Insomnia and it's management

Kawish Garg MD

Psychiatry and Sleep Medicine

Medical Director, Geisinger Holy Spirit Sleep Lab

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

Disclosure

- No conflict exists.
- Presentation will include discussion of unapproved or investigational uses of products or devices as indicated.

- Epidemiology
- Assessment and Diagnosis
- Pathophysiology
- Treatment

Sleep Requirements

- Newborns *(0-3 months):* 14-17 hours
- Infants *(4-11 months)* : 12-15 hours
- Toddlers *(1-2 years)* : 11-14 hours
- Preschoolers (3-5) : 10-13 hours
- School age children *(6-13)* : 9-11 hours
- Teenagers *(14-17)* : 8-10 hours
- Younger adults *(18-25)* : 7-9 hours
- Adults *(26-64)* : 7-9 hours
- Older adults *(65+)* : 7-8 hours

Epidemiology

- 10% meets criteria of Chronic Insomnia disorder
- Transient Insomnia 30-35%
- More in females
- Comorbid with other chronic medical/psychiatric and substance use disorders
- Lower socioeconomic status
- Older patients
- Higher in monozygotic twins relative to dizygotic twins, higher in first degree relatives, stronger association with mothers and daughters

Diagnostic Criteria – ICSD3

Diagnostic criteria for chronic insomnia - Criteria A–F must be met

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:

1. *Difficulty initiating sleep*
2. *Difficulty maintaining sleep*
3. *Waking up earlier than desired*
4. *Resistance to going to bed on appropriate schedule*
5. *Difficulty sleeping without parent or caregiver intervention*

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

B. The patient/parent/caregiver reports/observes, one or more of the following related to the nighttime sleep difficulty:

1. *Fatigue/malaise*
2. *Attention, concentration or memory impairment*
3. *Impaired social, family, occupational or academic performance*
4. *Mood disturbance/irritability*
5. *Daytime sleepiness*
6. *Behavioral problems (e.g. hyperactivity, impulsivity, aggression)*
7. *Reduced motivation/energy/initiative*
8. *Proneness for errors/accidents*
9. *Concerns about or dissatisfaction with sleep*

C. The reported sleep/wake complaints cannot be explained purely by **inadequate opportunity** (i.e. enough time is allotted for sleep) or **inadequate circumstances** (i.e. the environment is safe, dark, quiet and comfortable) for sleep

D. The sleep disturbance and associated daytime symptoms occur at least **three times per week**

E. The sleep disturbance and associated daytime symptoms have been present for at least **3 months**

F. The sleep/wake difficulty is not explained more clearly by another sleep disorder

- Patients having sleep latency of **30 mins** or more, periods of wakefulness during sleep (WASO) of **30 mins** or more, or Early morning awakenings – termination of sleep **30 mins** before the desired wake up time

- Types
  - Short term - < 3 months
  - Chronic – 3 times per week, lasting 3 months or more
  - **Insomnia with short sleep duration (average sleep time less than 6 hours)**

- Patients often complain about subjective daytime sleepiness/tiredness but rarely they fall sleep, unable to take a nap even if they try to do so

Consequences

- Poor cognition/decreased attention span and executive functioning
- Poor quality of life
- Increased Cardiovascular mortality and morbidity
- Increased risk of Diabetes and HTN
- **Increased risk of suicide**

Prevalence of Medical Problems in People with or Without Insomnia

Comorbidity of chronic insomnia with medical problems. *Sleep* 2007;30:213–8.

Medical Problem	Prevalence of Medical Problem (%)*		Adjusted Odds Ratio† (95% CI)
	PWI	PNI	
Heart disease	21.9	9.5	2.27 (1.13–4.56)‡
Cancer	8.8	4.2	2.58 (0.98–6.82)
Hypertension	43.1	18.7	3.18 (1.90–5.32)§
Neurologic disease	7.3	1.2	4.64 (1.37–15.67) ‡
Breathing problems	24.8	5.7	3.78 (1.73–8.27)‖
Urinary problems	19.7	9.5	3.28 (1.67–6.43)‖
Diabetes	13.1	5.0	1.80 (0.78–4.16)
Chronic pain	50.4	18.2	3.19 (1.92–5.29)§
Gastrointestinal problems	33.6	9.2	3.33 (1.83–6.05)§
Any medical problem	86.1	48.4	5.17 (2.93–9.12)§

Prevalence of Insomnia in People with or Without Medical Disorders

Comorbidity of chronic insomnia with medical problems *Sleep* 2007;30:213–8.

Medical Problem	Insomnia Prevalence (%)*		Adjusted Odds Ratio† (95% CI)
	PHM	PNM	
Heart disease	44.1	22.8	2.11 (1.07–4.15)‡
Cancer	41.4	24.6	2.50 (1.01–6.21)‡
Hypertension	44.0	19.3	3.19 (1.87–5.43)§
Neurologic disease	66.7	24.3	5.21 (1.22–22.21)‡
Breathing problems	59.6	21.4	2.79 (1.27–6.14)‡
Urinary problems	41.5	23.3	3.51 (1.82–6.79)§
Diabetes	47.4	23.8	2.03 (0.86–4.79)
Chronic pain	48.6	17.2	3.16 (1.90–5.27)§
Gastrointestinal problems	55.4	20.0	3.00 (1.66–5.43)§
Any medical problem	37.8	8.4	5.26 (2.82–9.80)§

CI, confidence interval; PHM, people who reported having the medical problem; PNM, people who did not report having the medical problem.

RESEARCH ARTICLE Open Access

Insomnia as an independent predictor of suicide attempts: a nationwide population-based retrospective cohort study

Han-Ting Lin[1], Chi-Huang Lai[1], Huey-Jen Perng[2], Chi-Hsiang Chung[2], Chung-Ching Wang[3], Wei-Liang Chen[3] and Wu-Chien Chien[1,2,4*]

Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT): A Randomized Clinical Trial

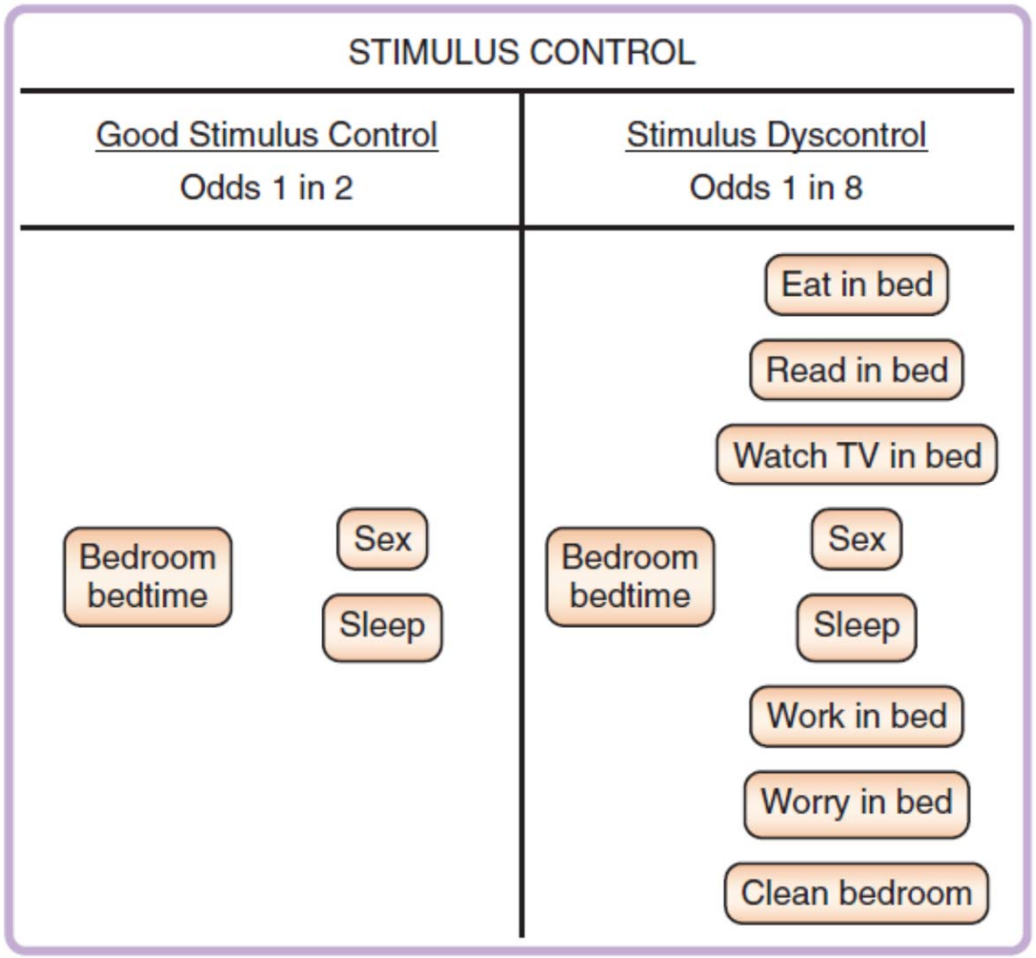
William V. McCall, M.D., Ruth M. Benca, M.D., Peter B. Rosenquist, M.D., Nagy A. Youssef, M.D., Laryssa McCloud, Ph.D., Jill C. Newman, M.S., Doug Case, Ph.D., **... Show all Authors**

