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HARVARD MEDICAL SCHOOL

Update on Diagnosis and Treatment of Sleep Disorders

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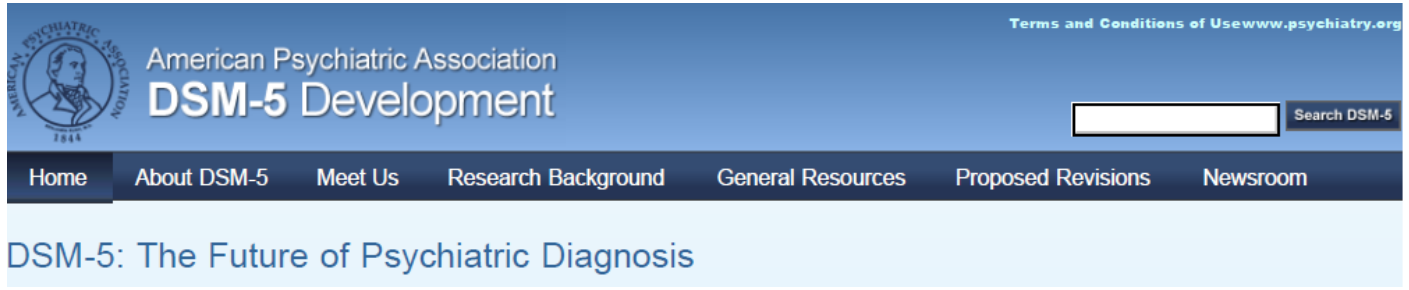
Disclosure Information

Type of Affiliation	Commercial Entity
Consultant/Honoraria	Advance Medical Avadel Eisai UpToDate
Research Grant	Luitpold Pharma Merck RLS Foundation

Sleep disorders

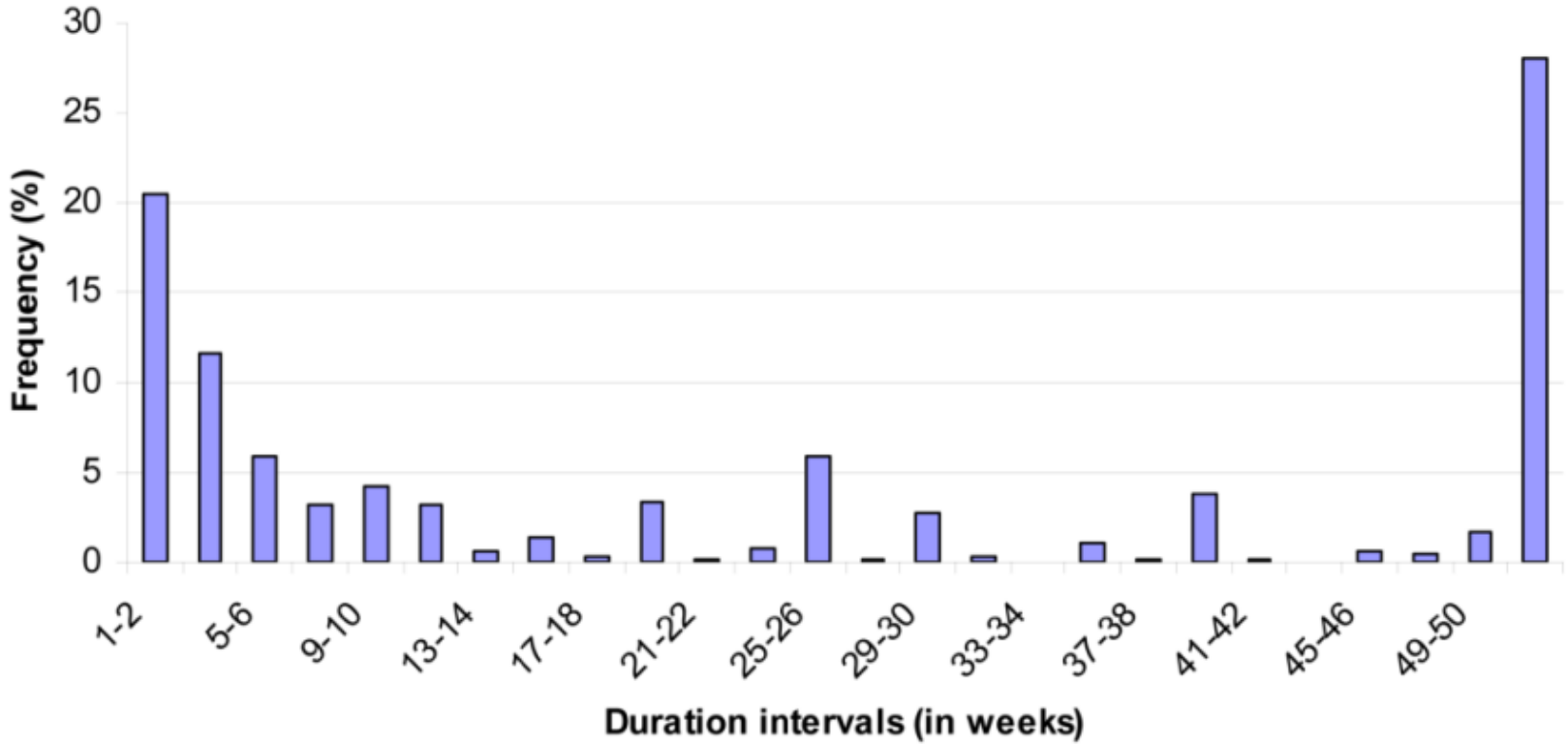
- **Insomnias**
  - **Insomnia, psychiatric/medical disorders, RLS, medications**
- Hypersomnias
  - Sleep apnea, medications, Periodic leg movements of sleep
- Parasomnias
  - Sleepwalking, sleep terrors, REM sleep behavior disorder
- Circadian rhythm disorders
  - Shift work sleep disorder, Delayed sleep phase disorder



DSM-5 Insomnia disorder

- Dissatisfaction with sleep quality or quantity associated with (at least one of):
  - difficulty initiating sleep
  - difficulty maintaining sleep
  - early morning awakening
- Distress or dysfunction related to sleep disturbance
- Minimum of 3x/wk for 3 months
- The insomnia does not co-occur with another sleep disorder
- The insomnia is not *explained* by coexisting mental disorders or medical conditions

Most sleep problems are transient but 25-30% last > 1 year



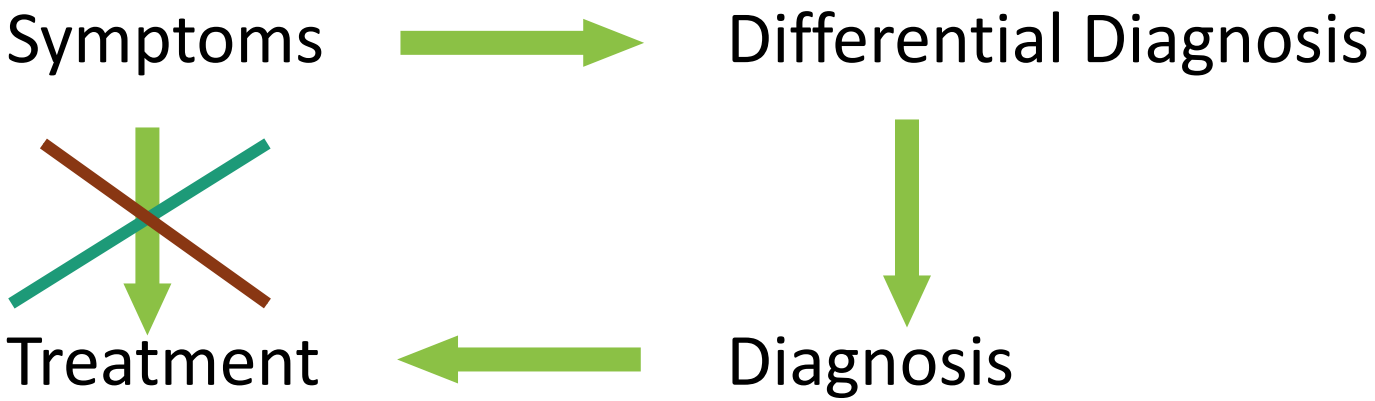
Roth et al, Biol Psych 2006

Medication treatment of sleep disturbance is warranted in patients with acute insomnia

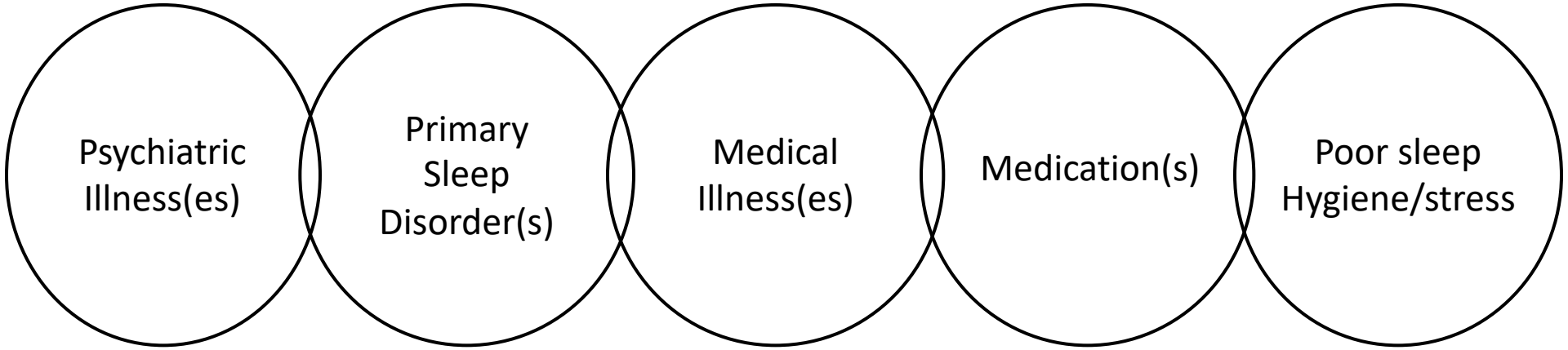
- Acute insomnia often has an identifiable precipitant
- Difficulty falling or staying asleep, or early AM awakening
- Have distress or dysfunction as a result of sleep disturbance
- No better explanation for sleep disturbance than current precipitant

- Assess risk of side effects with medication
- Evaluate risk of misuse/abuse/diversion
- Check PMP for use of other sedatives

Chronic Insomnia Requires a Thorough Evaluation



Sleep quality is only as strong as the weakest link and insomniacs often have many sleep-related issues



All contributing factors must be treated to achieve maximum benefit

Discuss and prioritize treatment goals with the patient

1. Primary Goals:
   - Improvement in sleep quality and/or time.
   - Improvement of insomnia-related daytime impairments such as improvement of energy, attention or memory difficulties, cognitive dysfunction, fatigue, or somatic symptoms.
2. Other Goals:
   - Improvement in an insomnia symptom (SOL, WASO, # awakenings) such as:
     - SOL <30 minutes and/or
     - WASO <30 minutes and/or
     - Decreased frequency of awakenings or other sleep complaints
     - TST >6 hours and/or sleep efficiency >80% to 85%.
   - Formation of a positive and clear association between the bed and sleeping
   - Improvement in sleep related psychological distress

Schutte-Rodin et al, JCSM, 2008

Our understanding of the regulation of sleep informs insomnia treatment approaches

Two processes control sleep timing, quality and quantity

1. Homeostatic Drive
   -Increases with the duration of waking and dissipates with sleep

2. Circadian Rhythms
   -Confines sleep and waking to different phases of the 24-hour day
   -Entrained to the light-dark cycle
   -Sleep-independent

Differential diagnosis of chronic insomnia

- Primary psychiatric disorders
- Medications
- Substances
- Medical disorders
- Restless Legs Syndrome (RLS)
- Sleep schedule disorders
- Obstructive sleep apnea

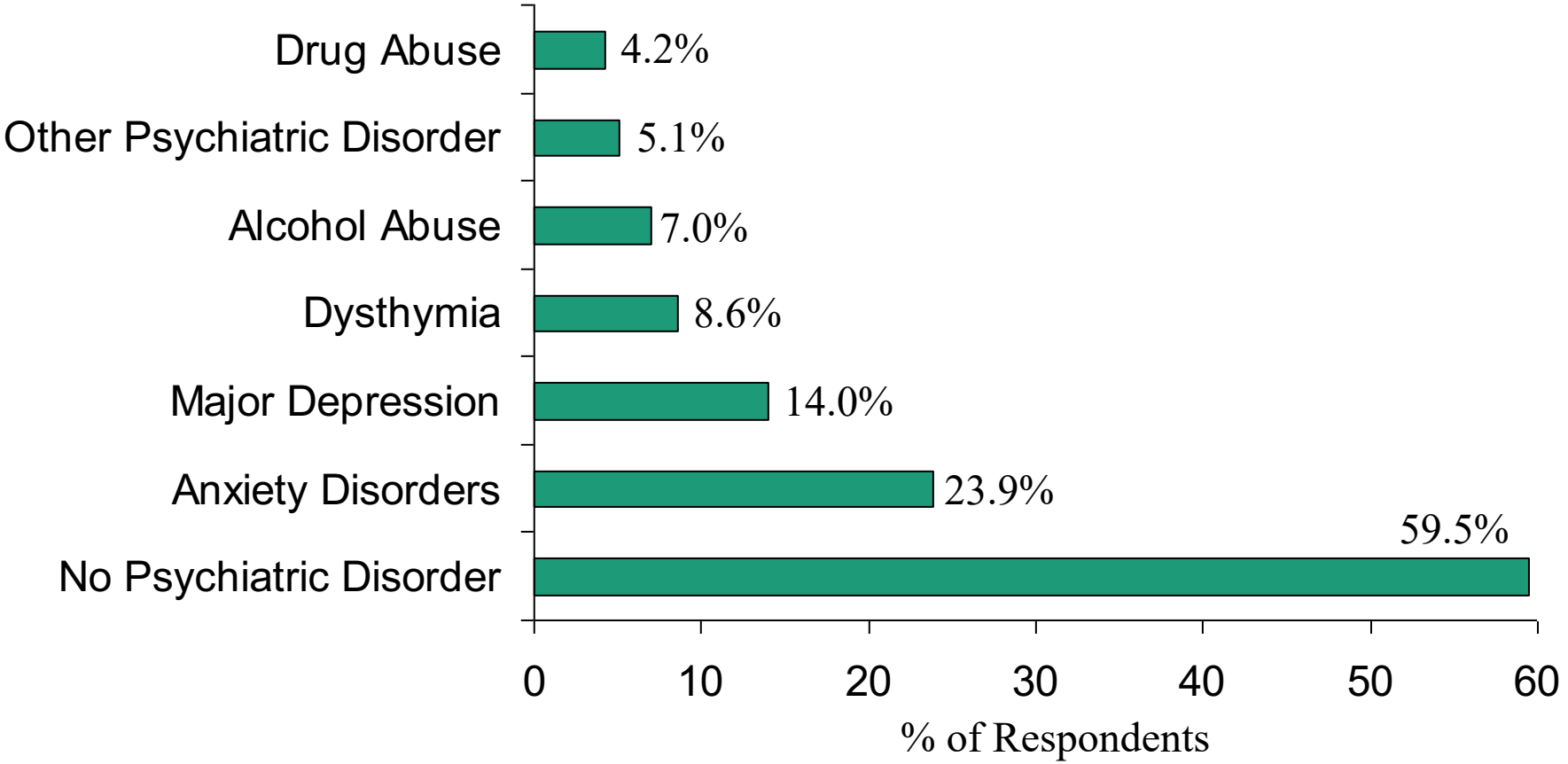
Indications for polysomnography

- Suspicion of sleep apnea (loud snoring *PLUS one of the following):*
  - daytime sleepiness
  - witnessed apneas
  - refractory hypertension
- Abnormal behaviors or movements during sleep
- Unexplained excessive daytime sleepiness
- Refractory sleep complaints, particularly repetitive brief awakenings

