



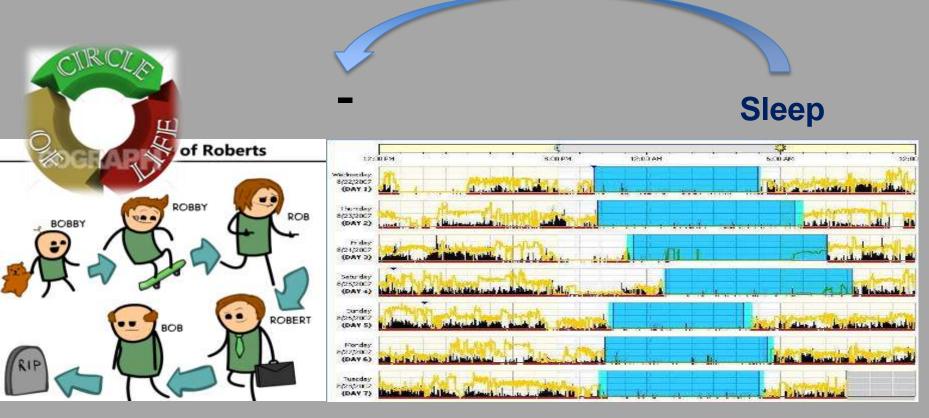
ΤΡΑΚΑΔΑ Π. ΓΕΩΡΓΙΑ

Αν. Καθηγήτρια Θεραπευτικής - Πνευμονολογίας

ΘΕΡΑΠΕΥΤΙΚΗ ΚΛΙΝΙΚΗ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΕΘΝΙΚΟΥ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟΥ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΑΘΗΝΩΝ

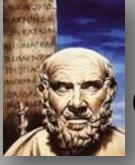








"...Ο ύπνος και η εγρήγορσις ανήκουσιν εις το αισθητικόν — είναι κοινά του σώματος και της ψυχής — διαδέχονται άλληλα — υπάρχουσιν εις πάντα τα ζώα και εις ουδέν φυτόν..." (ΑΡΙΣΤΟΤΕΛΟΥΣ - ΠΕΡΙ ΥΠΝΟΥ ΚΑΙ ΕΓΡΗΓΟΡΣΕΩΣ)



#### «ύπνος τ' αγρυπνίη του μετρίου μάλλον γιγνόμενον κακόν»

(ο ύπνος και η αγρύπνια που γίνεται <mark>πάνω από το μέτρο</mark> είναι κακό)

Ιπποκράτης

 sleepiness inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentional or at inappropriate times almost daily for at least 3 months

#### VS

• insomnia sleep initiation or maintenance problems, with adequate opportunity and circumstances to sleep, and daytime consequences, for at least 3 months, for at least three times per week

# The Heterogeneity of OSA: Excessive Daytime Sleepiness Does Not Tell the Full Story

EDS identification and characterization is important for sleep clinicians not only for the suspicion/diagnosis of sleep-disordered breathing, but also for determining appropriate treatment in order to prevent its detrimental health consequences, Plos Med. (2014)

- 19% of EDS, assessed with three subjective questions on sleepiness, among 30–60 year-old adults with OSA (AHI≥5), wisconsin Sleep Cohort study, New Engl J Med
  (1993)
- in USA, <50% of middle-aged and older subjects with moderate-to-severe sleep disordered breathing (AHI≥15) reported subjective sleepiness, sleep (2005)
- in Europe, >60% of OSA middle-aged patients have EDS, Sleep Breath (2015)
- in Asia, middle-aged population documented a relatively high prevalence (87.2%) of EDS, Sleep Med (2004)

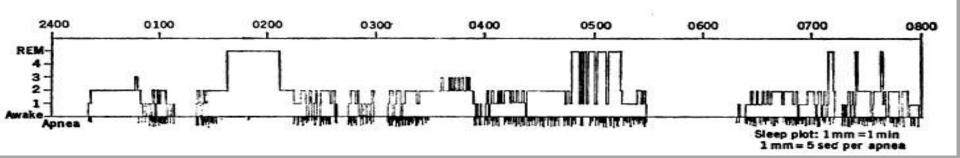
although EDS has been regarded as a classical feature of OSA, population-based studies suggest that complaints of EDS are absent in many patients, Eur Respir J. (2014)

#### sleepy vs insomniac OSA patient

many OSA patients, including some patients with severe OSA, complain about insomnia