Published Online: 20 Sep 2019 | https://doi.org/10.1176/appi.ajp.2019.19030267

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

Pathophysiology

- Stimulus control model
- Three factor model
- Microanalytic model
- Neurocognitive model
- Two factor model
- Psychobiologic inhibition
- Cognitive model
- Neurobiologic model



THE STIMULUS CONTROL MODEL

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

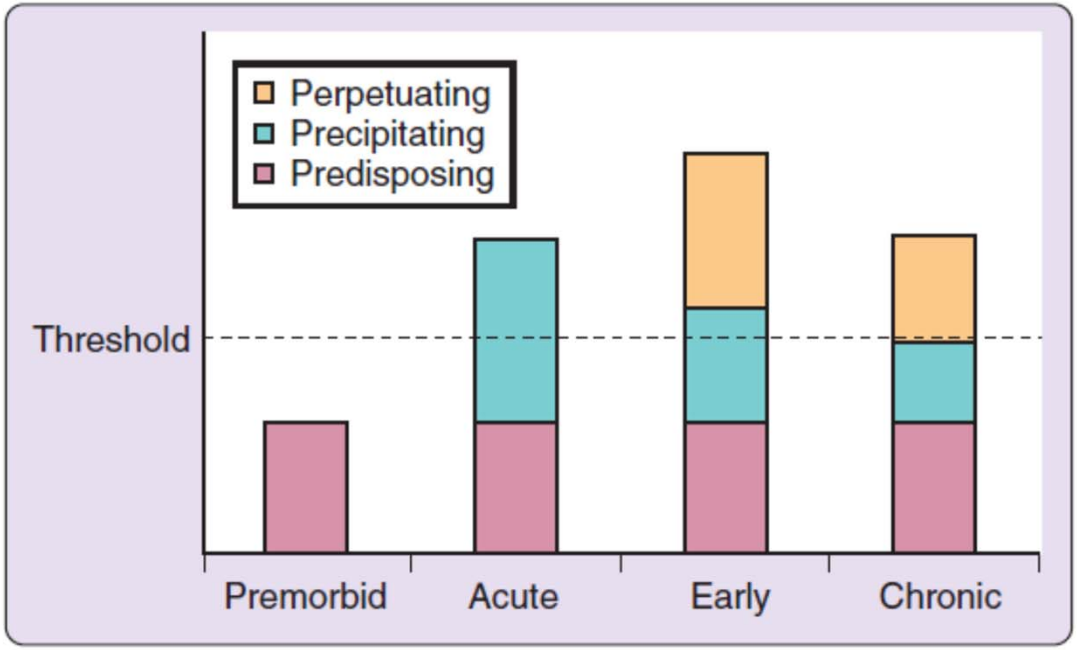
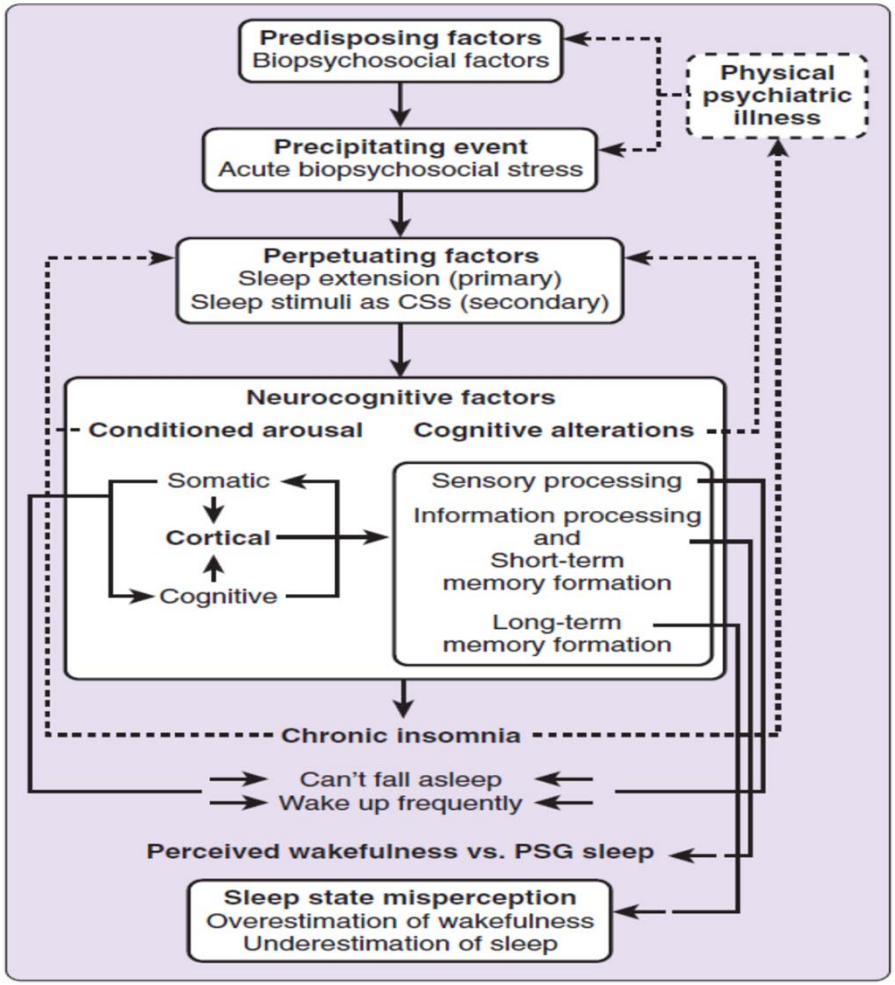


Figure 78-2 The classic 1987 rendition of the 3P model. There is a more recent representation of the model in Chapter 144. The reader is encouraged to compare the two versions of the model. The differences (e.g., allowing the predisposing factors to be represent as variable with time), while subtle, are theoretically important.

THE 3P MODEL



THE NEUROCOGNITIVE MODEL

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

THE PSYCHOBIOLOGICAL INHIBITION MODEL

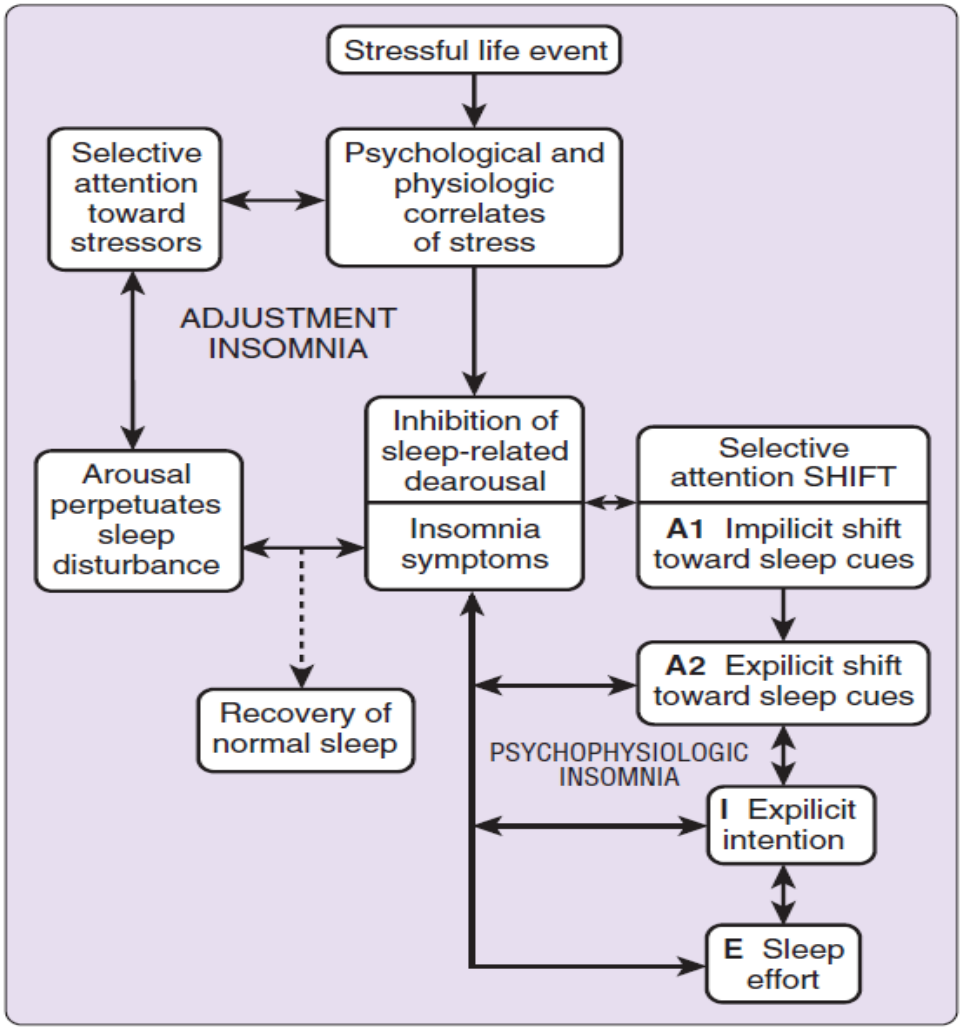


Figure 78-4 Proposed evolution of psychophysiologic insomnia from adjustment insomnia following the attention-intention-effort (A-I-E) pathway.

PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

- **Predisposing factors**
  - Genetics/Biological
  - Psychological – personality/worrier
  - Social – circadian mismatch, social pressures
- **Precipitating factors**
  - Stressful events/Psychiatric disorders
  - Medical disorders like heart failure, diabetes, cancer, chronic pain, pulmonary diseases, rheumatological disorders like fibromyalgia, Neurological disorders like Parkinson's and many more
  - Multiple medications for example – psychotropics/steroids/B-blockers/stimulants
- **Perpetuating factors**

Hyperarousal

- Physiological hyperarousal during sleep and wakefulness
  - Elevated heart rate
  - Altered heart rate variability
  - Increased whole-body metabolic rate
  - Elevated cortisol/ACTH
  - Elevated CRF
  - Increased body temperature
  - Increased high frequency EEG activity during NREM sleep

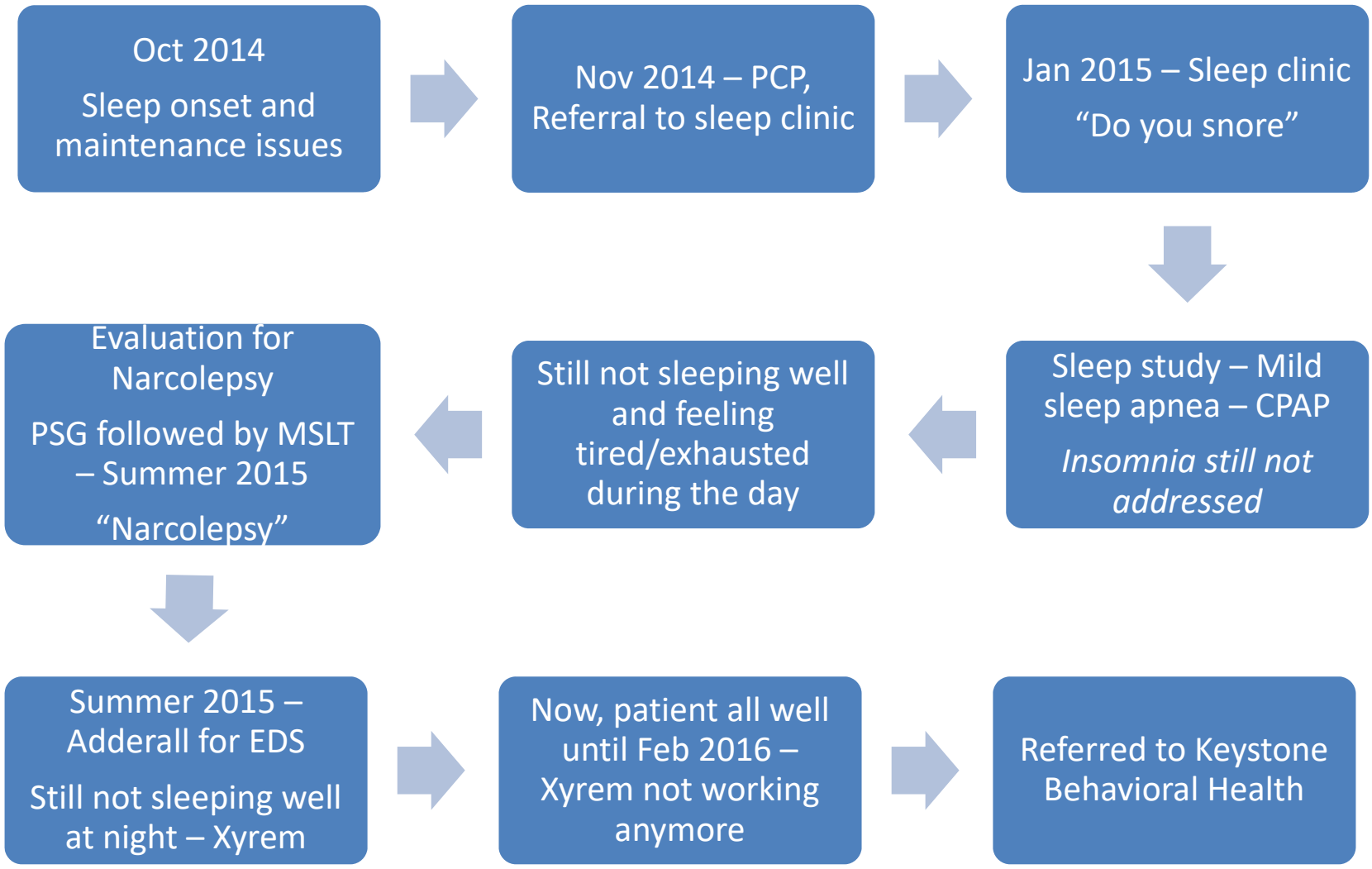
- In general patients with Insomnia have tendency to underestimate sleep duration and overestimate sleep latency and awakenings

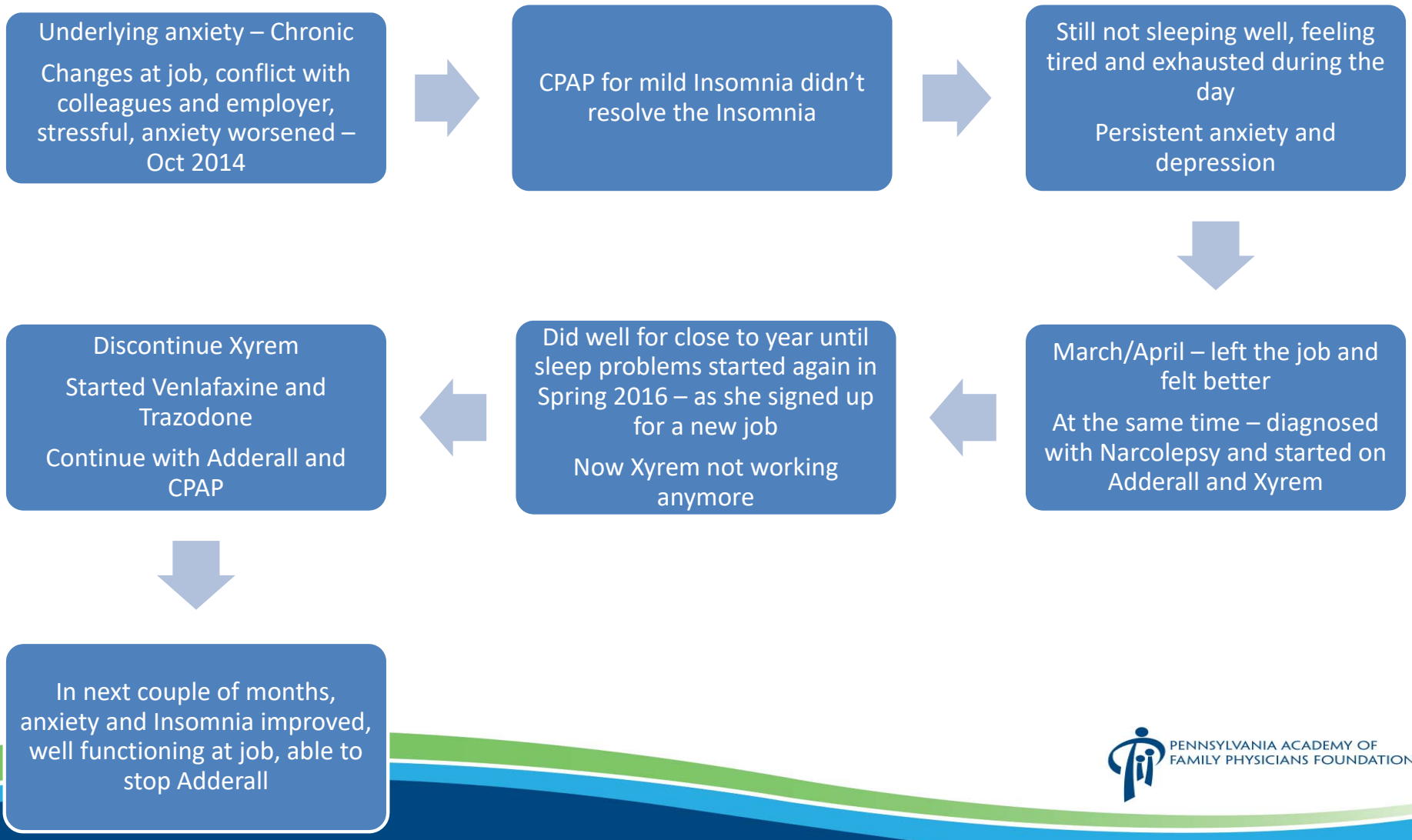
- Altered sleep wake perception

Diagnostic evaluation

- Detailed sleep history
- Sleep hygiene
- Caffeine intake
- Comorbid medical and psychiatric disorders
- Comorbid sleep disorders like RLS/OSA etc.
- Screening tools like PSQI (Pittsburg sleep quality index) or ISI (Insomnia severity index) can be utilized
- Labs – generally not indicated unless indicated for any other comorbid medical/psychiatric or sleep disorder
- **Sleep study – generally not indicated**

Case – Middle Age Female





PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Sleep testing

- Polysomnography generally not indicated unless there is suspicion regarding any other sleep disorder like OSA/Parasomnia etc.
- Actigraphy
- Role of new tech devices or applications

Treatment

- Pharmacological
- Non-Pharmacological – Cognitive behavioral therapy for Insomnia CBT-I

"It's nothing to lose any sleep over. You just have insomnia."