Common cognitive and behavioral issues which can produce/worsen insomnia

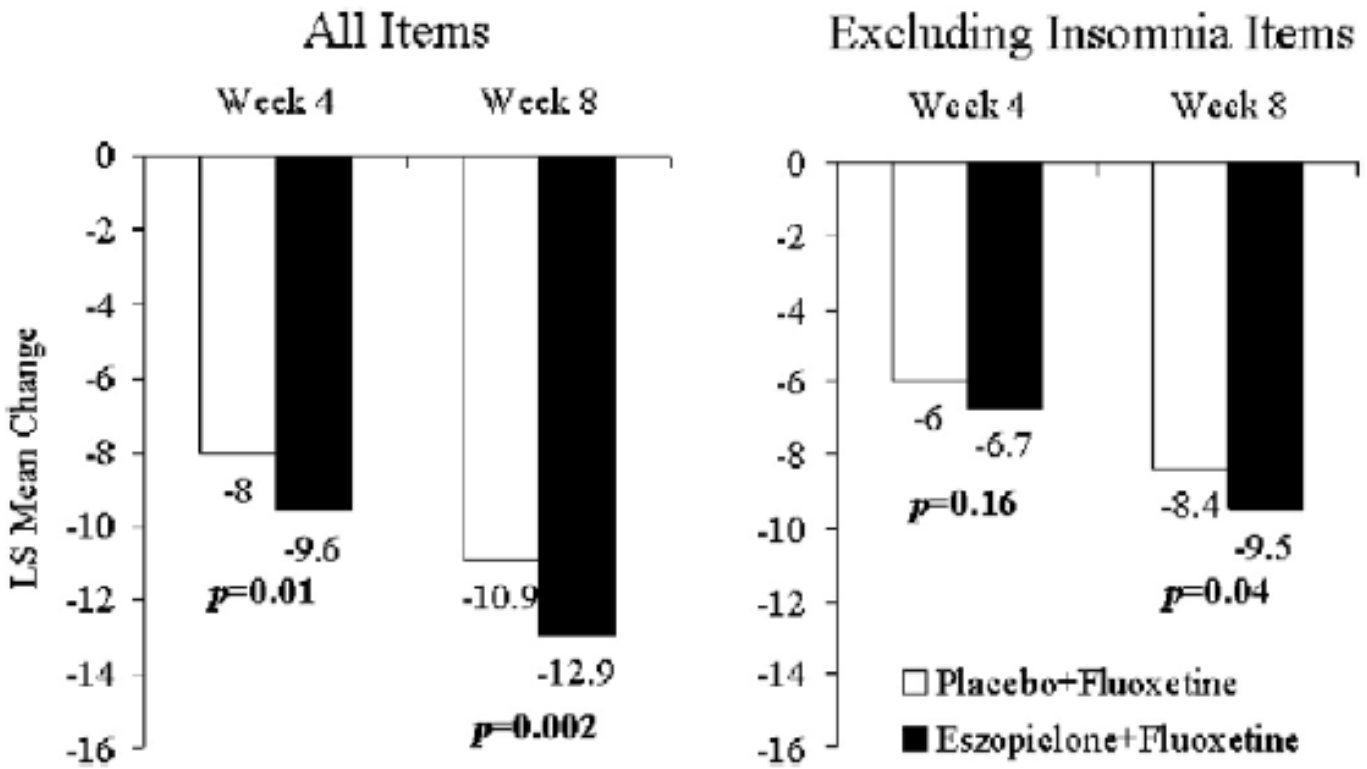
- Inconsistent bedtimes and wake times
- “Dozing” in evening before bed
- Excessive time in bed
- Sleep-related anxiety (“insomnia phobia”)
- Unrealistic expectations of total sleep time, sleep onset and number of awakenings
- Clock watching
- Use of electronics in bedroom
- Inappropriate attributions of daytime issues to sleep

Psychiatric disorders are present in only 30-40% of those with insomnia

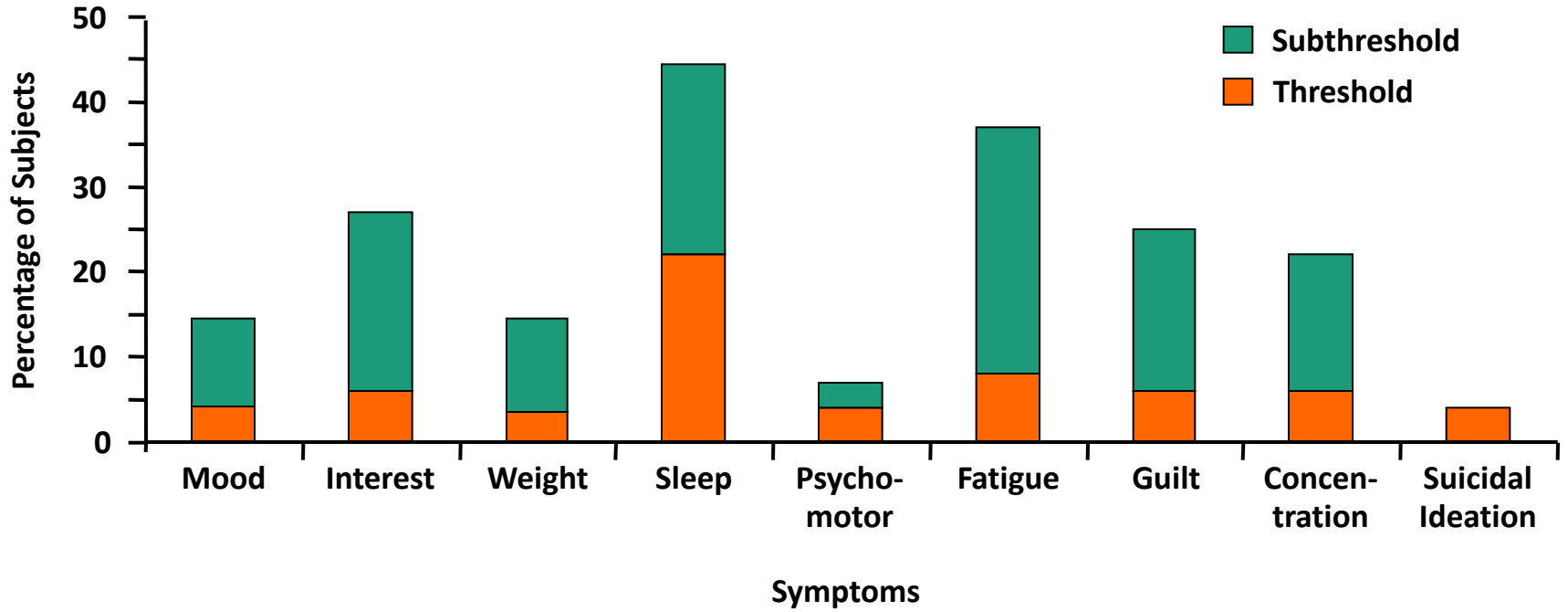


Ford DE, Kamerow DB. *JAMA*. 1989;262:1479-1484.

Independent treatment of insomnia in MDD improves depression treatment outcome



Sleep disturbance is the most common persistent symptom in treated MDD



25% had treatment-emergent onset of nocturnal awakenings (Nierenberg et al, 2012)

MDD = Major depressive disorder.

Nierenberg AA et al. *J Clin Psychiatry*. 1999.

MILITARY MEDICINE, 175, 10:759, 2010

Insomnia Is the Most Commonly Reported Symptom and Predicts Other Symptoms of Post-Traumatic Stress Disorder in U.S. Service Members Returning From Military Deployments

CDR Robert N. McLay, MC USNR; CAPT Warren P. Klam, MC USN; Stacy L. Volkert, MD

•PTSD is a disorder with an essential difficulty maintaining states of decreased vigilance

•PTSD will therefore nearly always interfere with sleep

•Specific questions as to the circumstances of traumatic episodes (eg night, bedroom) may shed light on sleep disturbance

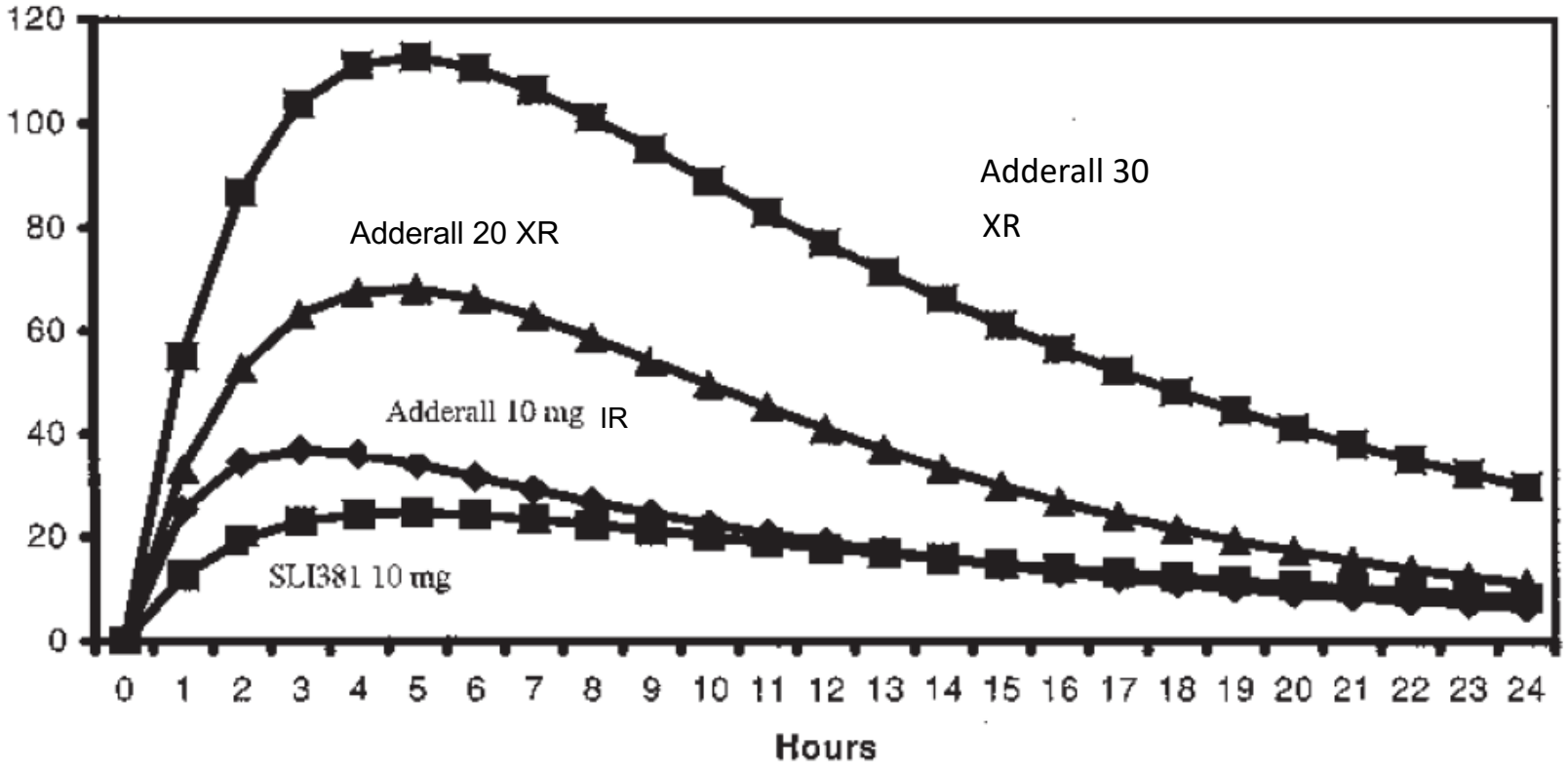
•Treatments:

- education as to relationship of PTSD to sleep disturbance
- safety of sleep environment
- judicious use of hypnotics
- prazosin or Image Rehearsal Therapy for nightmares

INSOMNIA RELATED TO MEDICATIONS

- Antidepressants
- Stimulants
- Steroids, bronchodilators
- Decongestants

Stimulant pharmacokinetics are not kind to sleep



Insomnia in the elderly is not related to age, but to medical illness

- Cardiac: angina, PND
- Pulmonary: COPD, coughing
- GI: Nocturnal reflux
- Musculoskeletal pain
- Endocrine: Hypo/ hyperthyroidism, diabetes, menopause
- Neurologic: Dementia, Parkinson's, CVA, migraine
- Urinary: Nocturia, renal failure

