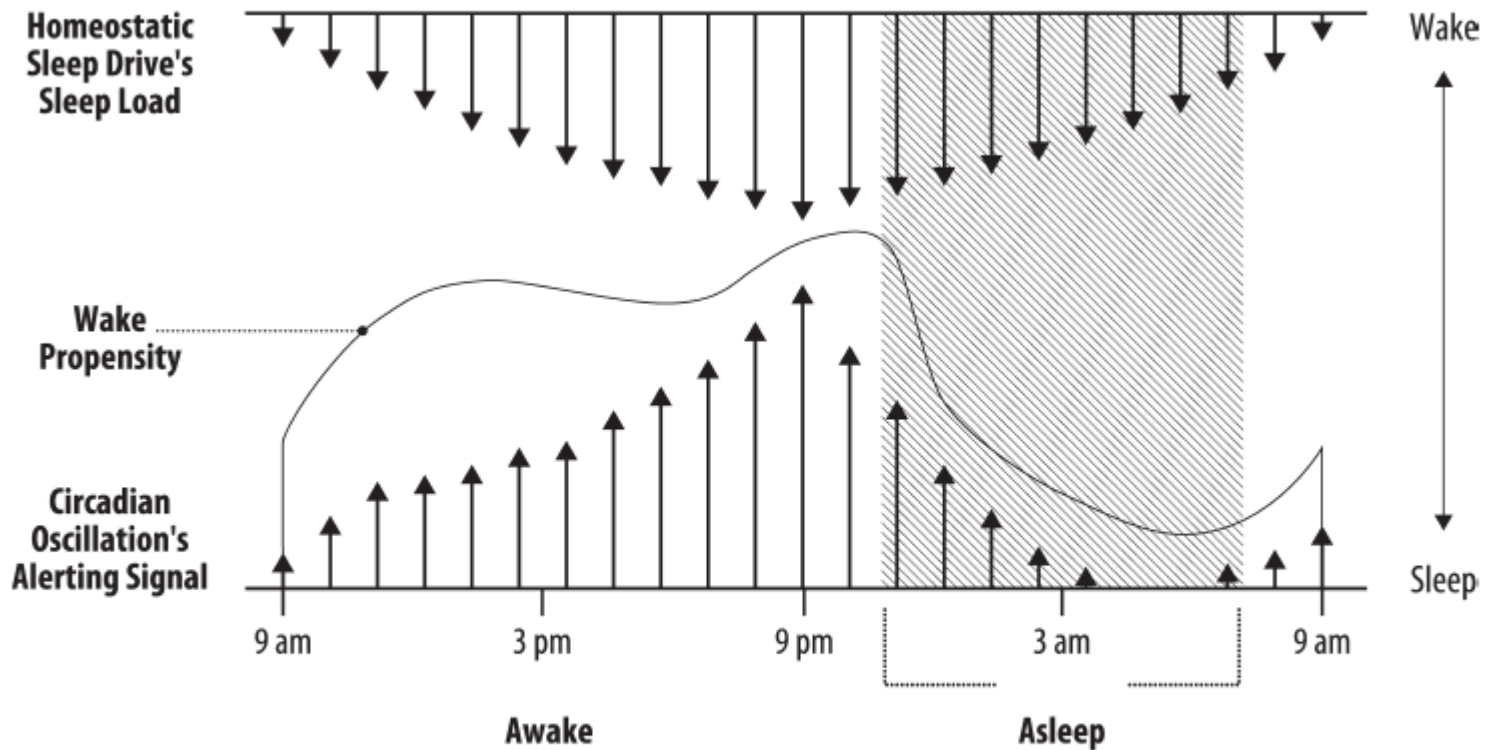


# Insonnia: dalla diagnosi alla terapia

*Marco Zucconi*

*Centro di Medicina del Sonno  
Dip di Neuroscienze Cliniche  
H San Raffaele, Milano*

# wake propensity and sleep drive



**Figure 1**—Circadian and Homeostatic Regulation of Sleep. Adapted with permission from Kiduff and Kushida<sup>75</sup> and Edgar et al.<sup>8</sup> The circadian cycle and the homeostatic drive interact to produce sleep and wakefulness at the appropriate times. The need for sleep (ie, sleep load) accumulates during wakefulness and dissipates during sleep.

# Organizzazione gerarchica delle strutture responsabili del sonno

( *L. Parmeggiani* )