Neurochemicals regulating sleep and wakefulness

Wake promoting

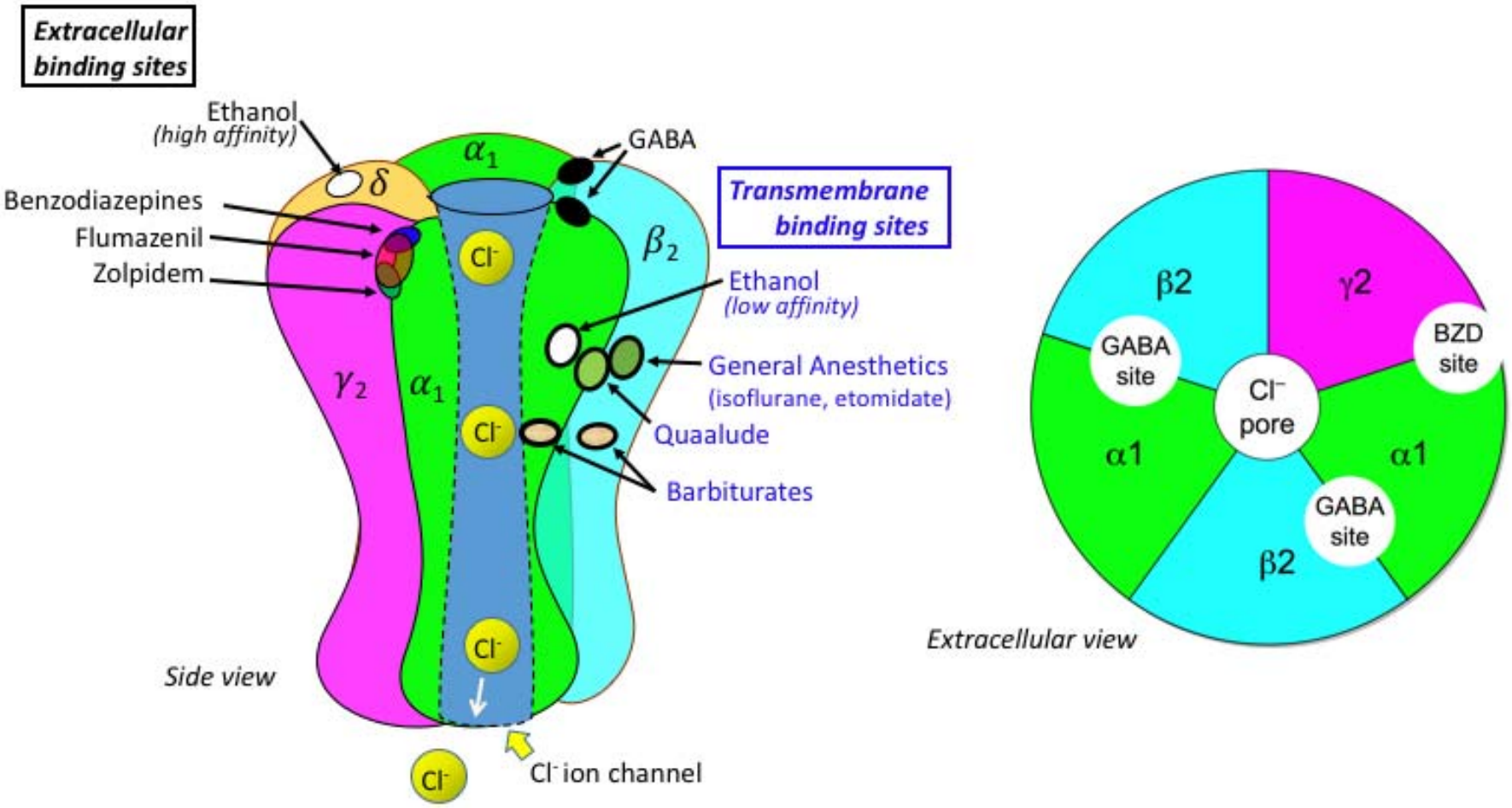
- Acetylcholine
- Norepinephrine
- Serotonin
- Histamine
- Dopamine
- Hypocretin

Sleep promoting

- Adenosine
- GABA
- Melatonin

Pharmacological

- **Benzodiazepine receptor agonists**
  - Triazolam, Temazepam, Estazolam, Quazepam, Flurazepam, Zaleplon, Zolpidem, Eszopiclone
- **Melatonin receptor agonists**
  - Ramelteon
- **Antihistaminics**
  - Doxylamine, Diphenhydramine
- **Sedating antidepressants**
  - Doxepin
- **Orexin receptor antagonists**
  - Suvorexant, Lemborexant


Extracellular binding sites
Ethanol (high affinity)
Benzodiazepines
Flumazenil
Zolpidem
GABA
Transmembrane binding sites
Ethanol (low affinity)
General Anesthetics (isoflurane, etomidate)
Quaalude
Barbiturates
Cl⁻
Cl⁻ ion channel
Side view
Extracellular view
β2
γ2
BZD site
GABA site
Cl⁻ pore
α1
GABA site
β2

GENERIC NAME	BRAND NAME	AVAILABLE DOSES (MG)	ELIMINATION HALF-LIFE (HR)
BENZODIAZEPINE RECEPTOR AGONISTS			
Benzodiazepine Immediate Release			
Estazolam	ProSom	1, 2	10 - 24
Flurazepam	Dalmane	15, 30	2.3/48 – 160 active metabolite
Quazepam	Doral	7.5, 15	39/73 active metabolite
Temazepam	Restoril	7.5, 15, 22.5, 30	3.5 – 18.4
Triazolam	Halcion	0.125, 0.25	1.5 – 5.5

GENERIC NAME	BRAND NAME	AVAILABLE DOSES (MG)	ELIMINATION HALF-LIFE (HR)
Nonbenzodiazepine Immediate Release			
Eszopiclone	Lunesta	1, 2, 3	6/ 9 in elderly
Zaleplon	Sonata	5, 10	1
Zolpidem	Ambien	5, 10	2.8 in males
Nonbenzodiazepine Extended Release			
Zolpidem ER	Ambien CR	6.25, 12.5	1.6 – 4.5
Nonbenzodiazepine Alternate Delivery			
Zolpidem oral spray	Zolpimist	5, 10	2.7 – 3.0
Zolpidem sublingual	Edluar	5, 10	~2.5
Zolpidem sublingual	Intermezzo	1.75, 3.5	~2.5

GENERIC NAME	BRAND NAME	AVAILABLE DOSES (MG)	ELIMINATION HALF-LIFE (HR)
SELECTIVE MELATONIN RECEPTOR AGONIST			
Ramelteon	Rozerem	8	1 – 2.6
SELECTIVE HISTAMINE RECEPTOR ANTAGONIST			
Doxepin (low dose)	Silenor	3, 6	15.3
DUAL OREXIN RECEPTOR ANTAGONIST			
Suvorexant	Belsomra	5, 10, 15, 20	12

U.S. FDA APPROVES EISAI'S DAYVIGO™ (LEMBOREXANT) FOR TREATMENT OF INSOMNIA IN ADULT PATIENTS

- Orexin 1 and Orexin 2 receptor antagonist
- 5,10 mg
- Elimination half life 17-19 hrs