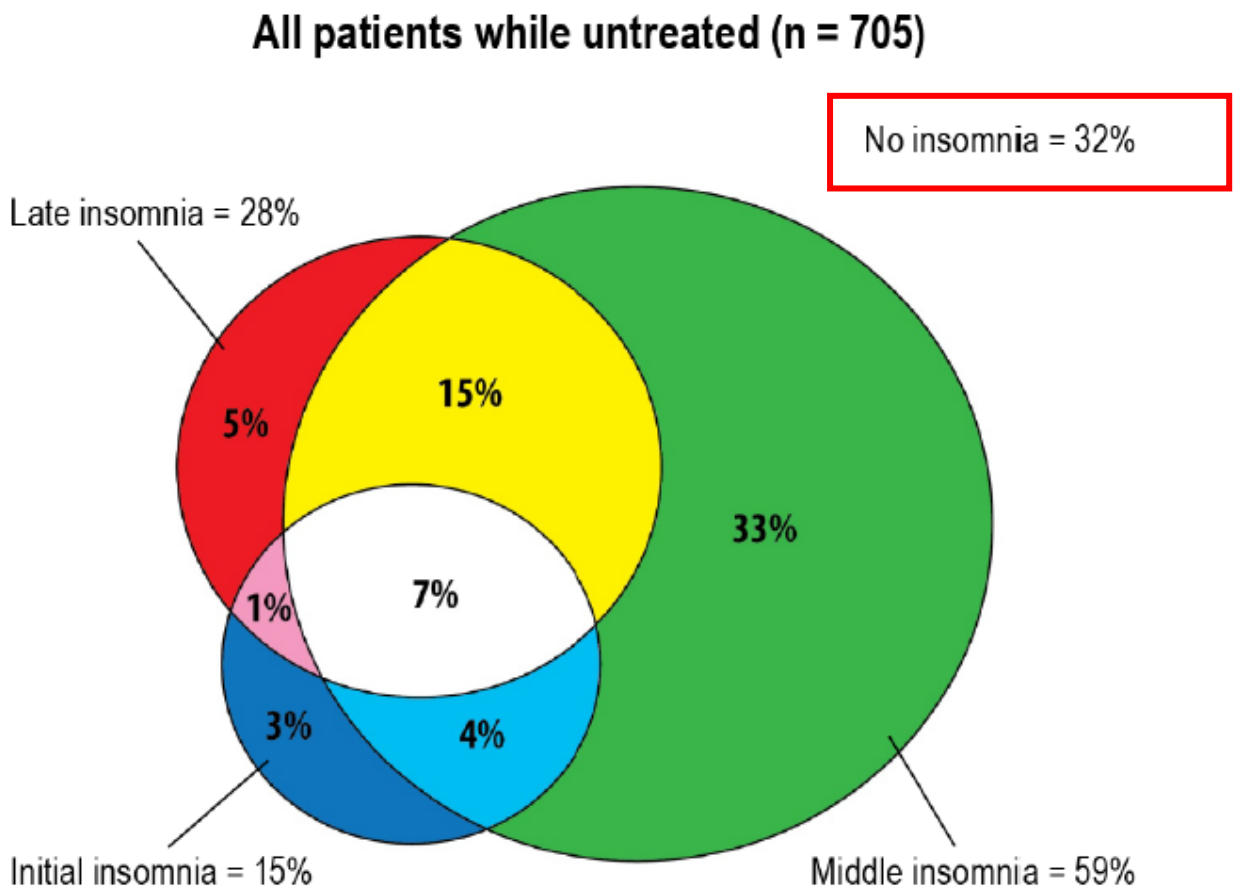
Diagnosis and Treatment of Restless Legs Syndrome

- URGE diagnostic criteria
- Modify reversible causes
  - Iron Deficiency (keep Ferritin > 50)
  - Medication-Induced (SRIs, DA antagonists, antihistamines)
- Pharmacologic approaches
  - Dopaminergic agonists (pramipexole, ropinirole, rotigotine patch) but watch for iatrogenic worsening of RLS ("augmentation")
  - Alpha 2 delta ligands (gabapentin, pregabalin)
  - Opioids (oxycodone, methadone)

SLEEP SCHEDULE DISORDERS

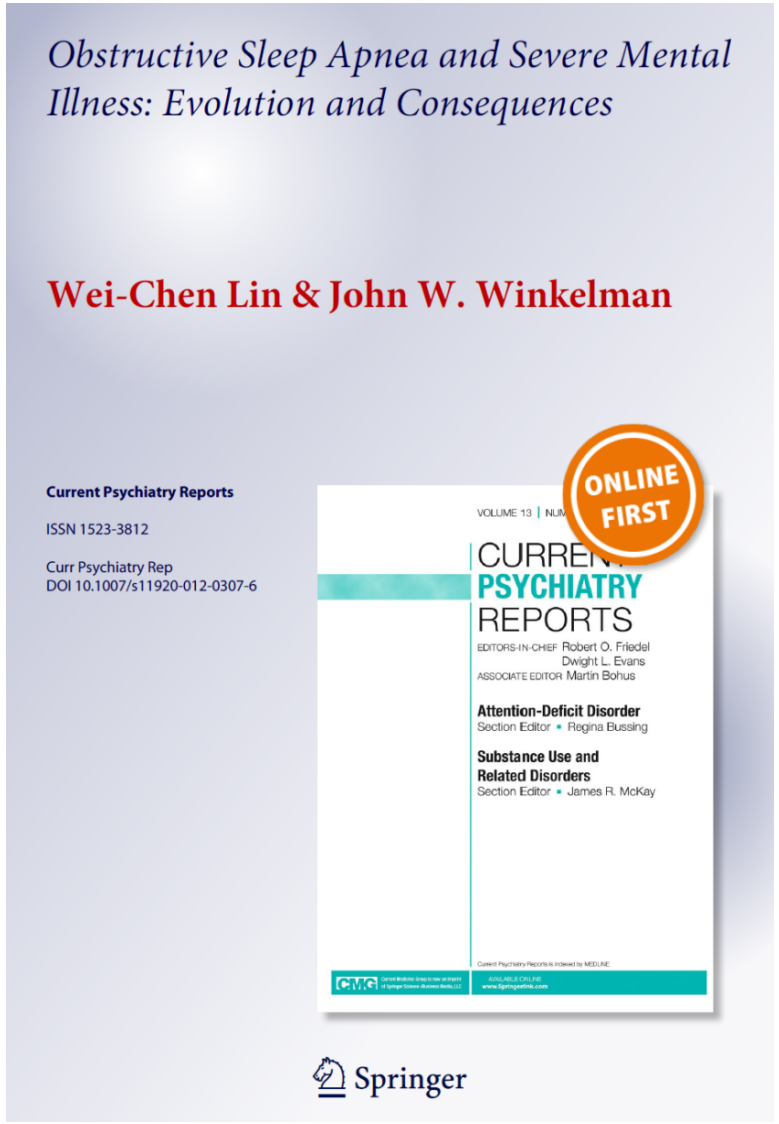
- Delayed Sleep Phase Syndrome
  - Most common in adolescents
  - Initial insomnia and difficulty awakening in AM
  - Daytime sleepiness
- Advanced Sleep Phase Syndrome
  - Most common in the elderly
  - Early AM awakening

Insomnia is more common than daytime sleepiness in those with sleep apnea (AHI>15)

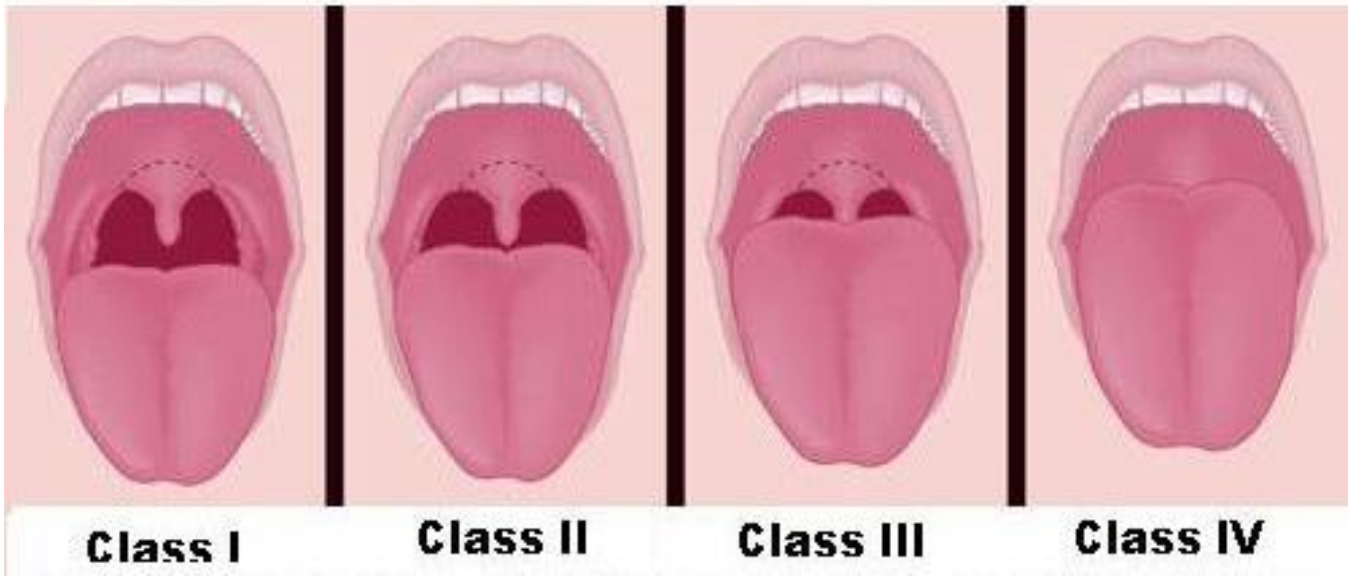


Bjornsdottir et al Sleep 2013

OSA is common in those with psychiatric illness

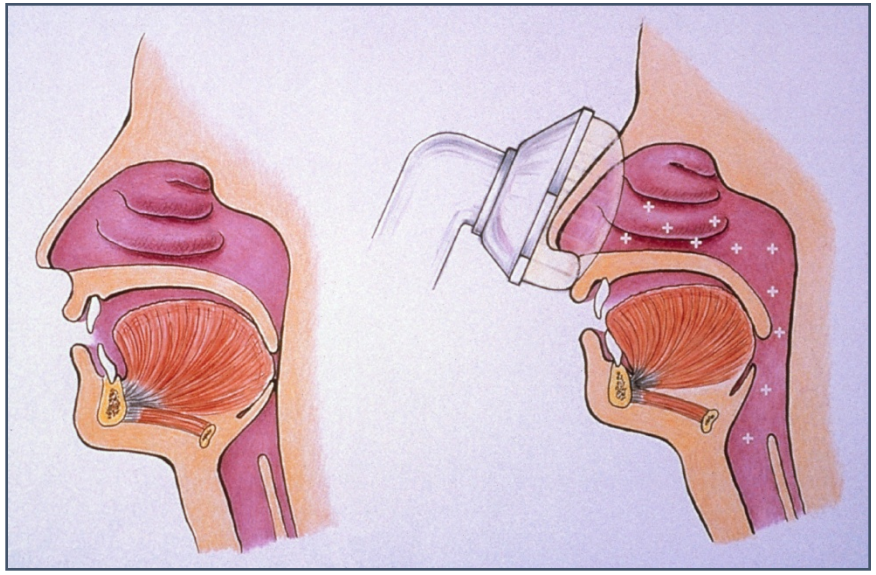


Physical exam (kind of) predicts likelihood of sleep apnea



OSA treatments

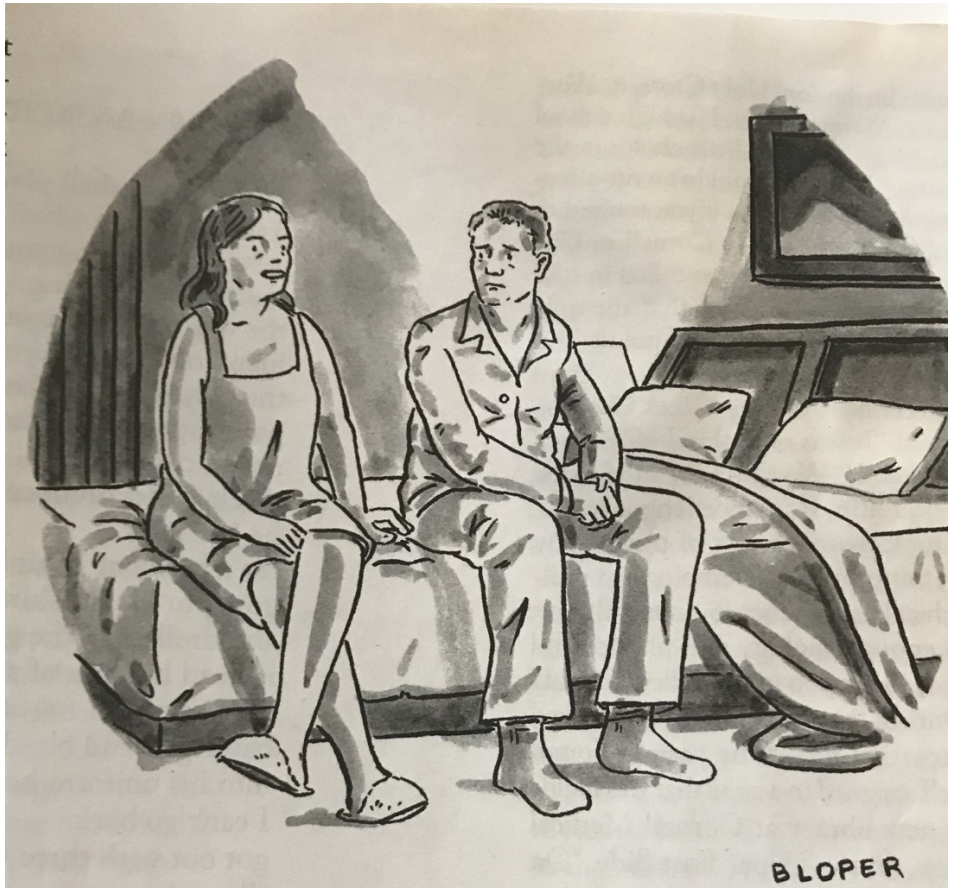
Positive Airway Pressure (PAP)



Auto-PAP is allowing both diagnostic and titration to be performed in the home (no sleep lab necessary)

Weight loss, upper airway surgery, positional treatment

Insomnia treatment



"You can't sleep? Have you tried meditating, then reading for an hour, then going to the couch, then back to bed, then counting backward from ten million, then taking a sleeping pill?"

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Recommendation 1: *ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*

Ann Intern Med. 2016;165:125-133. doi:10.7326/M15-2175 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 3 May 2016.

Table 2. Components of Cognitive Behavioral Therapy for Insomnia.