• Insomnia with Sleep Apnea: A New Syndrome Guilleminault, C., Eldridge, F. L., & Dement, W. C. Science, (1973)

"One obvious and important conclusion can be drawn from our data. An unknown percentage of the larger number of patients complaining of chronic insomnia have profound disorders of respiratory control mechanisms. There is probably a functional association between the sleep disturbance giving rise to the complaint and the apnea. Our patients have not only nocturnally disrupted sleep, but also long periods of conscious arousals. Yet, until now, their respiratory problem has been completely occult. We feel that respiratory function during sleep should be evaluated in patients who complain of chronic insomnia characterized by several conscious arousals throughout the night and early morning and who also have a short latency before onset of sleep and a history of heavy snoring."



#### Obstructive Sleep Apnea

Snoring

Breathing pauses

Breath holding, gasping, choking

Frequent arousals due to sleep disordered breathing events

#### Both

Frequent awakenings

Difficulty falling asleep

Unrefreshing sleep

Fatigue

Daytime sleepiness

Attention, concentration, memory impairment

Social, occupational dysfunction

Mood disturbances

Reduced motivation, energy

Accidents

Worry about sleep

Decreased quality of life

#### Insomnia

Increased arousal

Excessive focus on and high anxiety about sleep

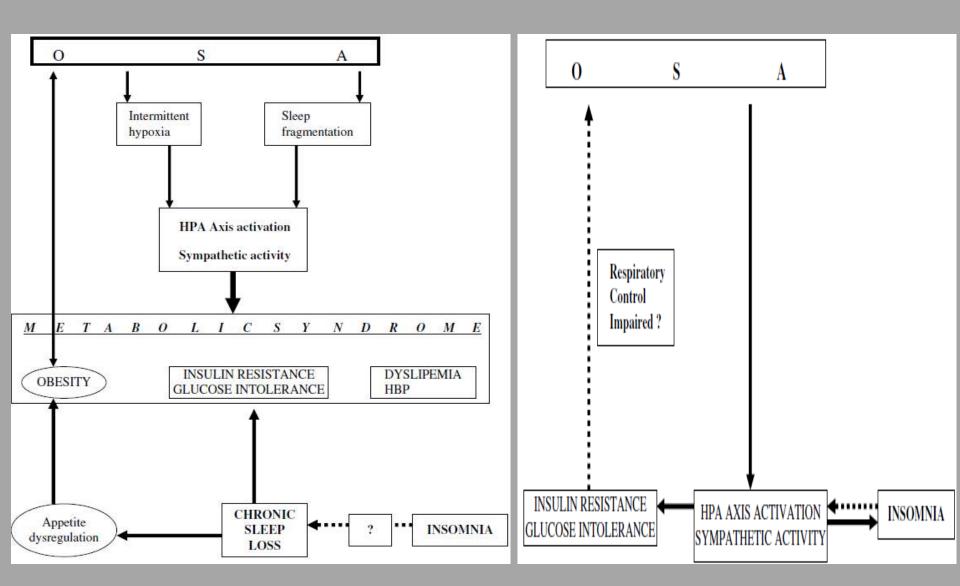
Learned sleeppreventing associations

### possible interactions between OSA and insomnia, Sleep Med Clin 2016

insomnia can exacerbate or contribute to the development of OSA? OSA can contribute to the development of insomnia? insomnia and OSA are engaged in a reciprocal relationship whereby each disorder exacerbates the other?

- the chronic hyperarousal, which is suggested to underlie chronic insomnia, may prolong the transition between wake and sustained sleep, and generally lighten the stages of sleep, thereby increasing the amount of the sleep period vulnerable to apneic events and increasing AHI
- sleep deprivation / fragmentation can increase collapsibility of the upper airway and consequently AHI

## possible interactions between OSA and insomnia, Sleep Med Rev 2009



### possible interactions between OSA and insomnia, Sleep Med Clin 2016

- repetitive respiratory awakenings during sleep-wake transitions may be perceived as periods of continued wakefulness
- insomnia patients misperceive prior sleep as wakefulness and overestimate their time spent awake during the sleep period
- with repeated nights of perceived sleep onset difficulties, worry and frustration are likely, and may trigger SNS and HPA axis activation
- following repetitive association of the bedroom environment, the time of night, and the desire to fall asleep with sympathetic activation, this physiologic activation response can become conditioned to those always present cues and underlie the development of psychophysiological or conditioned insomnia.

