopiclone versus Escitalopram + Placebo, N = 595)**

- **Combined (EsCIT + Eszopiclone) therapy relative to EsCIT + Placebo resulted in:**
  - **Significantly improved sleep and daytime function.**
  - **Significantly improved HAM-A scores.**
  - **Significantly greater rates of GAD remission and reduced time to onset of anxiolytic response.**

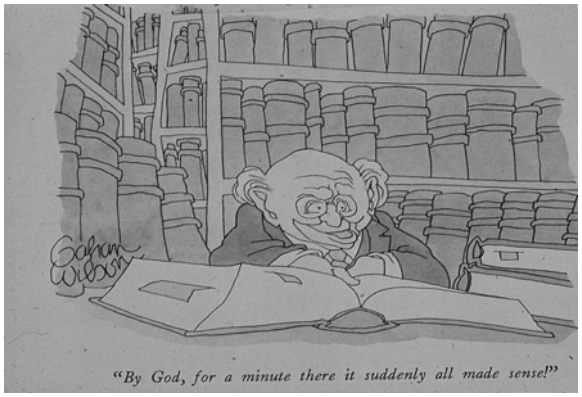
**Pollack et al. *Arch Gen Psychiatry* 2008**

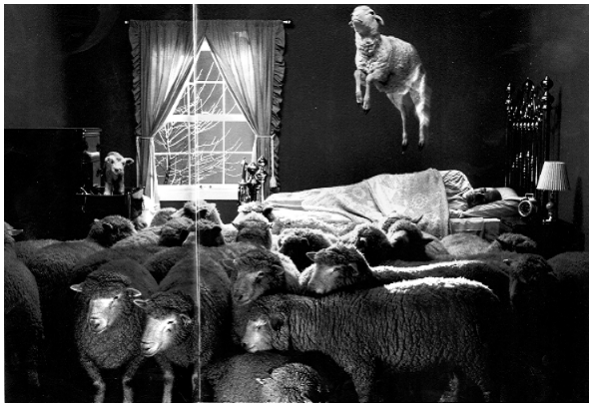
## The Take-Home Messages

- **Insomnia is common in older adults.**
- **Insomnia is a disorder not a symptom.**
- **Insomnia frequently presents co-morbid with medical and psychiatric illnesses.**
- **Insomnia, whether primary or co-morbid, warrants treatment in its own right.**

## The Take-Home Messages

- **CBT-I is an efficacious approach to treating both primary and co-morbid insomnia in older adults with demonstrated long term benefits.**
- **Effectively treating insomnia may have beneficial impact on co-morbid illness:**
  - **Osteoarthritis and possibly other pain syndromes.**
  - **Depression, GAD.**
  - **Others illnesses, e.g.; hypertension (?).**




**Resources**

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