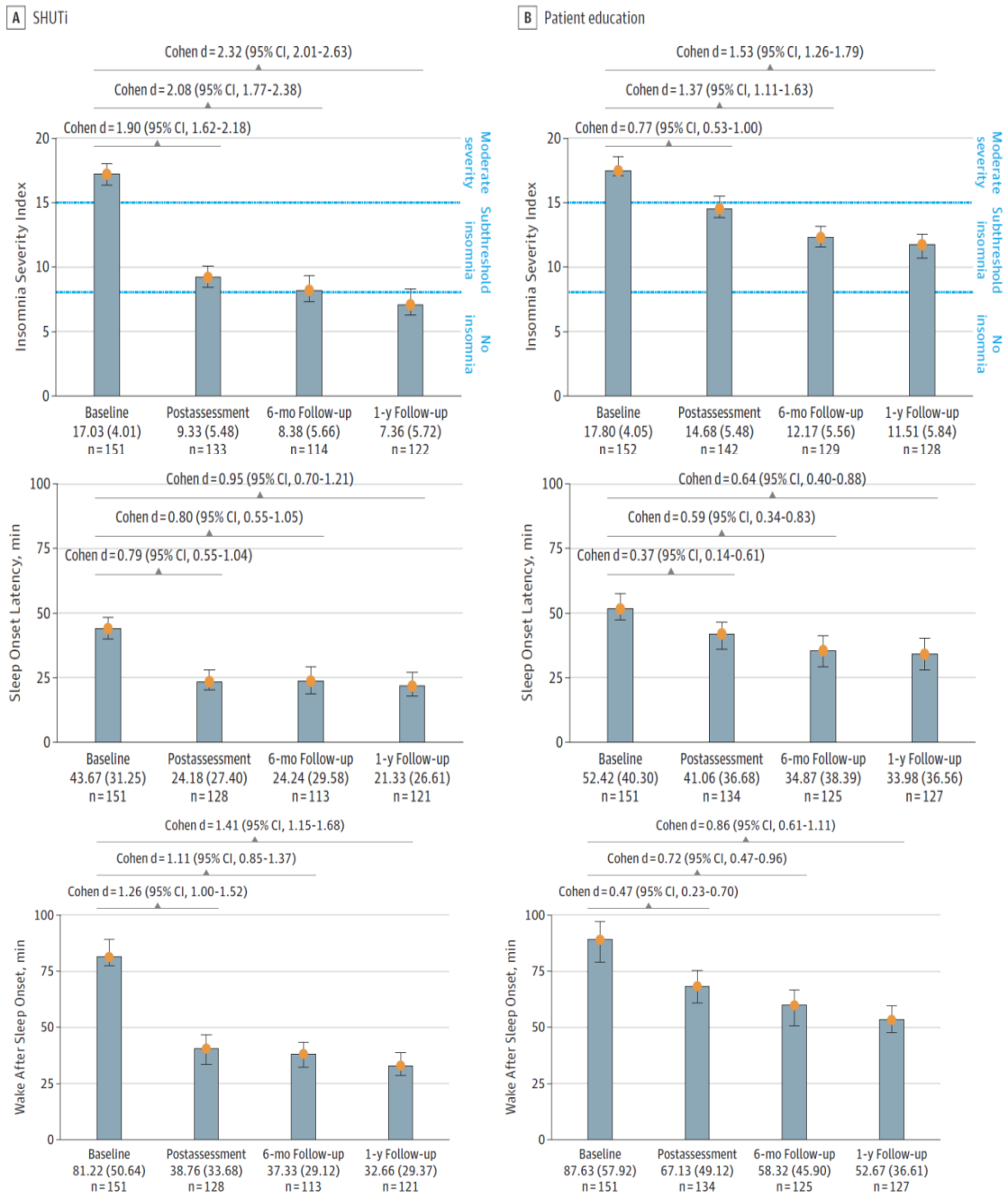
Component	Intended Effect	Specific Directions for Patients
Sleep restriction	Increase sleep drive and stabilize circadian rhythm	Reduce time in bed to perceived total sleep time (not less than 5–6 hours), choose specific hours on the basis of personal preference and circadian timing, increase time in bed gradually as sleep efficiency improves
Stimulus control	Reduce arousal in sleep environment and promote the association of bed and sleep	Attempt to sleep when sleepy, get out of bed when awake and anxious at night, use the bed only for sleep or sexual activity (e.g., no watching TV in bed)
Cognitive therapy	Restructure maladaptive beliefs regarding daytime and health consequences of insomnia	Maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences
Relaxation therapy	Reduce physical and psychological arousal in sleep environment	Practice progressive muscle relaxation, breathing exercises, or meditation
Sleep hygiene	Reduce behaviors that interfere with sleep drive or increase arousal	Limit caffeine and alcohol, keep bedroom dark and quiet, avoid daytime or evening napping, increase exercise (not close to bedtime), remove bedroom clock from sight

Winkelman JW. Insomnia Disorder. New England Journal of Medicine, 2015

Online CBT-I programs do work

SHUTi™

Sleep Healthy Using the Internet



CBT-I (online) effective for sleep latency, wake after sleep onset, but not for total sleep time

Sleep Variable	Patient Education No.	Patient Education Mean (SD)	Patient Education Cohen *d* (95% CI)	SHUTi No.	SHUTi Internet CBT-I, Mean (SD)	SHUTi Cohen *d* (95% CI)	*F* Value	*P* Value
Sleep Efficiency								
Baseline	151	70.47 (14.22)	NA	151	73.24 (12.56)	NA	$F_{3,1042} = 8.39$	<.001
Postassessment	134	77.17 (14.49)	0.49 (0.25-0.72)	128	85.59 (11.01)	0.92 (0.67-1.16)		
6-mo Follow-up	125	80.06 (14.64)	0.69 (0.45-0.94)	113	86.30 (10.48)	0.92 (0.67-1.18)		
1-y Follow-up	127	81.79 (11.96)	0.84 (0.59-1.08)	121	87.81 (10.73)	1.04 (0.79-1.30)		
No. of Awakenings								
Baseline	151	1.98 (1.27)	NA	151	1.87 (1.19)	NA	$F_{3,1042} = 3.41$	.02
Postassessment	134	1.66 (1.13)	0.34 (0.10-0.57)	128	1.31 (1.29)	0.65 (0.41-0.90)		
6-mo Follow-up	125	1.65 (1.18)	0.41 (0.17-0.64)	113	1.32 (1.30)	0.58 (0.33-0.82)		
1-y Follow-up	127	1.54 (1.18)	0.55 (0.31-0.79)	121	1.22 (1.32)	0.71 (0.47-0.96)		
Sleep Quality								
Baseline	151	2.75 (0.58)	NA	151	2.85 (0.52)	NA	$F_{3,1042} = 2.93$	.03
Postassessment	134	3.03 (0.69)	0.53 (0.29-0.77)	128	3.33 (0.65)	0.87 (0.63-1.12)		
6-mo Follow-up	125	3.13 (0.70)	0.70 (0.46-0.94)	113	3.38 (0.67)	0.95 (0.69-1.20)		
1-y Follow-up	127	3.24 (0.70)	0.88 (0.63-1.13)	121	3.54 (0.61)	1.23 (0.96-1.49)		
Total Sleep Time								
Baseline	151	5.59 (1.32)	NA	151	5.77 (1.24)	NA	$F_{3,1042} = 0.40$	.76
Postassessment	134	6.13 (1.36)	0.42 (0.18-0.65)	128	6.26 (1.22)	0.38 (0.14-0.61)		
6-mo Follow-up	125	6.41 (1.36)	0.62 (0.38-0.87)	113	6.46 (1.14)	0.52 (0.27-0.77)		
1-y Follow-up	127	6.53 (1.22)	0.72 (0.48-0.96)	121	6.60 (1.10)	0.62 (0.37-0.86)		

Ritterband et al, JAMA Psychiatry, 2017

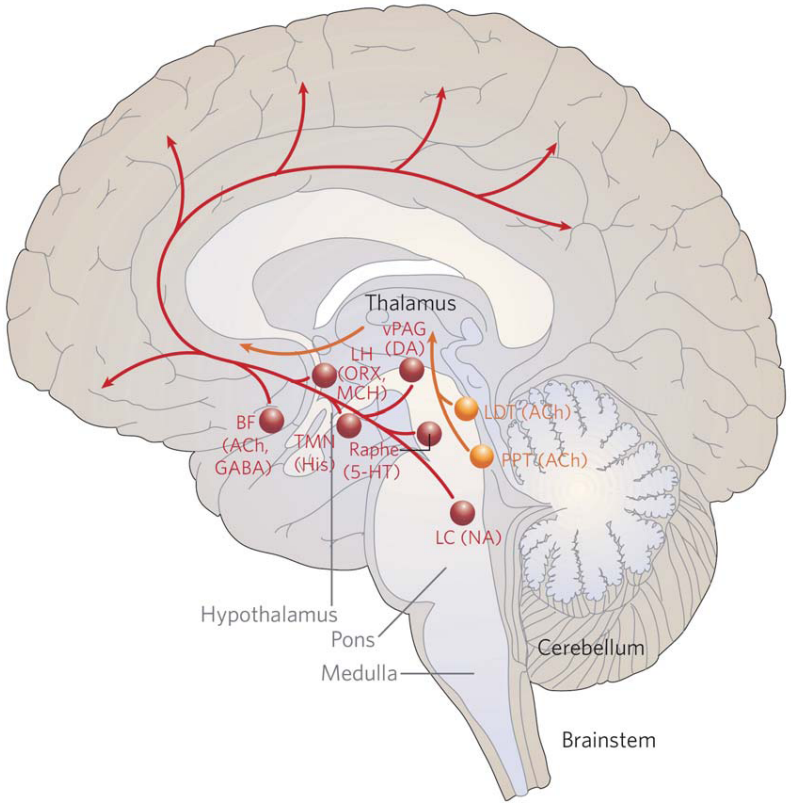
CBT-I non-response and medication initiation

- Ritterband (SHUTi, 2017): non-responder rate: 50% at 9 weeks, 40% at 6 months, and 30% at 1 year follow-up
- These are individuals for whom it is appropriate to consider a medication trial
- Whether to start medication depends on the severity of the persistent insomnia, comorbidities, and previous response to hypnotics

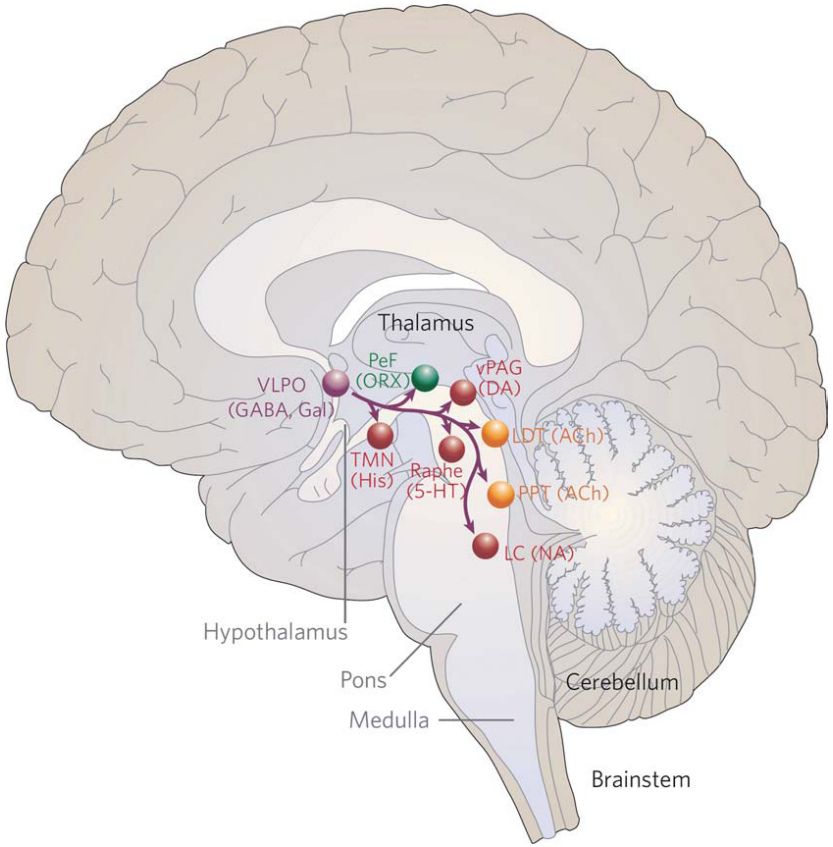
"A story? Honey, wouldn't you rather a mild sedative?"

The complex neurochemistry of sleep provides many treatment options

Ascending arousal pathways



Descending inhibitory pathways



Pharmacologic Treatments for Insomnia

- Benzodiazepine receptor agonists (BzRAs)
- Melatonin agonists
- Orexin antagonist
- Sedating antidepressants
- Anticonvulsants
- Dopaminergic antagonists (eg antipsychotics)
- Miscellaneous (eg prazosin, clonidine, hydroxyzine)

Benzodiazepine-Receptor Agonists (BzRA) Commonly Used as Hypnotics

Agent (brand name)	Dose range	Half-life
Clonazepam (Klonopin)	**0.25 -1.0 mg**	**40 hr**
Temazepam (Restoril)*	**7.5-30 mg**	**4-18 hr**
Lorazepam (Ativan)	**0.5-2.0 mg**	**10-20 hr**
Oxazepam (Serax)	**10-30 mg**	**5-10 hr**
Eszopiclone (Lunesta)*	**1-3 mg**	**5.5-8 hr**
Triazolam (Halcion)*	**0.125-0.25 mg**	**2-3 hr**
Zolpidem (Ambien)*	**3.75-12.5 mg**	**2-3 hr (CR extends duration of action)**
Zaleplon (Sonata)*	**5-10 mg**	**1-2 hr**

*FDA approved for insomnia.