## increasing evidence from studies suggests that insomnia and OSA frequently coexist,

Sleep Breath 2012

a high prevalence (39%-58%) of insomnia symptoms have been reported in patients with OSA

Table 1 Prevalence of comorbid insomnia in OSA patients

Study	Population	Prevalence	Onset insomnia	Maintenance insomnia	Early-morning awakening insomnia	
Krakow et al. [8]	231 patients with SBD	50%	NA	NA	NA	
Krell et al. [11]	228 OSA patients	54.9%	33.4%	38.8%	31.4%	
Smith et al. [12]	105 OSA patients	39%	NA	NA	NA	
Chung et al. [10]	157 OSA patients	42%	6%	26%	19%	
Lavie et al. [14]	358 OSA patients	27.9% in women 21.9% in men	NA	NA NA		
Gold et al. [19]	220 OSA, 137 UARS	-	UARS: 33.4% AHI>60, 15.6%	UARS: 59.9% AHI>60, 73.9%		
			AHI>30, 18.2%	AHI>30, 62.9%		
			AHI>10, 20.9%	AHI>10, 58.2%		
Wickwire et al. [13]	232 OSA patients	37%	16.6%	23.7%	20.6%	
Chung et al. [15]	119 OSA patients	-:	9%	33%	21%	
Al otair and BaHammam [9]	384 OSA patients	39.8% in women 25.9% in men	NA	NA NA		

## increasing evidence from studies suggests that insomnia and OSA frequently coexist,

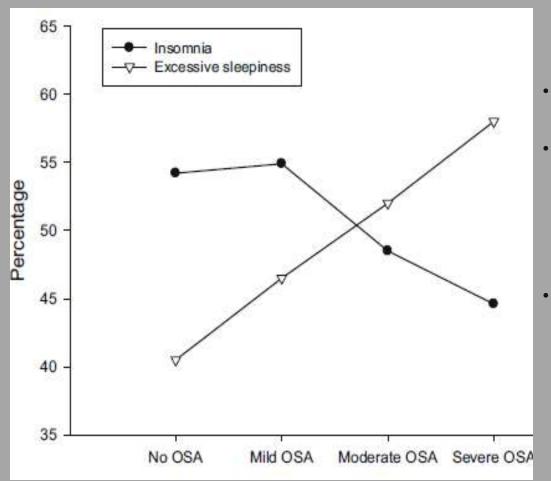
Sleep Breath 2012

25-75% of patients with insomnia have an apnea-hypopnea index of >5.

Table 2 Prevalence of comorbid OSA in insomnia patients

Study	Population	Insomnia/inclusion criteria	SBD criteria	Prevalence 29% or 43% OSA	
Lichstein et al. [20]	80	SOL>30 min or WASO>30 min, 6-min duration	AHI>5 or AHI>15		
BaHammam [22]	67	Difficulty initiating or maintaining sleep or non-restorative sleep, lasting>3 months	AHI>5	25.4% OSA+1 case CSA/CSR	
Stone et al. [21]	45	TST<6.5 h, SOL>30 min, WASO>30 min, 6-min duration	RDI>10 or RDI>5	40% or 64.4%	
Krakow et al. [111]	44	Weekly episodes of insomnia	RDI≥15	50% OSA 40.9% UARS	
Guilleminault et al. [23]	394	SOL>30 min or WASO>20 min, 1-min duration	AHI>5	67% OSA 15.7% UARS	
Gooneratne et al. [112]	100	Difficulty initiating or maintaining sleep or early-moming awakening≥3 nights/week and for≥3 weeks	AHI≥15	29.3% OSA	
Krakow et al. [25]	137	Patients using prescription sleep medication nightly for at least 6 months	AHI≥5	71% OSA	
Krakow et al. [24]	218	Use of hypnotic medication for≥6 months	AHI≥5	75% OSA	