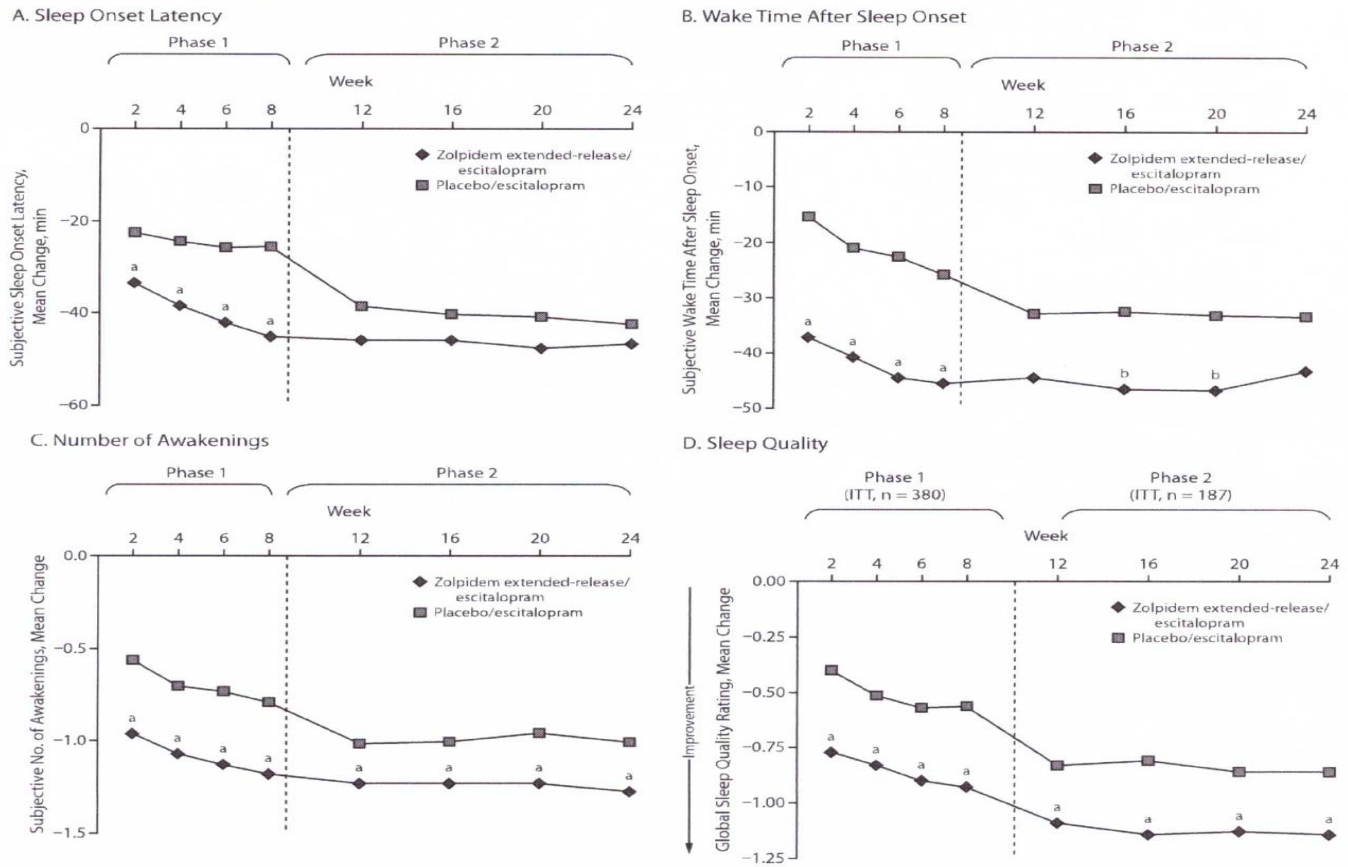
MEDICATION	UNSPECIFIED INSOMNIA	SLEEP ONSET	SLEEP MAINTENANCE	EARLY AWAKENING
Estazolam		✓	✓	✓
Flurazepam		✓	✓	✓
Quazepam		✓	✓	✓
Temazepam	✓			
Triazolam	✓			
Eszopiclone		✓	✓	
Zaleplon		✓		
Zolpidem		✓		
Zolpidem ER		✓	✓	
Zolpidem spray		✓		
Zolpidem sublingual		✓		
Zolpidem sublingual—MOTN			✓	
Ramelteon		✓		
Low-dose doxepin			✓	
Suvorexant		✓	✓	

Abbreviation: MOTN, middle of the night.

Improved Insomnia Symptoms and Sleep-Related Next-Day Functioning in Patients With Comorbid Major Depressive Disorder and Insomnia Following Concomitant Zolpidem Extended-Release 12.5 mg and Escitalopram Treatment: A Randomized Controlled Trial

Maurizio Fava, MD; Gregory M. Asnis, MD; Ram K. Shrivastava, MD; Bruce Lydiard, MD, PhD; Bijan Bastani, MD; David V. Sheehan, MD, MBA; and Thomas Roth, PhD

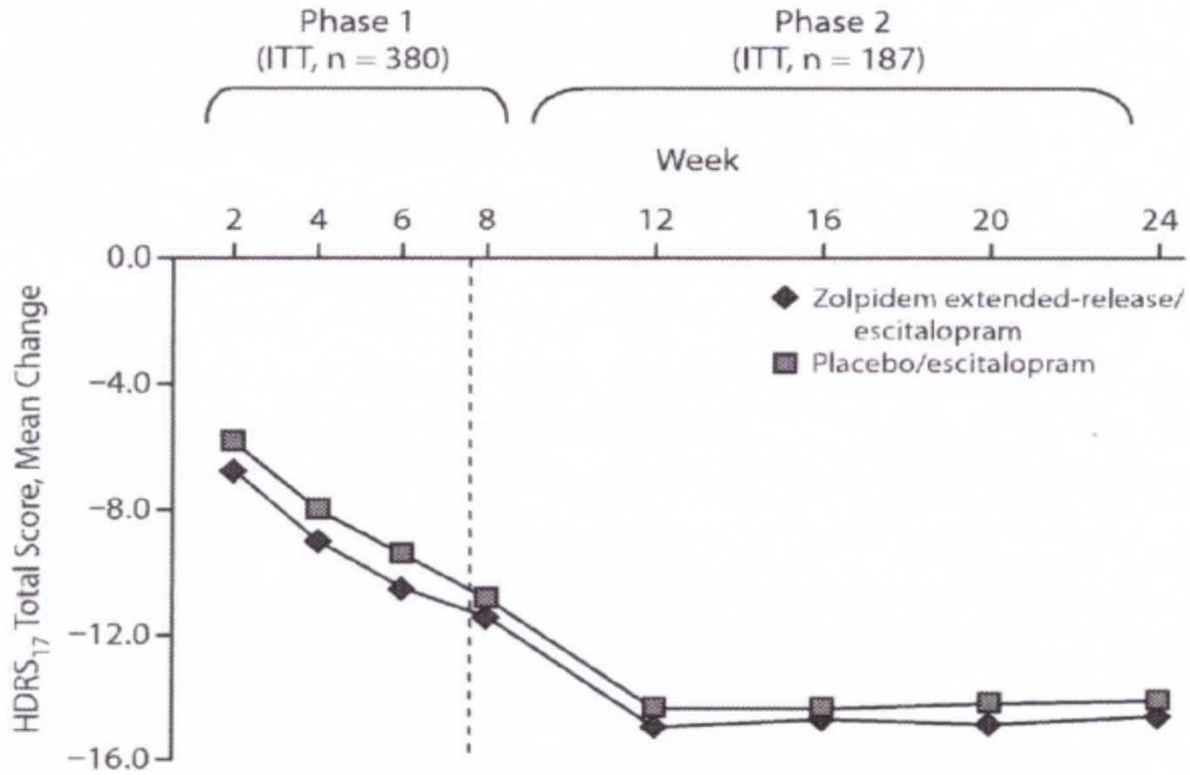
Figure 4. Mean Change From Baseline in Subjective (A) Sleep Onset Latency, (B) Wake Time After Sleep Onset, (C) Number of Awakenings, and (D) Sleep Quality



[a]$P \leq .001$ versus placebo/escitalopram, based on analysis of covariance (ANCOVA) model.
[b]$P < .05$ versus placebo/escitalopram based on ANCOVA model.
Abbreviation: ITT = intent-to-treat.

Improved Insomnia Symptoms and Sleep-Related Next-Day Functioning in Patients With Comorbid Major Depressive Disorder and Insomnia Following Concomitant Zolpidem Extended-Release 12.5 mg and Escitalopram Treatment: A Randomized Controlled Trial

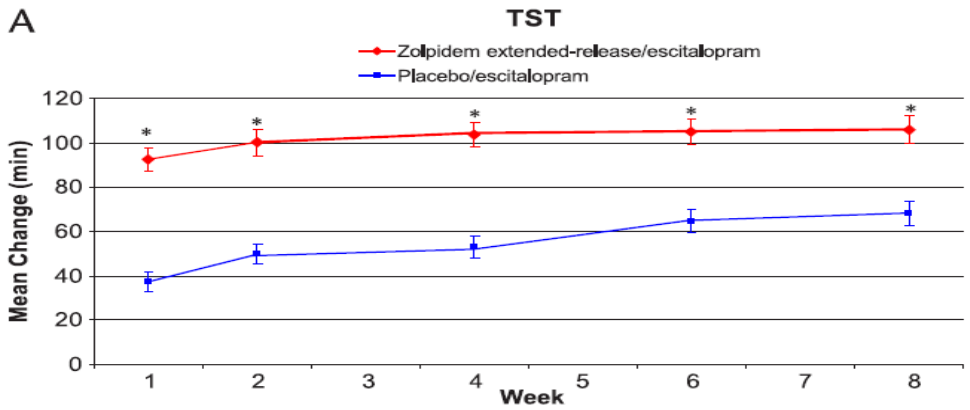
Figure 6. Mean Change From Baseline in 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$) Total Score