Response with BZRAs is common but remission is only ~ 50% in clinic patients

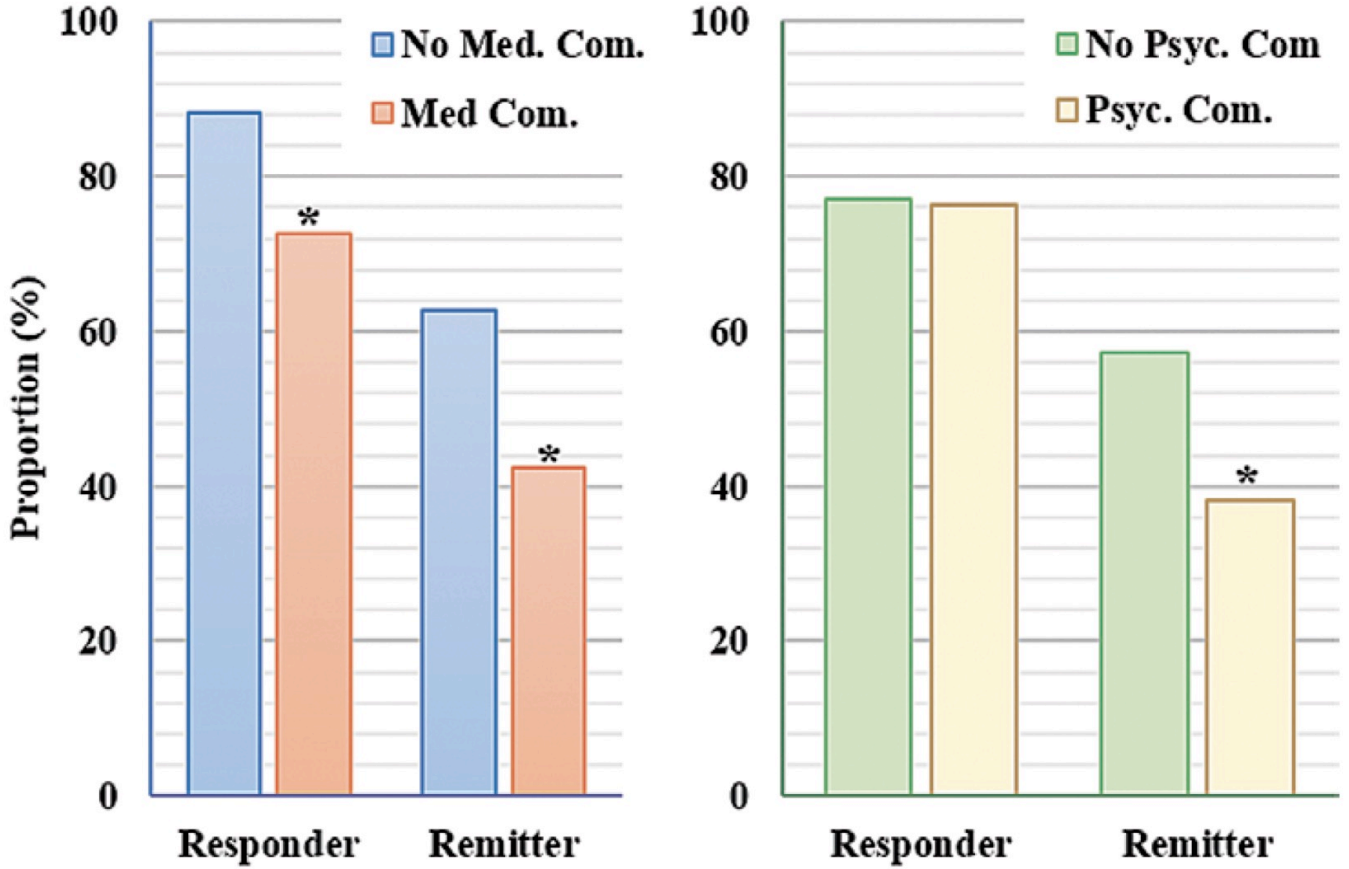


Figure 3—Response and remission rates, stratified by medical/psychiatric comorbidity. Med = medical; Pscy = psychiatric; Com = comorbidity. *$p < .05$.

Pillai et al 2017

“Are sleeping pills addictive?”

“Substance use disorders occur when their recurrent use causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home.”- DSM 5

- Tolerance
- Physiological dependence
- Psychological dependence
- Non-medical diversion

Misuse of sedative-hypnotics is age-related

Table 1
Prevalence of lifetime and past year sedative/tranquilizer use and lifetime, past year and past 30-day misuse by age group.

	12–17 years (adolescents) (a)	18–25 years (young adults) (b)	26–34 years (c)	35–49 years (d)	50–64 years (e)	65 and older (f)	Post hoc Comparisons
Sample size	27,857	28,213	17,835	22,530	10,398	7210	
Lifetime use	2229	5388	4871	7395	3901	2549	a < b < c < f < d, e
Weighted % of population (95% CI)	7.9 (7.5–8.3)	19.0 (18.3–19.7)	27.3 (26.4–28.2)	31.6 (30.8–32.3)	37.2 (36.1–38.4)	35.3 (34.0–36.6)	
Lifetime misuse	638	2143	1385	1279	549	167	f < a < e < d < b < c
Weighted % of population (95% CI)	2.3 (2.1–2.5)	7.8 (7.4–8.3)	8.1 (7.6–8.6)	5.4 (5.1–5.8)	5.3 (4.8–5.9)	2.2 (1.8–2.7)	
Weighted % of those with lifetime use (95% CI)	29.6 (27.3–31.9)	41.3 (39.5–43.2)	29.6 (27.9–31.3)	17.2 (16.0–18.4)	14.3 (13.0–15.8)	6.3 (5.2–7.6)	f < e < d < a < b, c
Past year use	1682	3816	2943	4445	2413	1574	a < b < c–f; c, f < e
Weighted % of population (95% CI)	6.0 (5.6–6.4)	13.5 (13.0–14.0)	16.6 (15.9–17.3)	18.8 (18.2–19.4)	22.8 (21.8–23.8)	21.9 (20.7–23.1)	
Past year misuse	523	1543	687	541	197	65	f < a, e < d < b, c
Weighted % of population (95% CI)	1.9 (1.7–2.1)	5.8 (5.4–6.2)	4.0 (3.7–4.4)	2.4 (2.1–2.6)	1.9 (1.6–2.3)	0.9 (0.7–1.2)	
Weighted % of those with past-year use (95% CI)	31.4 (28.4–34.6)	42.8 (40.6–45.2)	24.2 (22.5–26.0)	12.6 (11.5–13.8)	8.4 (7.0–10.0)	4.2 (3.1–5.5)	b < a, c < d < e < f
Past 30-day misuse	171	471	232	205	62	18	f < a–e; a < b–d; d, e < b, c
Weighted % of population (95% CI)	0.7 (0.5–0.8)	1.8 (1.5–2.0)	1.4 (1.2–1.6)	0.9 (0.8–1.0)	0.5 (0.4–0.7)	0.3 (0.1–0.6)	

Source: NSDUH, 2015–16 cohorts.
Notes: Post hoc comparisons controlled for race/ethnicity and sex and were only noted when the *p*-value was at or below a Bonferroni-corrected value of 0.00333 (0.05/15 = 0.00333). Unweighted samples and weighted percentages are provided, with 95% confidence intervals following the weighted percentages.

Misuse: “using the medication in any way a doctor did not direct you to use them…including: Using it without a prescription of your own; Using it in greater amounts, more often, or longer than you were told to take it; Using it in any other way a doctor did not direct you to use it.”

Are benzodiazepines dangerous?

- ? Complex sleep-related disorers
- ? dementia
- ? mortality

HEALTH

Raiding the Refrigerator, but Still Asleep

RANDI HUTTER EPSTEIN AP

Shirley Koec
she can reme
she started e
kitchen — ey

Like so many

Sleeping pills are as dangerous as smoking a packet of cigarettes A DAY, expert claims

- A worrying body of evidence is emerging over the dangers of sleeping tablets
- Recent studies have seen them linked to cancer, falls and even heart attacks

ASK WELL

Ask Well: Do Sleeping Pills Induce Restorative Sleep?

BY KAREN WEINTRAUB DECEMBER 11, 2015 5:45 AM 110

Stuart Bradford

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Q **Is sleep induced by a benzodiazepine counted as restorative sleep?**

Reader Question • 489 votes

A

Researchers hate to admit it, but they don't know enough about sleep to answer this question. Their best guess, several experts said, is that sleep is sleep.

Dr. John Weyl Winkelman, a sleep disorders expert at Massachusetts General Hospital and Harvard Medical

Harvard docs study bizarre diet proble

I CAN'T STOP EATING IN MY SLEEP

Star April 1, 1997 EXCL $1.39 Canada $1.69

DESPERATE dieter Karen Fuller can't lose weight because she has a weird disorder that makes her eat in her sleep.

Karen eats like a bird during the day, but piles the pounds back on at night.

The pretty Los Angeles antiques dealer sleepwalks around the kitchen in search of sweets.

Her husband has even found her with her head in the garbage, eating old chewing gum, cookie crumbs — even cigarettes covered in jelly.

"It is a form of sleepwalking in which the person has a compulsion to eat food that they wouldn't normally have," says Harvard psychiatrist Dr. John Winkleman. The doctor is studying more than a hundred cases of sleep-related eating disorders.

"The best solution," he says, "is to throw away all fattening food and put a padlock on the refrigerator."

Karen, 28, tried that, but she found the key in her sleep — and emptied the fridge.

"Despite trying every diet, nothing seems to work because I can't stop eating in my sleep," says Karen, who is 5-foot-9 and weighs 152 pounds.

"It all started when I was 16. I had become a vegetarian and was only eating brown rice, vegetables and beans.

"I stopped eating sugar, but my mind and body were craving it.

"One weekend I stayed at a girlfriend's house. She says that she watched me in the middle of the night, grabbing a family-size bag of M&Ms and devouring them noisily in minutes.

"The next day I woke up feeling queasy, and she told me what had happened. But I had no recollection of it. I thought she was just making it up."

When Karen was a teen, her mom would come downstairs in the morning to find the refrigerator door wide open and lots of ice cream and desserts on the kitchen counters.

It really got out of hand when Karen got married five years ago. She says her husband James "would find me staggering kitchen at night of sugar into m

"He would breakfast every I would search crumbs and ev the floor.

"Then I woul ettes and smea and eat them. I lieve what he v

"One night

...and I've raided everything from fridge to the garbage can

No trash can goes unraided when sleeping Karen prowls for sweets.

'Sleep-driving' defense wins man acquittal

By Lisa Redmond, lredmond@lowellsun.com

UPDATED: 12/01/2007 07:19:30 PM EST

Ki Yon
innoce

LOWELL -- In what could prove to be a precedent-setting case, an Andover attorney was cleared yesterday of a charge of motor-vehicle homicide because he may have been "sleep driving" while under the influence of Ambien.

Ki Yong O struck and killed 43-year-old Anthony Raucci on June 30, 2006, as the Methuen man was changing a tire in the breakdown lane on Interstate 93 in Tewksbury.

Lowell Superior Court Judge Kenneth Fishman accepted expert testimony that O may have been "sleep driving" when he hit and killed Raucci.

As Fishman announced that O was innocent of motor-vehicle homicide and leaving the scene accident after property damage, Raucci's widow, Elena Raucci, sobbed uncontrollably in the b the courtroom.

She declined to comment after the verdict.

O merely nodded his head and left the courtroom without comment -- his career, his livelihoo his freedom intact.

In announcing his verdict following the jury-waived trial, Fishman said the only disputable el the case, which centered on the use of prescription drugs, is whether O knew of the side effect drug and the "voluntariness" of O's actions.

Given the "uncertainty within the scientific community" regarding the effects of Ambien, Fish said he was unwilling to speculate that O was aware of the side effects of the powerful sleepin

The Current Status of BzRA Risks in the Treatment of Insomnia

- Motor vehicle accidents in elderly: long $T_{1/2}$ agents
- Hip fractures in elderly: long $T_{1/2}$ agents?
- Anterograde amnesia: $T_{1/2}$ dependent
- Rebound insomnia: depends upon dose, duration of use, and speed of taper

Hemmelgarn B et al. *JAMA*. 1997;278:27-31. Cumming RG, Le Couteur DG. *CNS Drugs*. 2003;17:825-837.
Woods JH, Winger G. *Psychopharmacology*. 1995;118:107-115. Krystal AD et al. *Sleep*. 2003;26:793-799.

Benzodiazepines do increase risk for dementia

Table 3| **Risk of Alzheimer's disease associated with benzodiazepine use (variables assessed five to up to 10 years before diagnosis) in people with Alzheimer's disease (cases) and controls**

	No (%) of cases (n=1796)	No (%) of controls (n=7184)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95% CI)	
				Model 1*†	Model 2*‡
Benzodiazepine ever use:					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
Users	894 (49.8)	2873 (40.0)	1.52 (1.37 to 1.69)	1.51 (1.36 to 1.69)	1.43 (1.28 to 1.60)
Benzodiazepine density exposure (No of prescribed daily doses):					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
1-90	234 (13.0)	1051 (14.6)	1.08 (0.92 to 1.27)	1.09 (0.92 to 1.28)	1.05 (0.89 to 1.24)
91-180	70 (3.9)	257 (3.6)	1.33 (1.01 to 1.75)	1.32 (1.01 to 1.74)	1.28 (0.97 to 1.69)
>180	590 (32.9)	1565 (21.8)	1.85 (1.63 to 2.09)	1.84 (1.62 to 2.08)	1.74 (1.53 to 1.98)
Benzodiazepine elimination half life:					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
Short half life (<20 h)	585 (32.6)	1996 (27.8)	1.43 (1.27 to 1.61)	1.43 (1.27 to 1.61)	1.37 (1.21 to 1.55)
Long half life (≥20 h)	309 (17.2)	877 (12.2)	1.72 (1.48 to 1.99)	1.70 (1.46 to 1.98)	1.59 (1.36 to 1.85)

*Matched for age, sex, and follow-up length.

†Adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).

‡Further adjusted for anxiety, depression, and insomnia diagnosis.