## higher excessive sleepiness and lower insomnia in greater OSA severity, Sleep Breath 2015



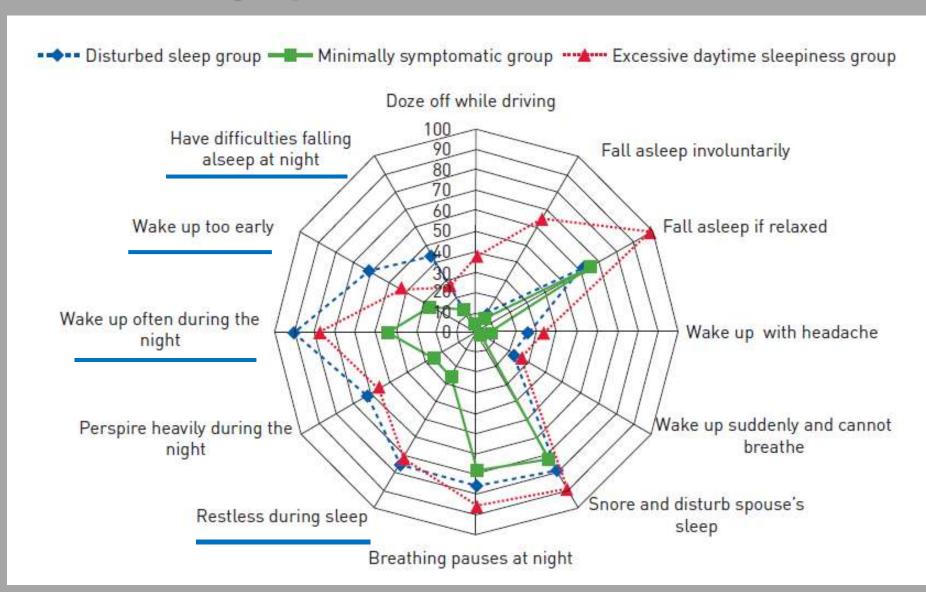
- OSA was diagnosed in 59.4% of the 1115 referred patients.
- The prevalence of excessive sleepiness was higher with greater severity of OSA: 40.5 % in the patients without OSA (AHI <5), 46.5 % in mild OSA (AHI 5–14.9), 52.0%in moderate OSA (AHI 15–29.9), and 58.0% in severe OSA (AHI≥30).
- The prevalence of insomnia using the 2014 diagnostic criteria showed an opposing prevalence: 54.2 % no OSA, 54.9 % mild OSA, 48.5 % moderate OSA, and 44.6 % severe OSA.

Logistic and linear regression analyses showed that sleepiness was positively associated, whereas insomnia was negatively associated with OSA severity and AHI.

### subtypes of patients with OSA who experience distinct symptoms and comorbidities, Eur Respir J 2014

- Cluster 1, the "disturbed sleep group": 32.7%, highest probability of experiencing insomnia-related symptoms (difficulty falling asleep at night 44.3%, waking up too early and difficulty falling back to sleep 60.8%, and most prominently, waking up often during the night 90.3%) other nocturnal symptoms were also prominent, such as heavy perspiration 61.7%, being restless 74.8%, RLS symptoms 42.6%, and sudden awakening due to gasping for breath 21.1%.
- Cluster 2, the "minimally symptomatic group": 24.7%, less symptoms, much more likely to feel rested upon waking up 78.3% (vs 1 38.7% or 3 24.3%).
- Cluster 3, the "excessive daytime sleepiness group": 42.6%, with a significantly higher sleepiness (ESS score 15.7 vs 1 9.5 and 2 7.9), and a markedly higher probability of complaining of sleepiness-related symptoms, such as falling asleep involuntarily during the day (64.6%), and dozing off when driving (38.2%) higher likelihood of presenting with classic OSA symptoms, such as night-time breathing pauses and loud snoring disturbing their spouse's sleep.

### subtypes of patients with OSA who experience distinct symptoms and comorbidities, Eur Respir J 2014



### subtypes of patients with OSA who experience distinct symptoms and comorbidities, Eur Respir J 2014

# the probabilities of having comorbid hypertension, diabetes and cardiovascular disease were highest in cluster 2, but lowest in cluster 3

		Cluster 1 <i>versus</i> cluster 2		Cluster 1 <i>versus</i> cluster 3		Cluster 2 versus cluster 3	
	OR	p-value	OR	p-value	OR	p-value	
Major comorbidities present	0.00	0.002	1 20	0.001	1 20	<0.001	
Hypertension Diabetes	0.93 0.83	<b>0.002</b> 0.083	1.29 1.20	<b>0.001</b> 0.079	1.38 1.44	<0.001 0.023	
Cardiovascular disease Obstructive lung disease	0.76 1.40	0.012 0.007	1.27 1.21	0.007 <b>0.001</b>	1.67 0.87	0.001 0.002	