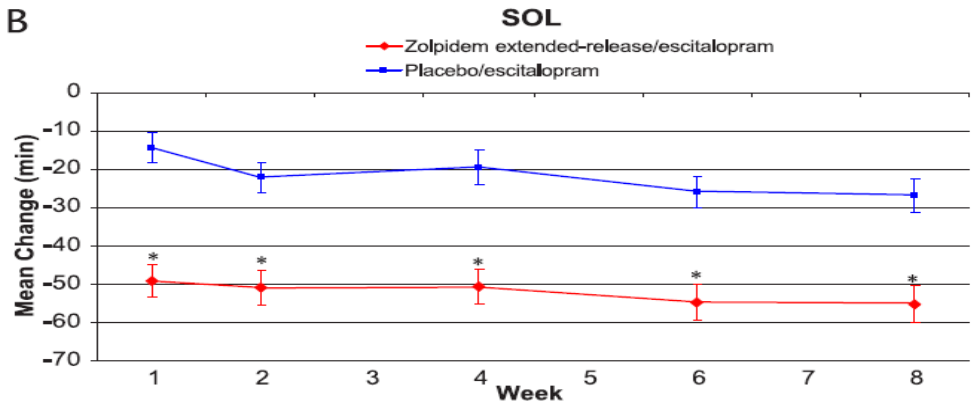


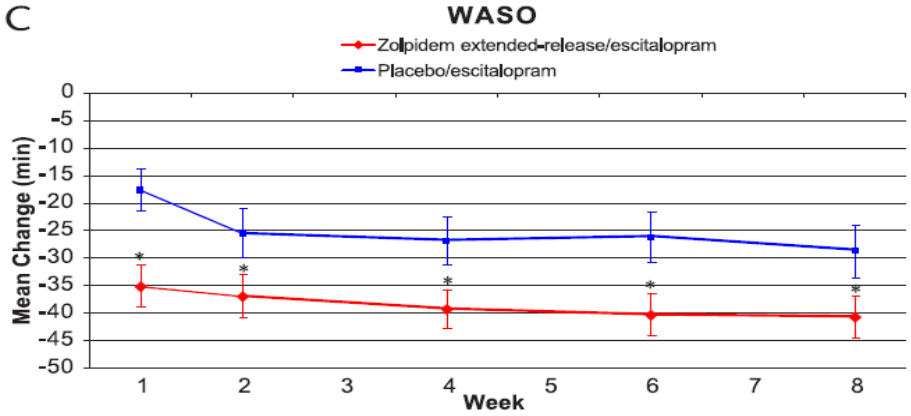
Abbreviation: ITT = intent-to-treat.

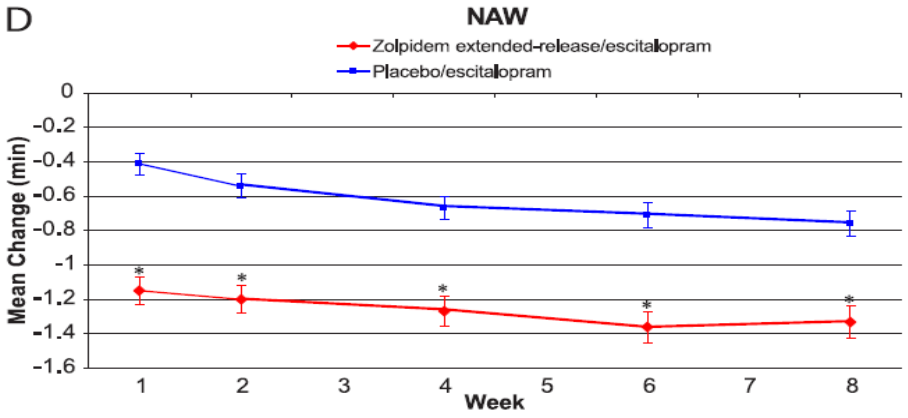
Zolpidem Extended-Release Improves Sleep and Next-Day Symptoms in Comorbid Insomnia and Generalized Anxiety Disorder

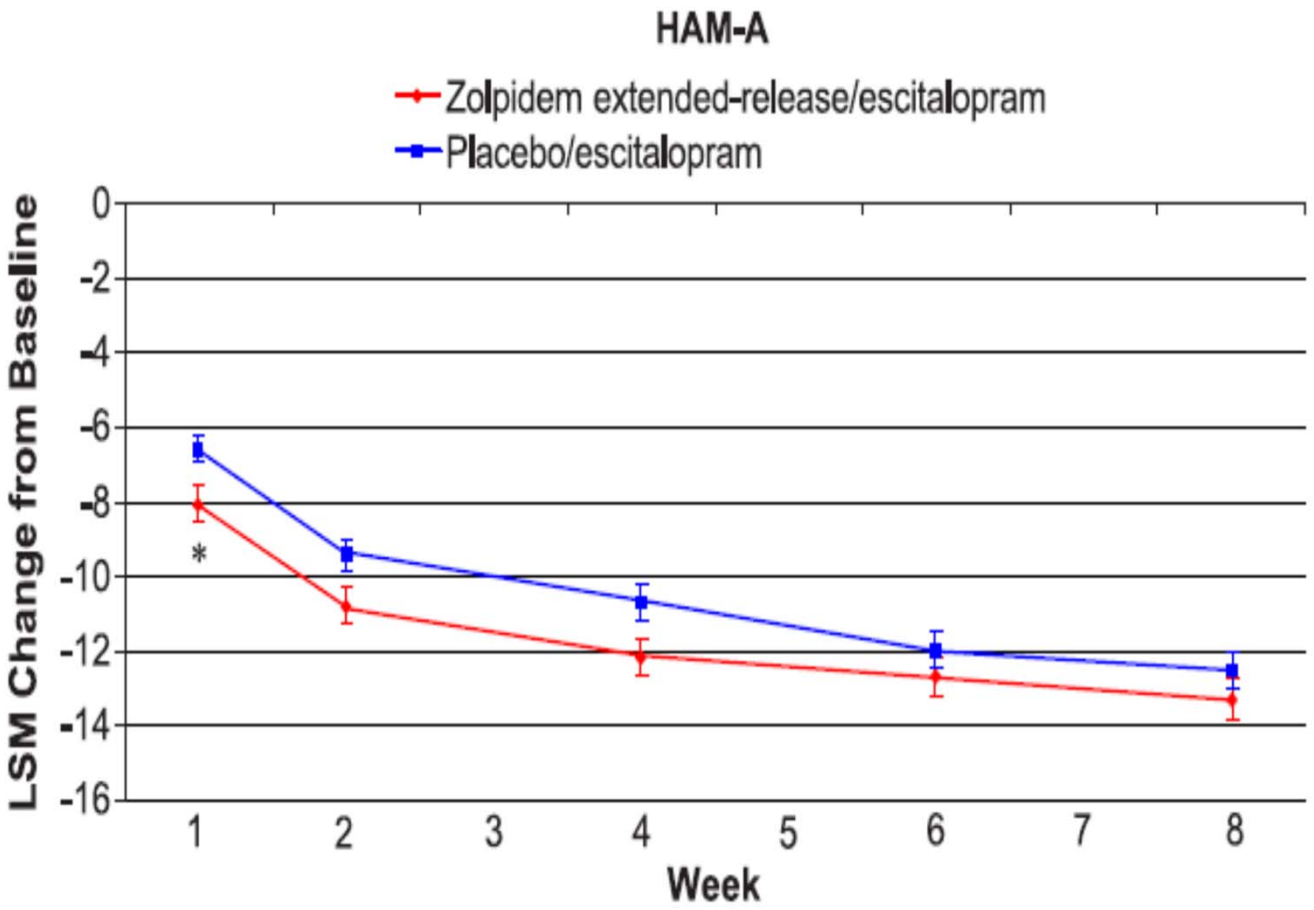
Maurizio Fava, MD, Gregory M. Asnis, MD,† Ram Shrivastava, MD,‡ Bruce Lydiard, MD, PhD,§ Bijan Bastani, MD,// David Sheehan, MD, MBA,¶ and Thomas Roth, PhD#*