Billioti de Gage et al, BMJ, 2014

Benzodiazepines do not increase risk for dementia

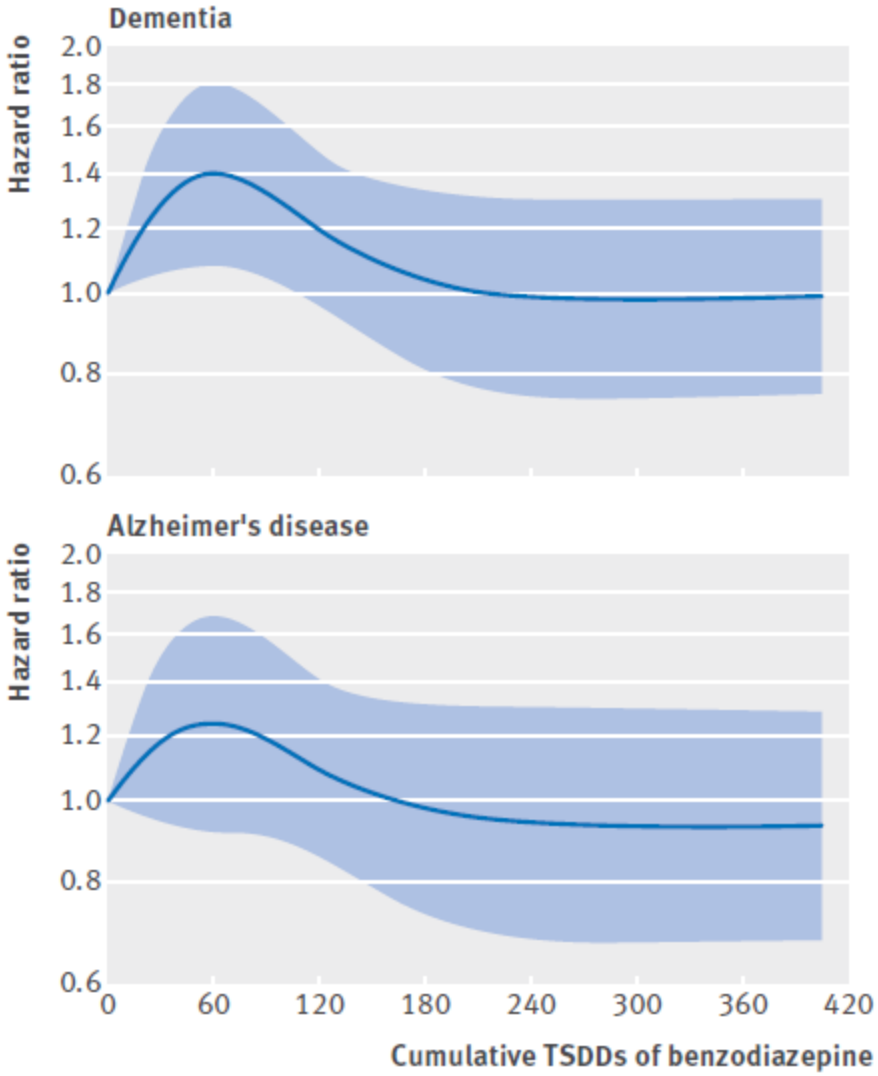
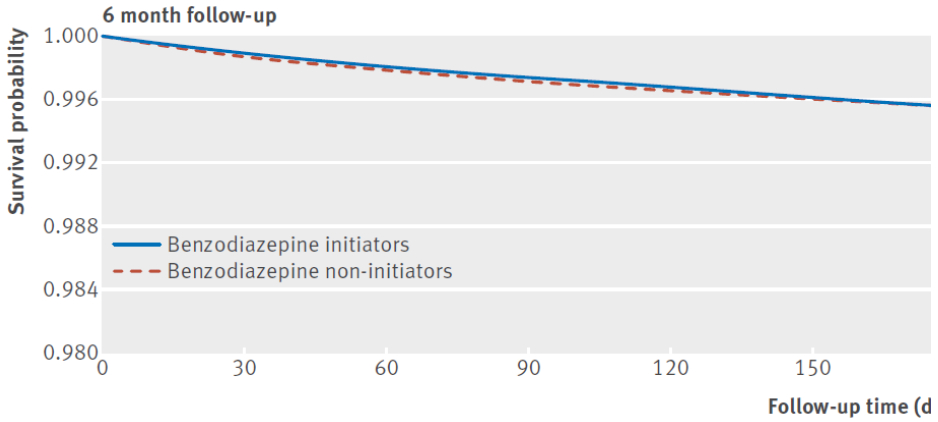
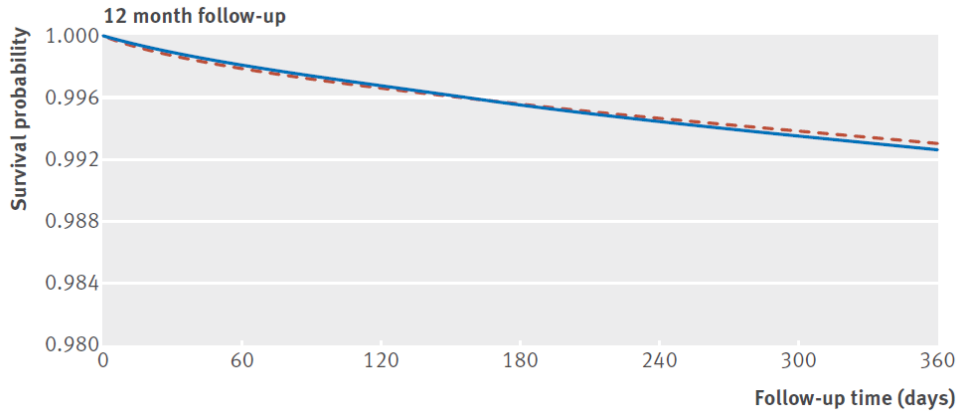


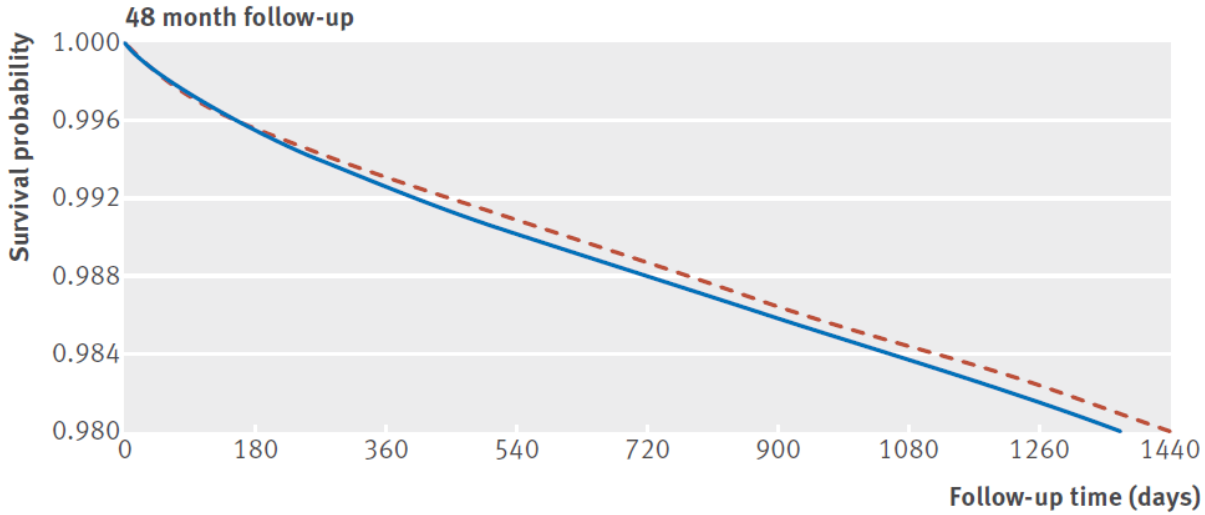
Fig 4 | Association between cumulative benzodiazepine use modeled as spline and risk of incident dementia or Alzheimer's disease

Gray et al, BMJ, 2016

Do benzodiazepines increase mortality risk?







Patorno et al, BMJ, 2017

Melatonin leads to small benefits for insomnia

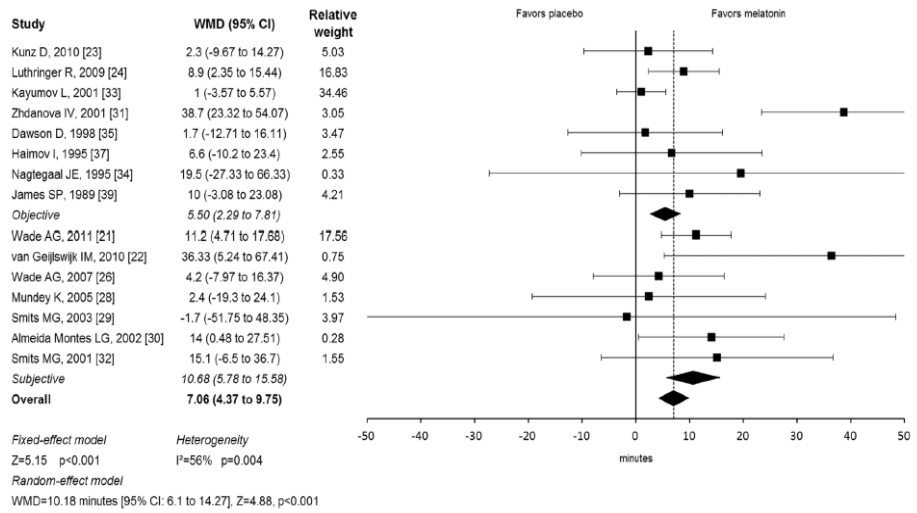


Figure 1. Efficacy of Melatonin in Reducing Sleep Latency. Forest plot depicting reduction of sleep latency in melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in reducing sleep latency. WMD = weighted mean difference; CI = confidence interval.

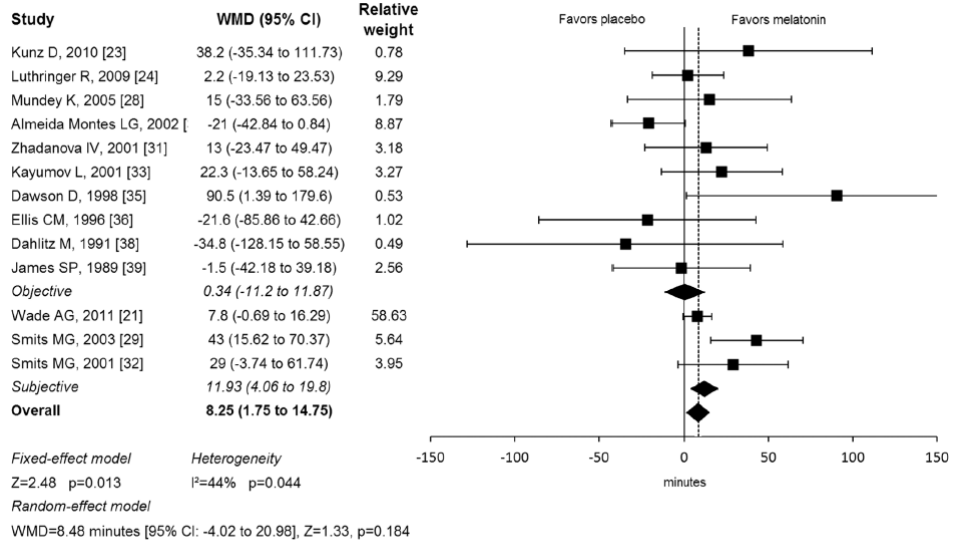


Figure 2. Efficacy of Melatonin in Increasing Total sleep Time. Forest plot depicting change in total sleep time with melatonin compared to placebo treatment. Meta-analysis demonstrated a significant benefit of melatonin in increasing total sleep time. WMD = weighted mean difference;

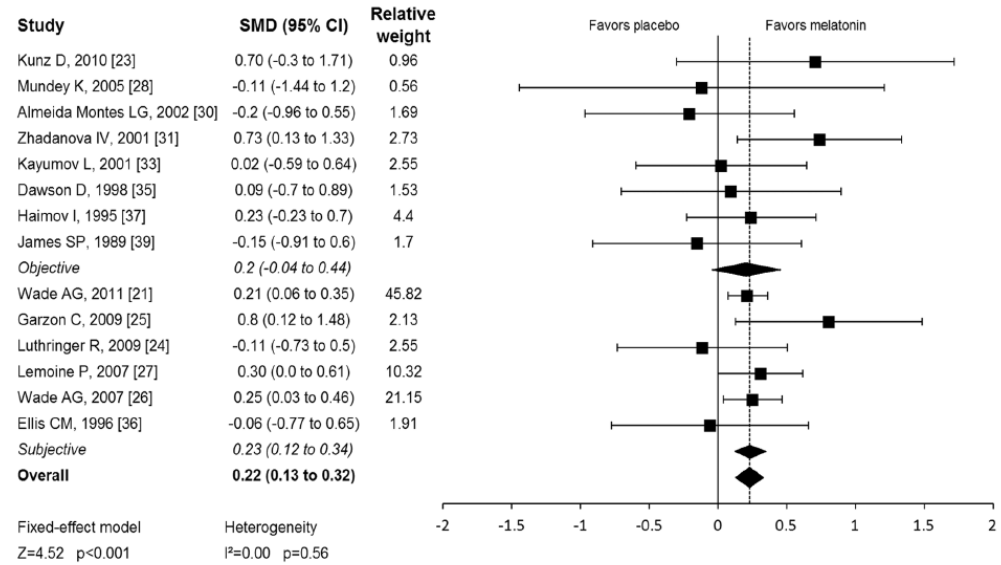


Figure 3. Effect of Melatonin on Sleep quality. Forest plot depicts sleep quality with melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in improving sleep quality. SMD = standardized mean difference; CI = confidence interval.

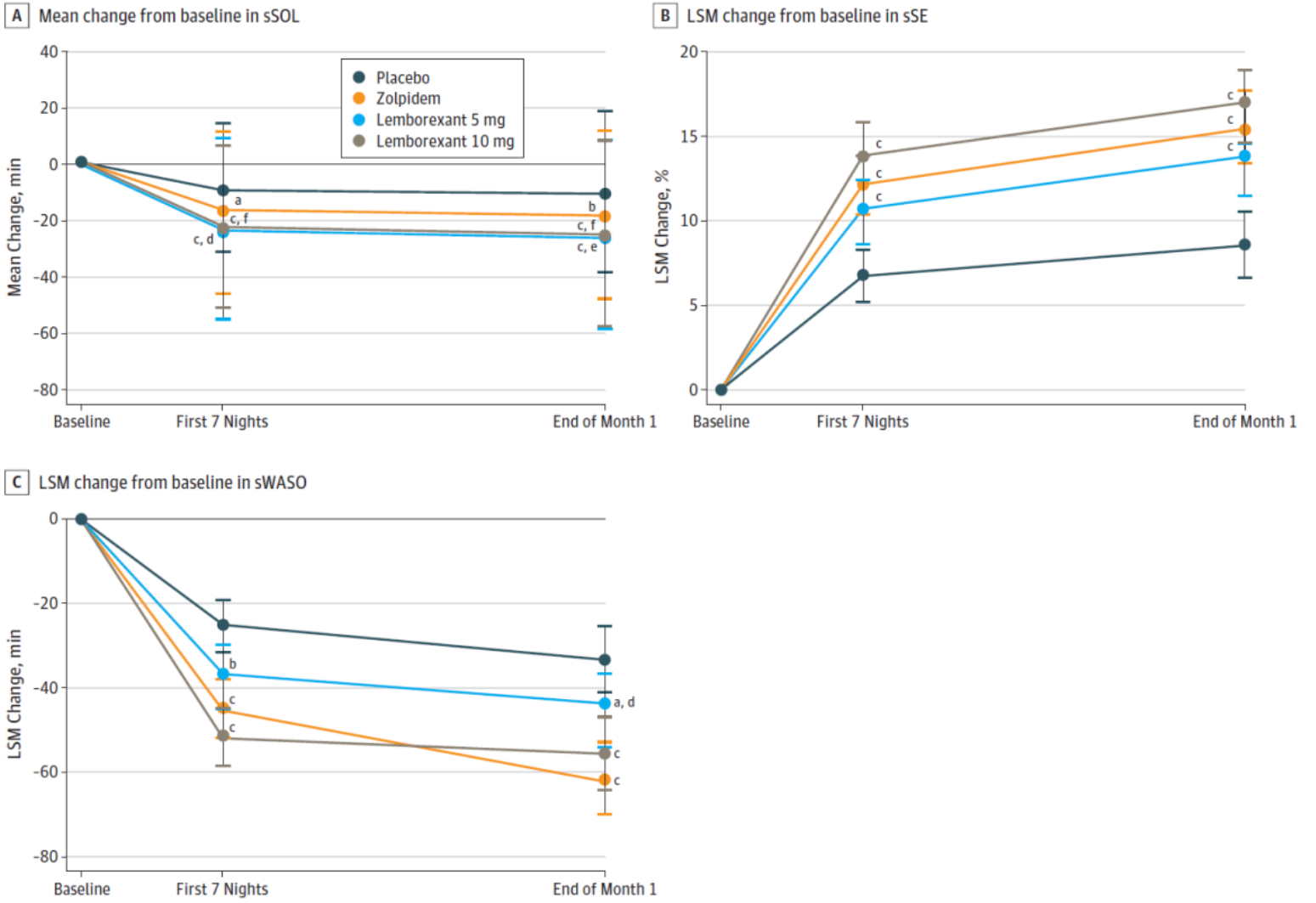
Orexin antagonist in the treatment of insomnia