#### different phenotypes of OSA, ESADA, , PLOS 2018

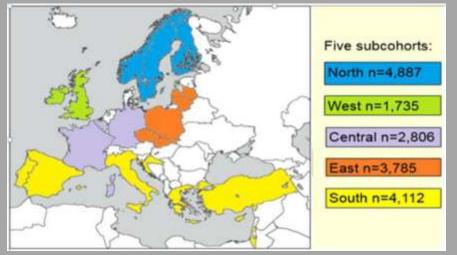
- 4 clinical phenotypes, according to daytime symptoms (EDS) and characteristics suggestive of insomnia (self-reported sleep duration, sleep latency, diagnosed insomnia, or hypnotic use: N05)
- EDS (daytime+/nighttime-), EDS/insomnia (daytime+/nighttime+), non-EDS/non-insomnia (daytime-/nighttime-), and insomnia (daytime -/nighttime+).
- Daytime+ indicates that the patient had daytime sleepiness defined by ESS score >10 and daytime- that ESS score was ≤10.
- Nighttime+ indicates at least one of the following: diagnosis
  of insomnia, self-reported sleep latency ≥30 min, selfreported sleep duration ≤6 h, or use of hypnotics. Nighttimereferred to situation where none of the nighttime+ criteria
  were fulfilled.

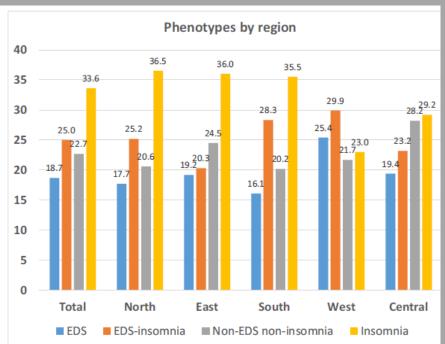
#### different phenotypes of OSA, ESADA, PLOS 2016

- The EDS phenotype comprised 20.7%, the non-EDS/non-insomnia type 25.8%, the EDS/ insomnia type 23.7%, and the insomnia phenotype 29.8% of the entire cohort. Thus, clinical presentation phenotypes with insomnia symptoms were dominant with 53.5%, but only 5.6% had physician diagnosed insomnia.
- Cardiovascular comorbidity was less prevalent in the EDS and most common in the insomnia phenotype (48.9% vs. 56.8%, p<0.001) despite more severe OSA in the EDS group (AHI 35.0±25.5/h vs. 27.9±22.5/h, p<0.001, respectively). Psychiatric comorbidity was associated with insomnia like OSA phenotypes independent of age, gender and body mass index (HR 1.5 (1.188–1.905), p<0.001).</li>

#### different phenotypes of OSA in Europe,

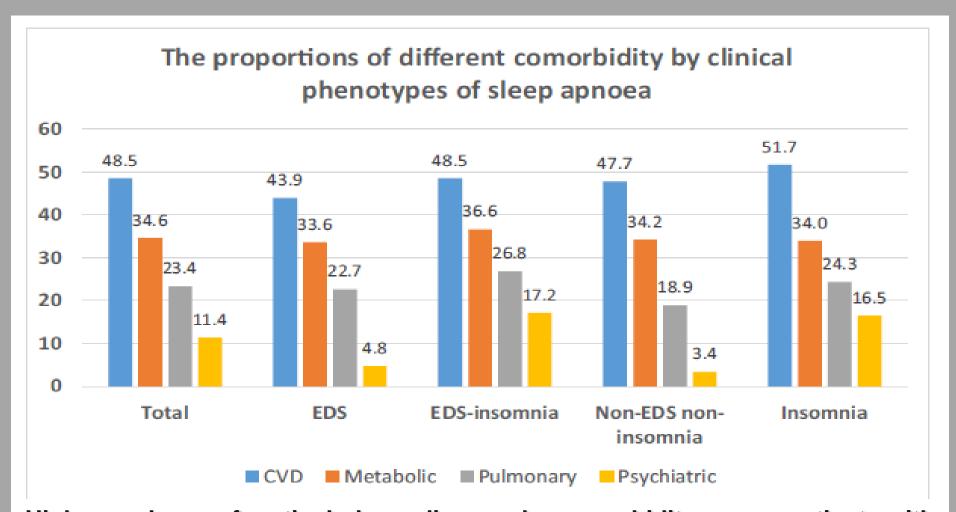
**ESADA Sleep Breath 2018** 





- The youngest, but most obese and sleepy patients, were found in the West, the most severe OSA in the South and the mildest degree of the disorder in the North region.
- The insomnia phenotype
  (alone or together with EDS)
  was the dominant phenotype
  in all regions. Isolated
  insomnia, however, was less
  common in the West.
- Insomnia and EDS-insomnia phenotypes were more prevalent among women than men