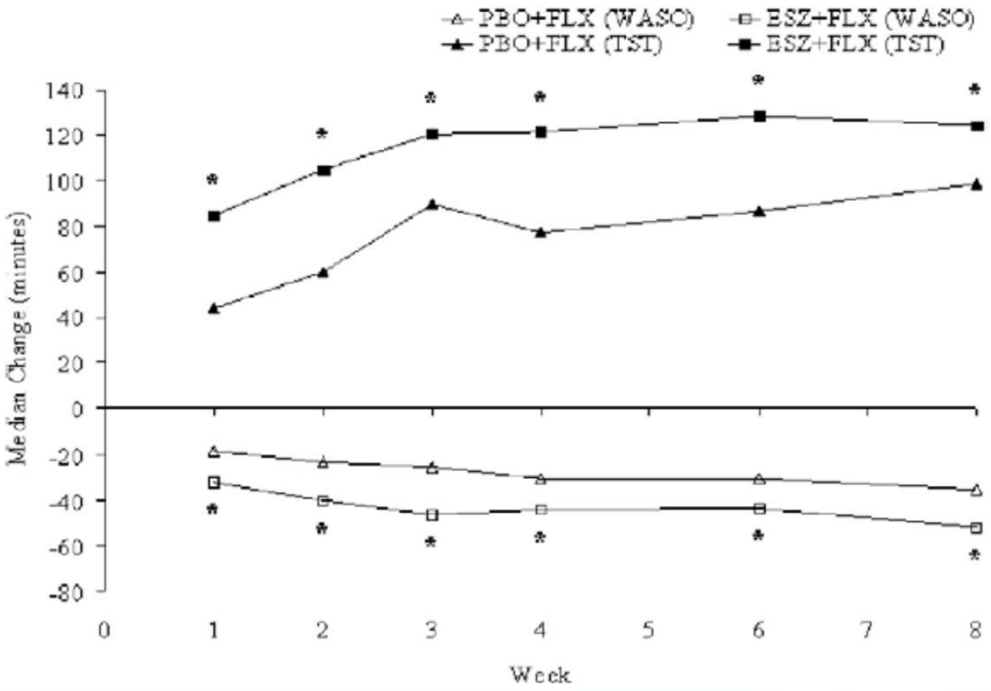




PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

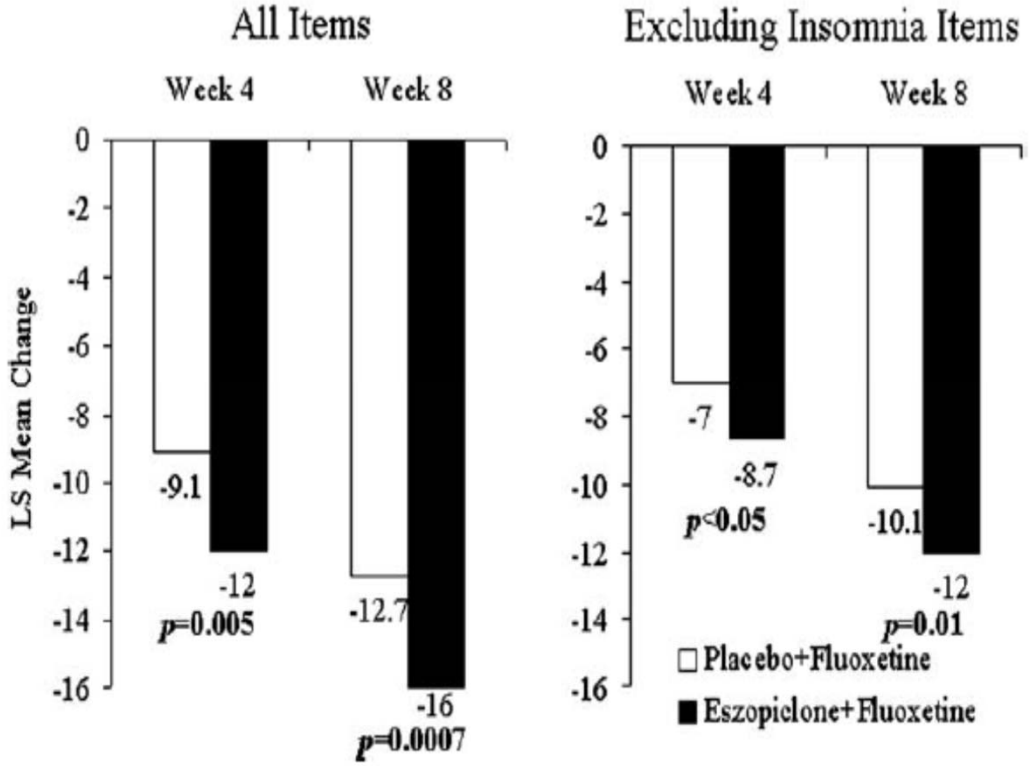
Eszopiclone Co-Administered With Fluoxetine in Patients With Insomnia Coexisting With Major Depressive Disorder

Maurizio Fava, W. Vaughn McCall, Andrew Krystal, Thomas Wessel, Robert Rubens, Judy Caron, David Amato, and Thomas Roth



PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

Mean change in 17-item Hamilton Rating Scale for Depression



PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

Eszopiclone Coadministered With Escitalopram in Patients With Insomnia and Comorbid Generalized Anxiety Disorder

Mark Pollack, MD; Gustavo Kinrys, MD; Andrew Krystal, MD; W. Vaughn McCall, MD, MS; Thomas Roth, PhD; Kendyl Schaefer, MS; Robert Rubens, MD, MBA; James Roach, MD; Holly Huang, MS; Ranga Krishnan, MD

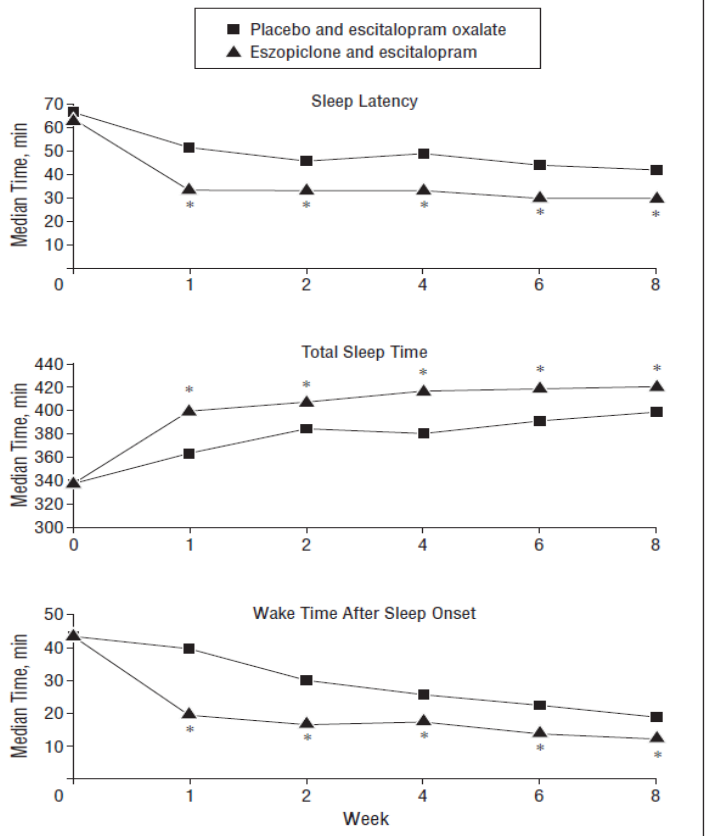
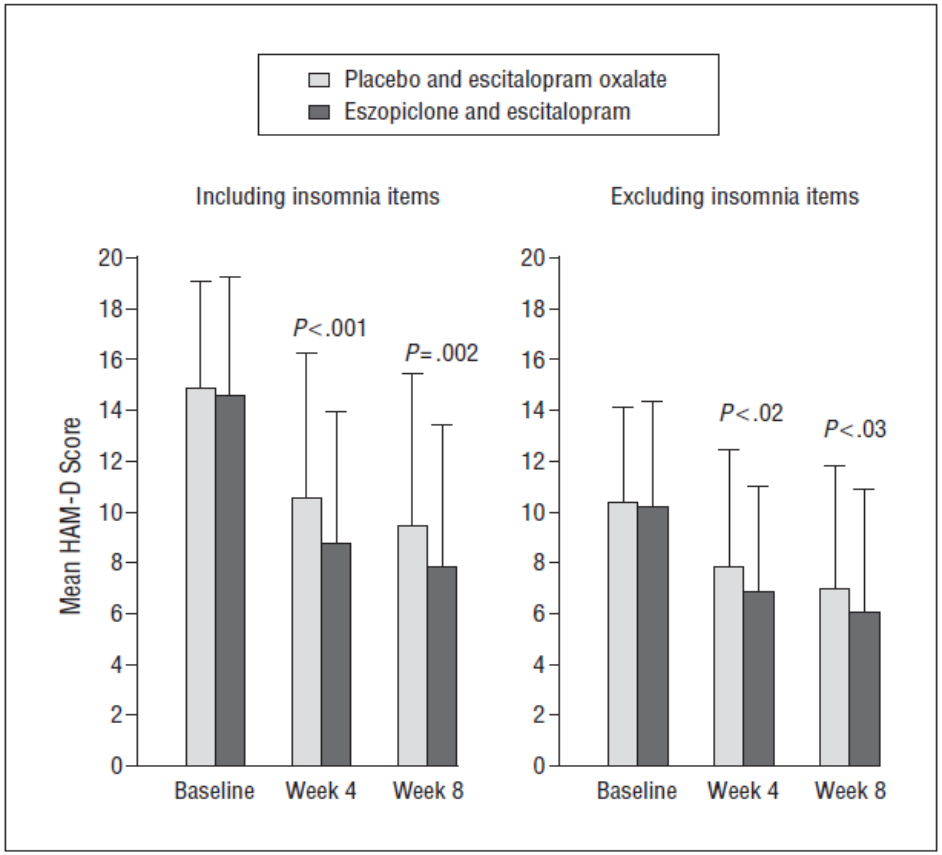
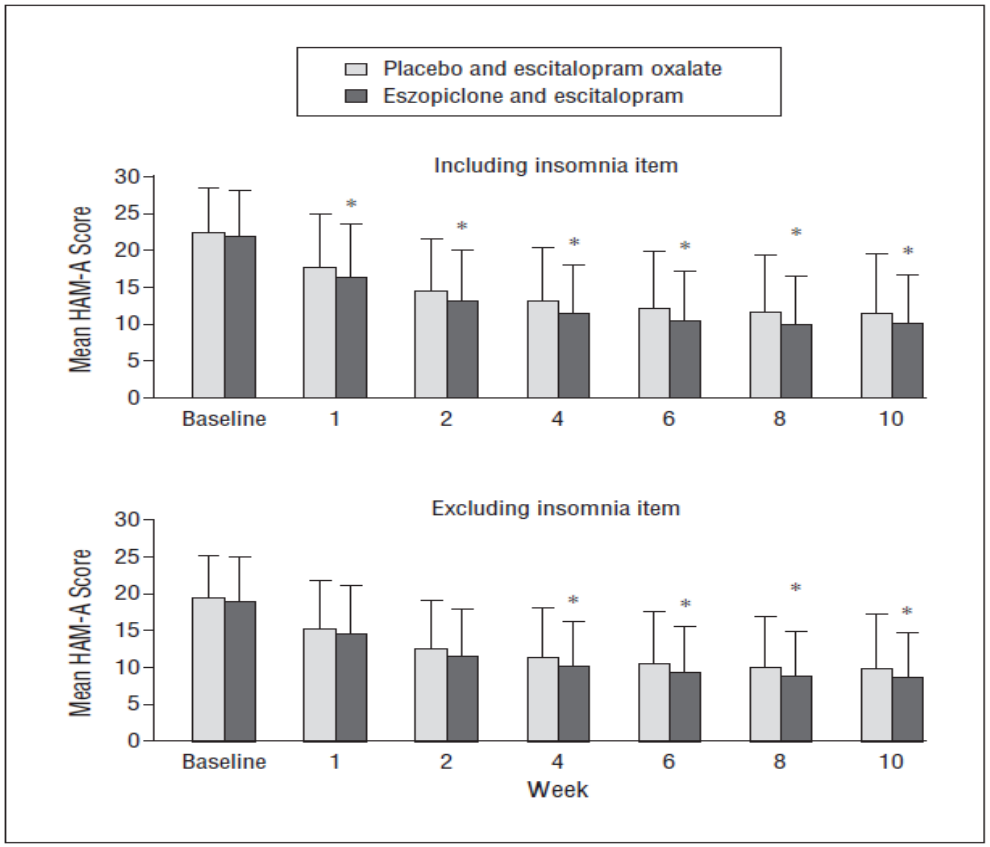