-*Suvorexant 10-20 mg, Lemborexant 5-10 mg*

- Advantages: little abuse liability, 1-year efficacy data (at 40 mg), few side effects
- Disadvantages: unclear efficacy vs BzRAs, prior authorization

Lemborexant vs zolpidem 6.25 mg CR, sleep diary

Figure 3. Sleep Onset and Sleep Maintenance Outcomes Assessed by Sleep Diary, by Treatment Group



Antidepressants in the treatment of insomnia

-*Mirtazapine (15-30 mg), Trazodone (25-100 mg), Amitriptyline and Doxepin (10-50 mg)*

- Advantages: little abuse liability
- Disadvantages: probably not as effective as BzRAs, daytime sedation, weight gain, anticholinergic side effects

Anticholinergic medications and incident dementia

Association of Incident Dementia and Alzheimer's Disease with 10-year Cumulative Anticholinergic Medication Use[a]

			Unadjusted[c,d]		Adjusted[d,e]	
TSDD[b]	Follow-up time (person-years)	Number of Events	HR	95% CI	HR	95% CI
Dementia						
0	5618	136	1.00	Reference	1.00	Reference
1-90	7704	203	0.96	0.77-1.20	0.92	0.74-1.16
91-365	5051	172	1.31	1.04-1.65	1.19	0.94-1.51
366-1095	2626	102	1.39	1.07-1.82	1.23	0.94-1.62
>1095	4022	184	1.77	1.40-2.23	1.54	1.21-1.96
Alzheimer's Disease						
0	5618	112	1.00	Reference	1.00	Reference
1-90	7704	168	0.96	0.75-1.24	0.95	0.74-1.23
91-365	5051	128	1.21	0.93-1.58	1.15	0.88-1.51
366-1095	2626	83	1.38	1.03-1.85	1.30	0.96-1.76
>1095	4022	146	1.73	1.34-2.24	1.63	1.24-2.14

TSDD Total Standardized Daily Dose; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

[a] Observations with missing adjustment variables are excluded from the model (n=115; 3.3%).

[b] TSDD example; the minimum effective daily dose for oxybutynin is 5 mg daily (=1 TSDD); a person would fall into the following TSDD category if they were using 5 mg daily for 45 days (TSDD 1-90); 5 mg daily for 180 days (TSDD 91-365); 5 mg daily for 720 days (TSDD 366-1095); 5 mg daily for 4 years (TSDD>1095)

[c] Age adjustment via the time-axis.

[d] Test for trend *P* value <0.001 for an association between exposure categories and each outcome

[e] Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, education, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes, stroke, coronary heart disease, Parkinson's disease, history of depressive symptoms, and current benzodiazepine use.

"We found that among the heaviest users, people who had past heavy use had a similar dementia risk as those with recent or continued heavy use. This suggests that the risk for dementia with anticholinergic use may persist despite discontinuation."

Gray et al, JAMA Int Med, 2015

Atypical antipsychotics in the treatment of insomnia

Quetiapine (25-100 mg)

- Advantages: anxiolytic, mood stabilizing in bipolar disorder, little abuse liability
- Disadvantages: less effective than BzRAs, daytime sedation, weight gain, risks of extrapyramidal symptoms and glucose + lipid abnormalities

Anticonvulsants in the treatment of insomnia

Gabapentin (300-900 QHS or split dosing)

- Advantages: mildly analgesic, anxiolytic
- Disadvantages: less effective than BzRAs, cognitive impairment, daytime sedation, dizziness, weight gain, concerns re abuse

Issues with non-BzRA hypnotics in the treatment of insomnia

(eg antidepressants, anticonvulsants, antipsychotics)

- Paucity of short-term efficacy data
- Absence of long-term efficacy data
- Assumptions of lack of tolerance and rebound insomnia are unsubstantiated
- Anecdotally less effective hypnotics than BzRAs
- May have deleterious side effects

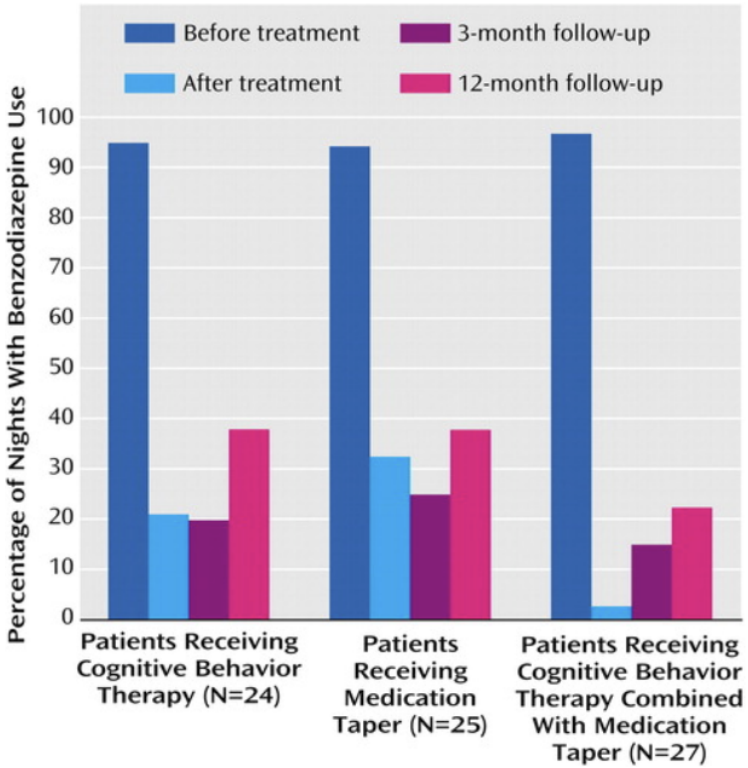
Article

Full Access

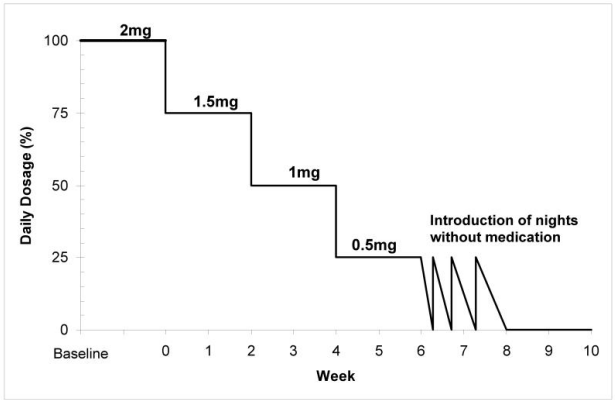
Randomized Clinical Trial of Supervised Tapering and Cognitive Behavior Therapy to Facilitate Benzodiazepine Discontinuation in Older Adults With Chronic Insomnia

Charles M. Morin, Ph.D., Célyne Bastien, Ph.D., Bernard Guay, M.D., Monelly Radouco-Thomas, M.D., Jacinthe Leblanc, B.C.P.P., and Annie Vallières, Ph.D.,

Published Online: 1 Feb 2004 | https://doi-org.ezp-prod1.hul.harvard.edu/10.1176/appi.ajp.161.2.332



- Severe primary insomniacs on BZRA x 19 yrs
- At 7 weeks:
  - Small improvements in sleep latency, WASO; large reductions in total sleep time
  - Substantial improvements in ISI
- Medication tapering + CBT modest superiority to either alone



Psychological Treatment of Hypnotic-Dependent Insomnia in a Primarily Older Adult Sample

Kenneth L. Lichstein[1], **Sidney D. Nau**[1,2], **Nancy M. Wilson**[2], **R. Neal Aguillard**[3], **Kristin W. Lester**[3], **Andrew J. Bush**[4], and **Christina S. McCrae**[5]

- Taper and discontinuation of hypnotics in insomniacs with persistent poor sleep did not produce worsened sleep
- CBT was not of particular benefit in enhancing sleep endpoints beyond supervised medication taper

Behav Res Ther, 2013

Sleep disorders

- Insomnias
  - Insomnia, psychiatric/medical disorders, RLS, medications
- **Hypersomnias**
  - **Sleep apnea, medications, Periodic leg movements of sleep**
- Parasomnias (4%)
  - Sleepwalking, sleep terrors, REM sleep behavior disorder
- Circadian rhythm disorders
  - Shift work sleep disorder, Delayed sleep phase disorder

Summary

- Insomnia is common, both acute and chronic
- Differential diagnosis and assessment of chronic insomnia is essential to treatment success
- Prioritize goals of therapy and reassess treatment efficacy regularly
- CBT-I is first line therapy of chronic insomnia
- Many medication options are available if CBT-I is not effective
- Medication choice is a shared decision between provider and patient based on comparative risks of insomnia and medications, rather than on shaming
- Medication tapering should be discussed with patients on long-term therapy, particularly in older patients and those with persistent insomnia

Differential diagnosis of hypersomnia

- “Tired”:
  - excessive daytime sleepiness (EDS)
  - fatigue
  - apathy

- *If* EDS:
  - inadequate sleep time
  - impaired sleep quality
  - excessive sleep drive

Epworth Sleepiness Scale

"how likely to dose off or fall asleep"

0= not likely at all; 3= very likely

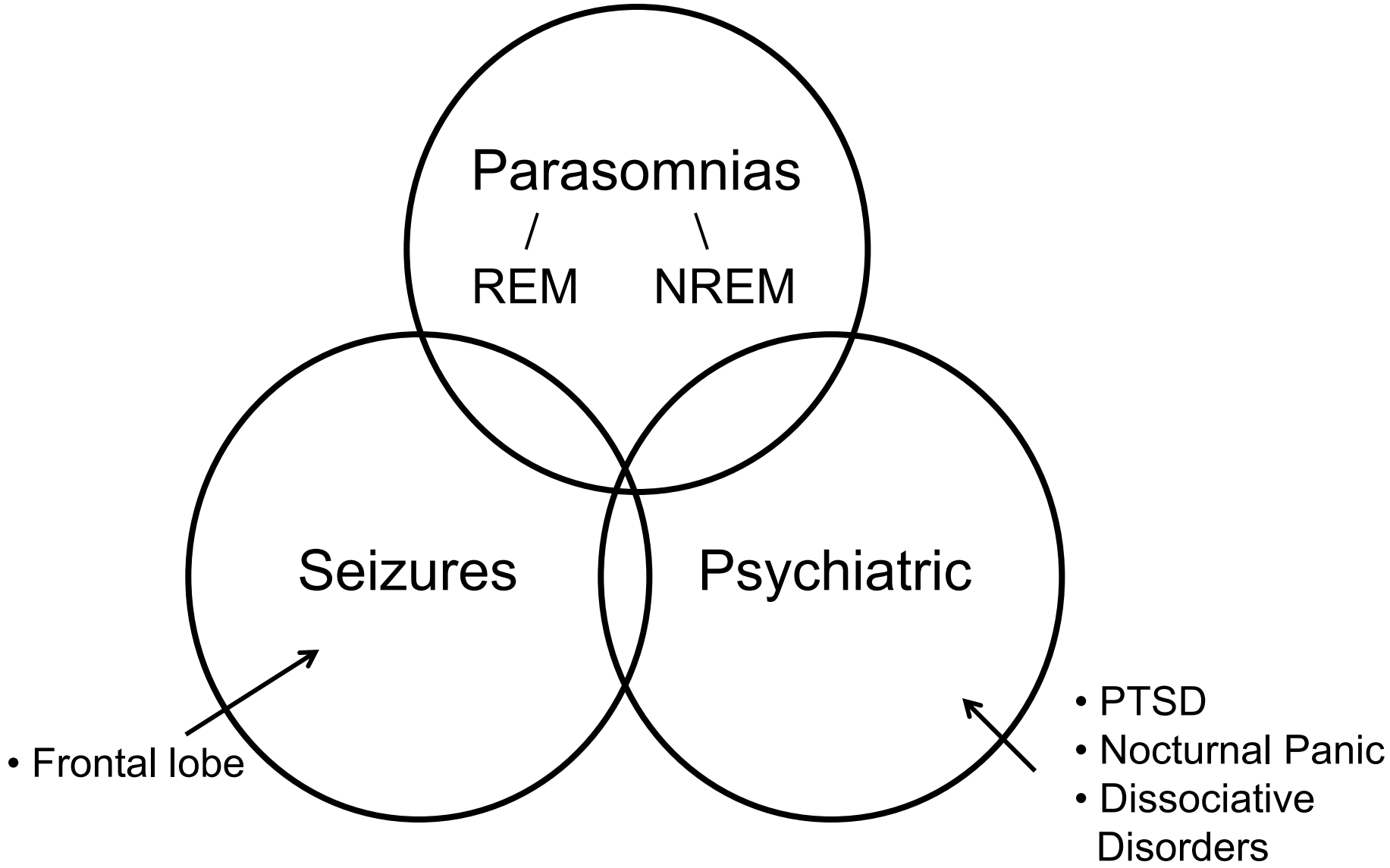
(range of scale 0-24, with abnormal > 10)

- sitting and reading
- watching TV
- sitting inactive in public place
- passenger in a car for an hour
- Lying down to rest in afternoon
- sitting and talking to someone
- sitting quietly after lunch
- in a car stopped in traffic for a few minutes

Sleep disorders

- Insomnias
  - Insomnia, psychiatric/medical disorders, RLS, medications
- Hypersomnias
  - Sleep apnea, medications, Periodic leg movements of sleep
- **Parasomnias (4%)**
  - **Sleepwalking, sleep terrors, REM sleep behavior disorder**
- Circadian rhythm disorders
  - Shift work sleep disorder, Delayed sleep phase disorder