# different comorbidities in different phenotypes, ESADA Sleep Breath 2018



High prevalence of particularly cardiovascular comorbidity among patients with insomnia-like symptoms was linked to nocturnal hypoxemia.

- the comorbid patients generally experience the additive detrimental effects from both disorders manifested in their sleep symptoms, as well as daytime impairments
- enormous individual and societal costs, in terms of both direct healthcare expenditures and the indirect costs associated with untreated diseases, Chest 2010

# treatment of Insomnia comorbid with OSA, Sleep Med Clin 2016

- If the insomnia symptoms in the OSA clinical population are entirely secondary to the OSA, there would be no purpose in expending any resources to treat the insomnia directly treatment as usual.
- If insomnia exists independently of the OSA (eg, precursor to OSA or conditioned insomnia developed from initial OSA), the separate treatment of the insomnia would be an independent benefit because it would increase PAP compliance, make treatment of the OSA more effective, and generally result in better health outcomes.
- These possibilities are, of course, not mutually exclusive and may be present to varying degrees.

### adherence to PAP therapy,

ESADA, PLoS 2016, Sleep 2013, Sleep Breath. 2013

- Symptoms of insomnia in OSA patients have been reported to be associated with lower CPAP adherence.
- When taking age, gender, BMI, and OSA severity into account, the association of adherence with the different phenotypes remained unchanged.
- In this highly selected subsample of CPAP users, the relatively good short-term CPAP adherence is likely to be predictive of good long-term adherence.

CV events and all-cause mortality

Road accidents and near-miss accidents risk DNA methylation

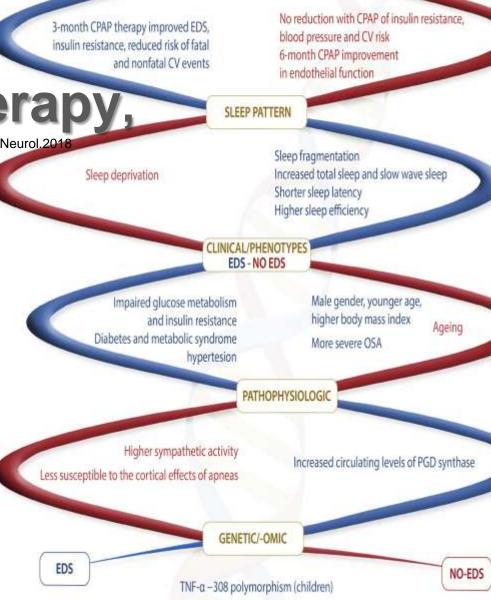
RISK FACTORS/
EPIGENETICS

No reduction with CPAP of insulin resistance, blood pressure and CV risk 6-month CPAP improvement in endothelial function

#### effect of PAP therapy,

MOSAIC randomized controlled trial, Torax 2012, Front. Neurol. 2018

In patients with minimally symptomatic OSA (no-EDS), CPAP can reduce subjective and objective daytime sleepiness, and improve self-assessed health status, but does not appear to improve calculated vascular risk.



# treatment of Insomnia comorbid with OSA, Sleep Med Clin 2016

- behavior change therapies: stimulus control therapy (SCT) and bed period or sleep restriction therapy (SRT).
- Do not have a predetermined bedtime, go to bed only when sleepy
- ✓ Get out of bed if not asleep within 15 minutes.
- ✓ Repeat 1 and 2 until a rapid sleep occurs
- Maintain the same wake-up time regardless of sleep length
- Do not nap during the day
- cognitive elements and therapy
- Inaccurate and maladaptive cognitions, perceptions, and beliefs can contribute to insomnia and, therefore, be a target for therapy
- drugs: BzRAs, Non-BzRAs, Z drugs, sleep-promoting antidepressives

consider to treat the insomnia before or concurrent with PAP or other OSA therapy