Figure 1. Sleep outcomes in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. * Indicates $P < .001$ compared with placebo (analysis of covariance).


Placebo and escitalopram oxalate
Eszopiclone and escitalopram
Including insomnia items
Excluding insomnia items
Mean HAM-D Score
P<.001
P=.002
P<.02
P<.03
Baseline
Week 4
Week 8


Placebo and escitalopram oxalate
Eszopiclone and escitalopram
Including insomnia item
Excluding insomnia item
Mean HAM-A Score
Baseline
1
2
4
6
8
10
Week

Non-FDA approved

- Trazodone
  - Very frequent off label use for Insomnia
  - 25 -150 mg
  - Tmax 1-2 hrs. and elimination half life 7-15 hrs.
  - 5HT2a antagonism, antihistaminic/anticholinergic, alpha1 antagonism
- Mirtazapine
  - 5HT2/3 antagonist, alpha 1 and 2 antagonism and H1 antagonism
  - 7.5 – 15 mg
  - Lower dose more sedating (increased adrenergic effects on higher dose)
  - Tmax 0.25-2 hrs. and elimination half life 20-40hrs
- Other drugs include Olanzapine, Quetiapine, Gabapentin, Pregabalin, Amitriptyline, Lorazepam, Clonazepam, Diazepam

- Valerian
  - 400-900 mg
  - Probably increase GABA (increasing release, inhibiting breakdown and reducing re-uptake)
  - Not enough evidence of efficacy
- Tryptophan, Magnesium, Chamomile
- Heltioz (Tasimelteon) - Non-24-Hour Sleep-Wake Disorder
  - Melatonin receptors agonist
  - 20 mg every day at the same time

Non-Pharmacological

- **Cognitive behavior therapy for Insomnia – CBT-I**
  - Sleep Hygiene
  - Stimulus control
  - Sleep restriction
  - Relaxation training
  - Cognitive therapy

Sleep hygiene

- Maintain regular sleep wake schedule
- Avoid stimulants like caffeine, nicotine close to bedtime
- Limit alcohol intake
- Bedroom to be dark, cool and quiet
- No TV/Phone/read in bed – remove electronic devices from bedroom
- Allow at least 1 hr. to unwind before bedtime
- Exercise regularly

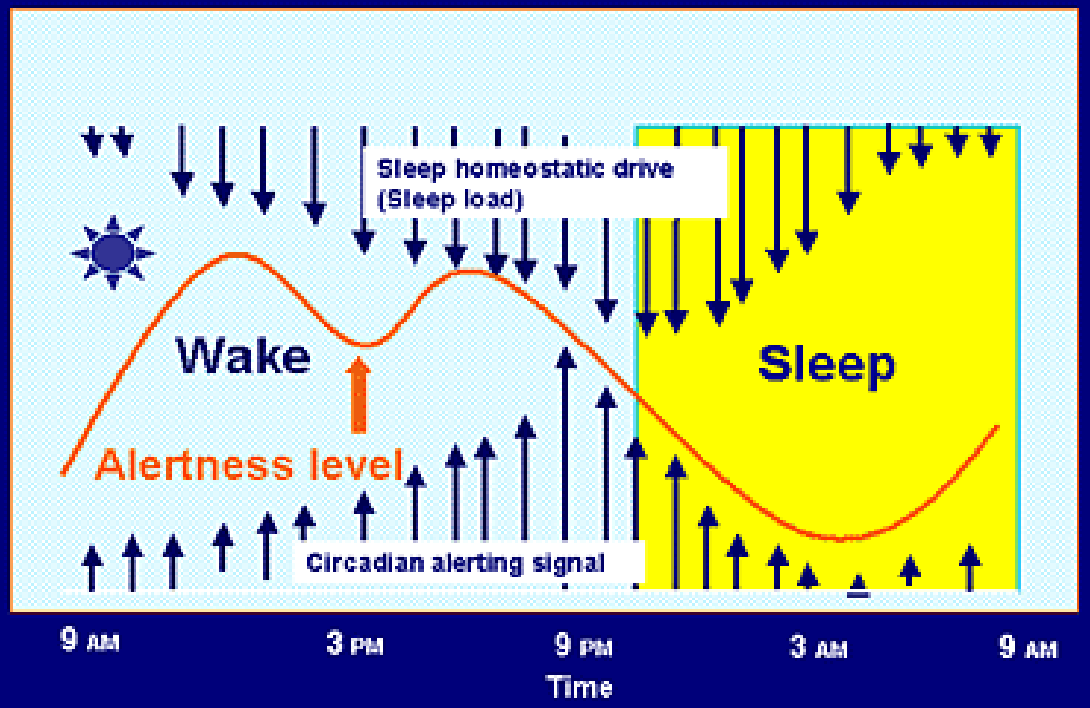
Stimulus control

- Go to bed only when sleepy
- If not able to fall sleep within 15-20 minutes, leave the bed and bedroom at least for 30 minutes. Do not watch clock during this period
- Use the bed and bedroom for sleep only, no TV watching, reading, working on phone or computer or other activities in bed
- Set regular wake up time, do not snooze
- Avoid daytime nap

Sleep restriction

- Restricting time awake in bed, like leaving the bed in unable to fall sleep, or if wake up in night and not able to fall back sleep – improving sleep efficiency
- Strengthening the homeostatic drive to help falling sleep
- Maintain a strict bed and wake up time, try to sleep only in between this time, no naps during the day

Interaction of Circadian Rhythms and Sleep



Relaxation therapy

- Progressive muscle relaxation
- Guided imagery
- Deep breathing
- Mindfulness/Meditation

Cognitive therapy

- Challenge irrational beliefs
  - Overestimation of number of hours of sleep needed to be rested
  - Worrying about sleep and consequences if not able to sleep
  - Fear of missing opportunities for sleep
- Never try to sleep because it exacerbates sleep difficulties
- Do not give too much importance to sleep
- Do not catastrophize after poor night's sleep
- Thoughts journaling to help with rumination

Online resources for CBT-I

- CBT-I coach
- SHUT-I
- Restore
- CBTforInsomnia.com
- Sleepio

New/Future therapies

- Cervella (Cranial electrostimulation)
- Cereve/Ebb – Frontal cooling device
- Kortex – Fisher Wallace stimulator
- TMS
- Lorediplon
- Piromelatine
- Zolpidem 5 mg, diphenhydramine 50 mg and 0.5 mg Lorazepam

PENNSYLVANIA ACADEMY OF
FAMILY PHYSICIANS FOUNDATION