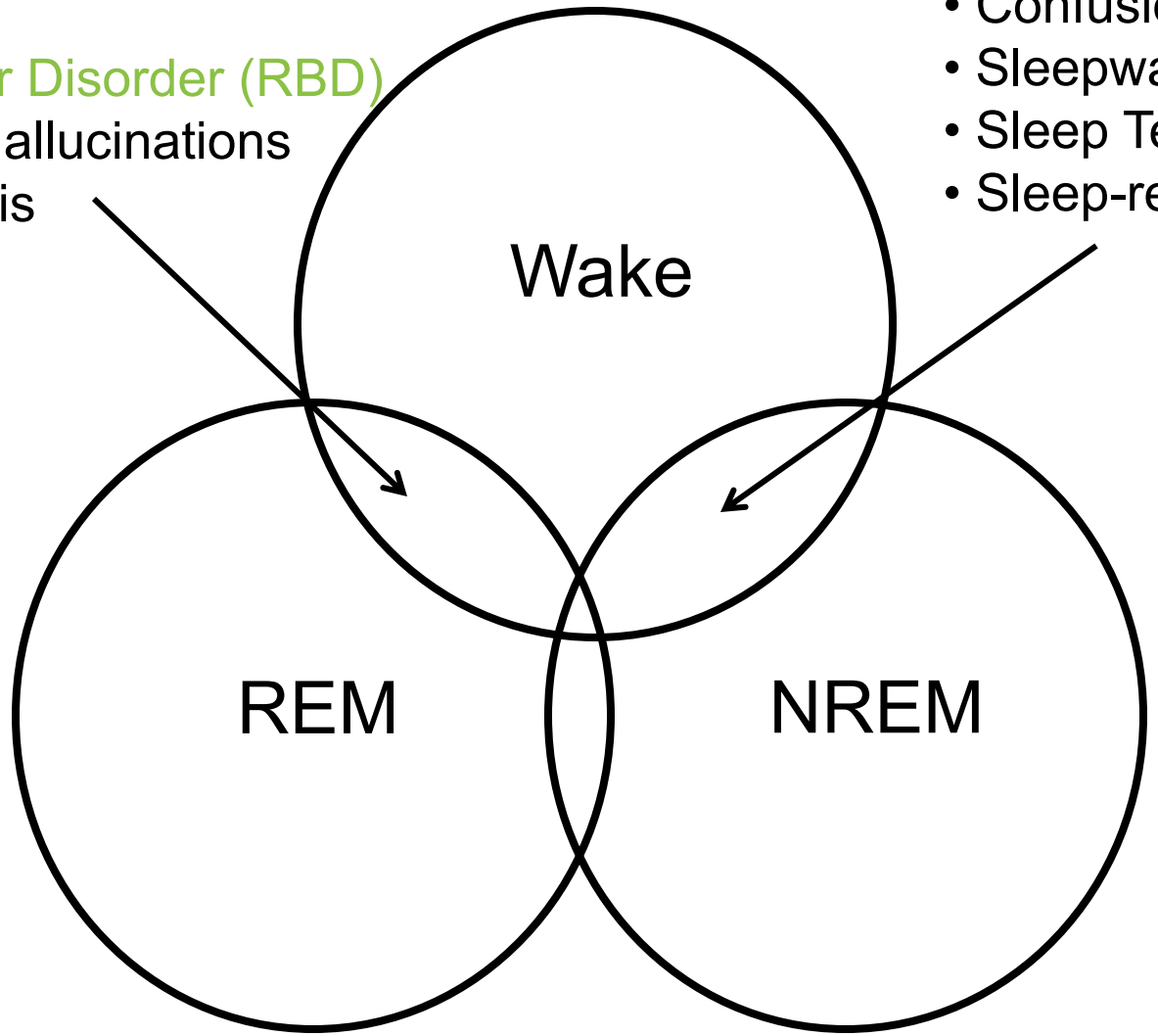
Differential diagnosis of abnormal sleep-related behaviors



Parasomnias are mixtures of the primary states

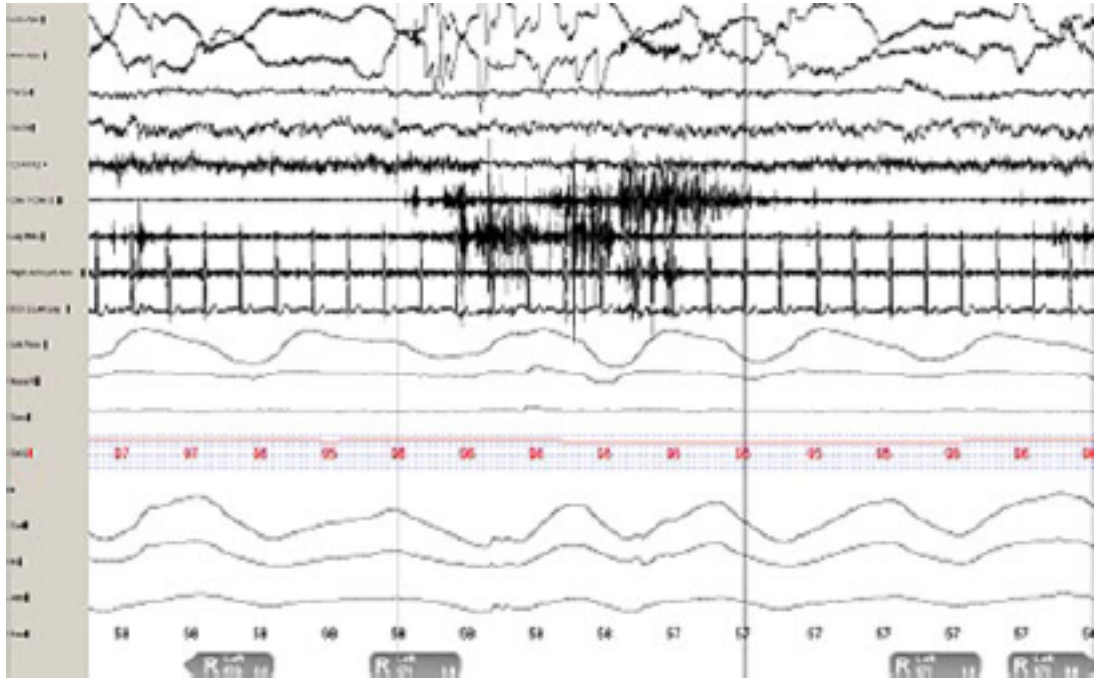
- REM Behavior Disorder (RBD)
- Hypnagogic Hallucinations
- Sleep Paralysis
- ? Nightmares

- Confusional Arousals
- Sleepwalking
- Sleep Terrors
- Sleep-related eating

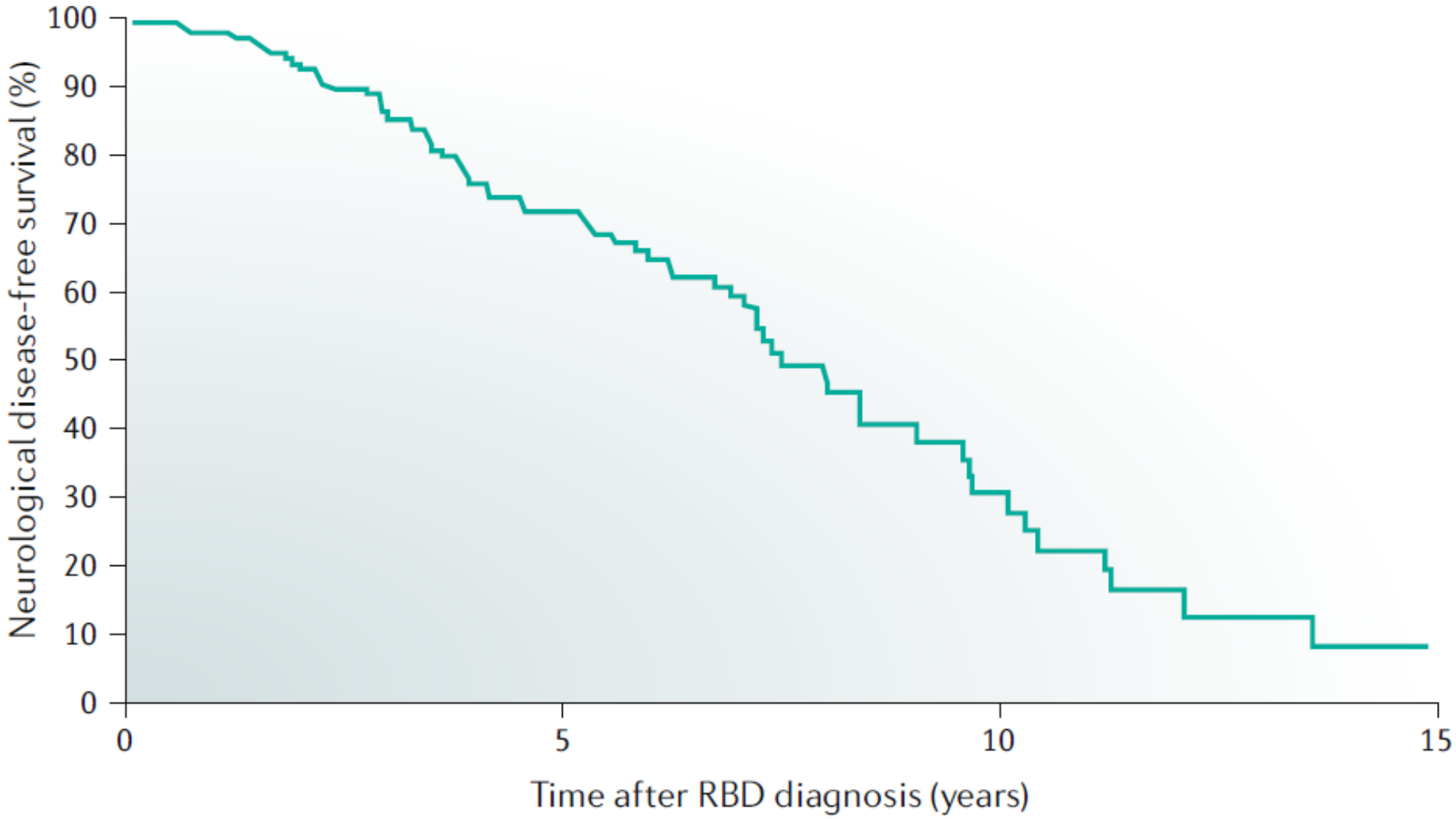


Causes of RBD

- Alpha synucleinopathies
  - Parkinson's, Lewy Body, Multiple System Atrophy
- Serotonergic antidepressants
- Narcolepsy



The bad news about RBD



http://dx.doi.org/10.5665/sleep.3102

Antidepressants and REM Sleep Behavior Disorder: Isolated Side Effect or Neurodegenerative Signal?

Ronald B. Postuma, MD, MSc[1,2]; Jean-Francois Gagnon, PhD[2,3]; Maria Tuineaig, BSc[2]; Josie-Anne Bertrand, PhD[2,4]; Veronique Latreille, PhD[2,4]; Catherine Desjardins, PhD[2]; Jacques Y. Montplaisir, MD, PhD[2,5]

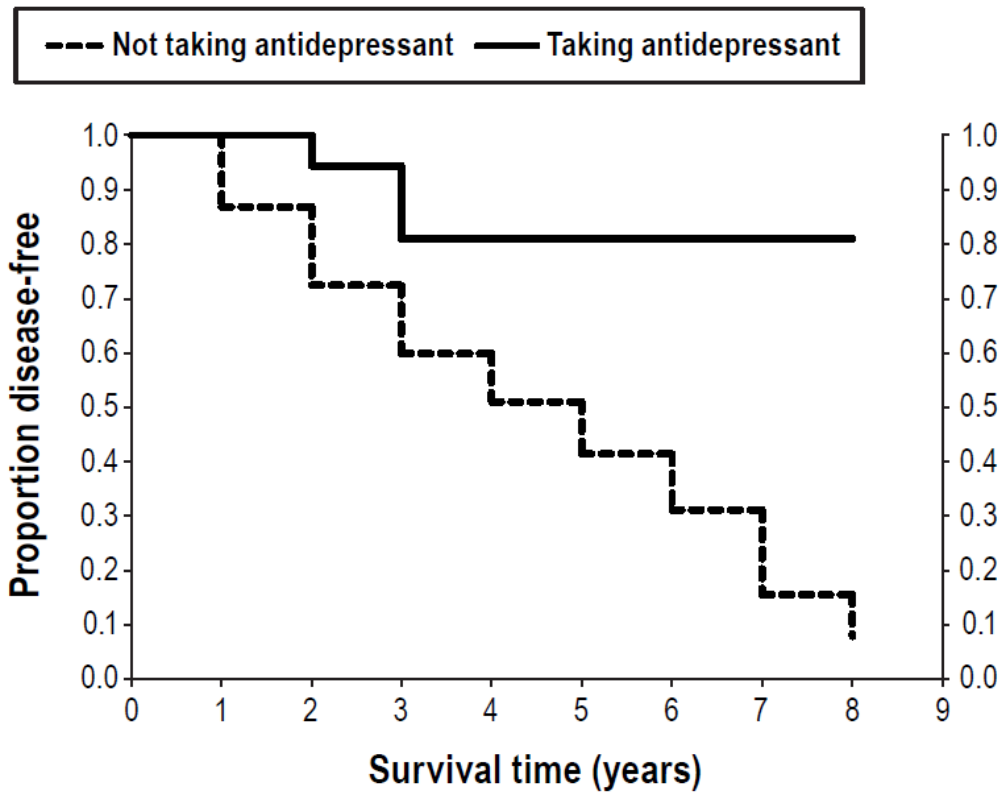


Figure 2—Kaplan-Meier life table analysis of disease-free survival in patients with idiopathic RBD according to history of antidepressant use. Cox proportional hazards P = 0.016 for antidepressant vs. no antidepressant.

Treatment of parasomnias

- Night terrors/sleepwalking
  - Short-acting benzodiazepines (eg triazolam)
- REM behavior disorder
  - Discontinue serotonergic antidepressant (if present)
  - Benzodiazepines (short, long)
  - Melatonin (6-10 mg)
  - +/- pramipexole
- Sleep-related eating disorder
  - Treat RLS, if present
  - SSRRI or topiramate

45 | 1 Neuropsychopharmacology Volume 45 Number 1 January 2020 Pages 1-242

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Neuropsychopharmacology
At the intersection of brain, behavior, and therapeutics **REVIEWS**

Official Journal of the American College of Neuropsychopharmacology

Sleep and Neuropsychiatric Illness

CO-EDITORS: Luis de Lecea and John W. Winkelman

SPRINGER NATURE