**Veglia**



**NREM**

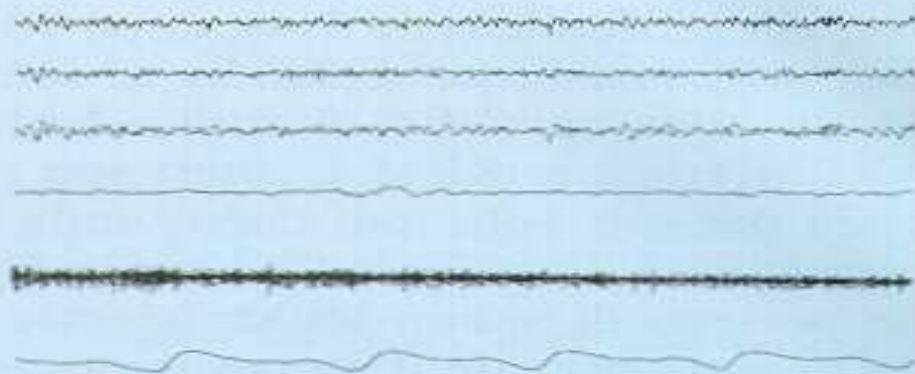
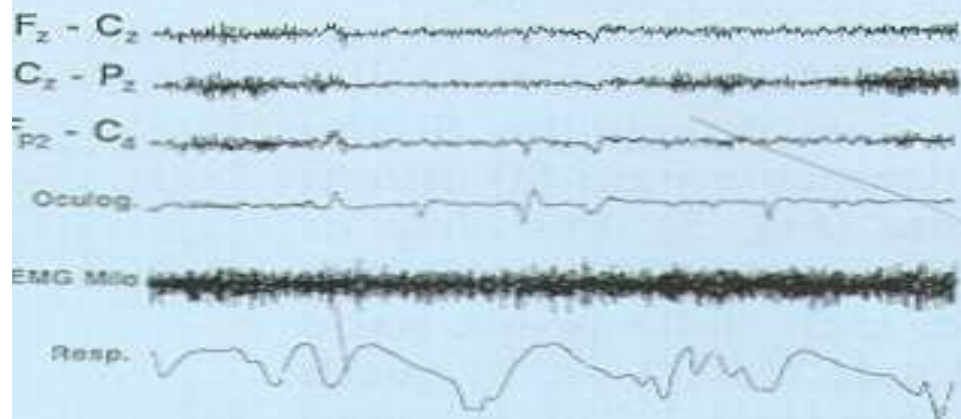


**REM**



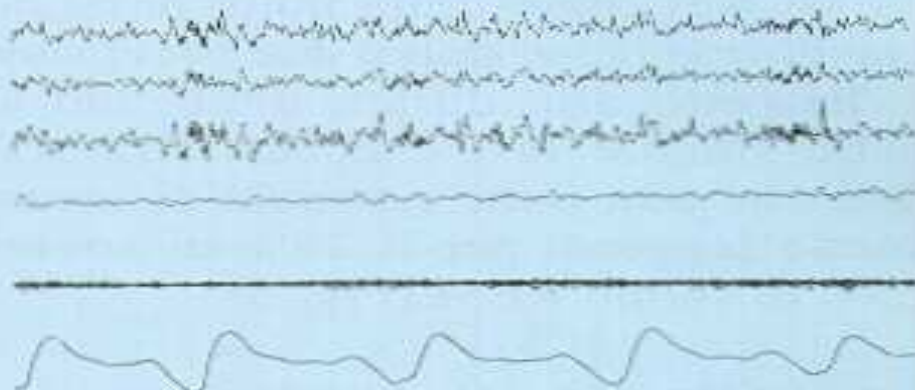
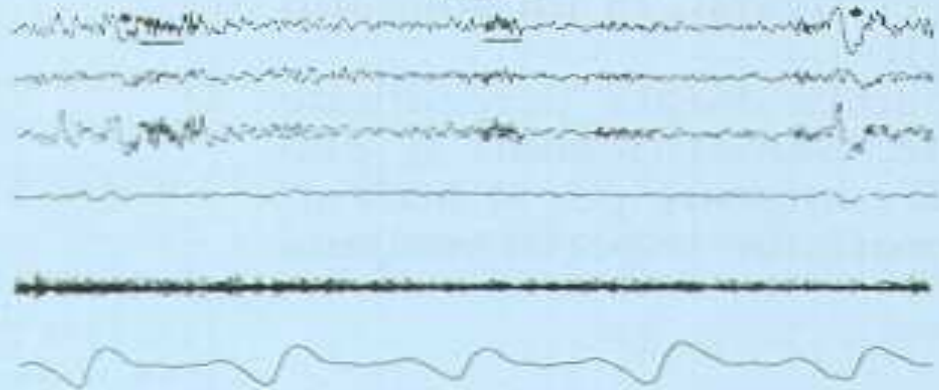
VEGLIA

FASE 1



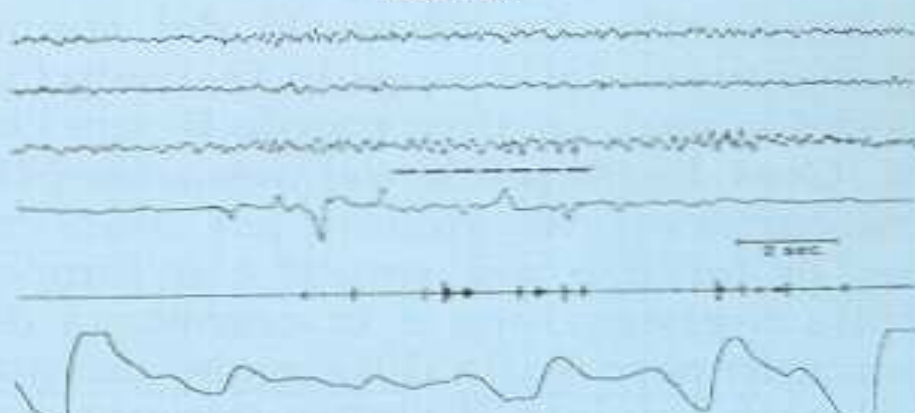
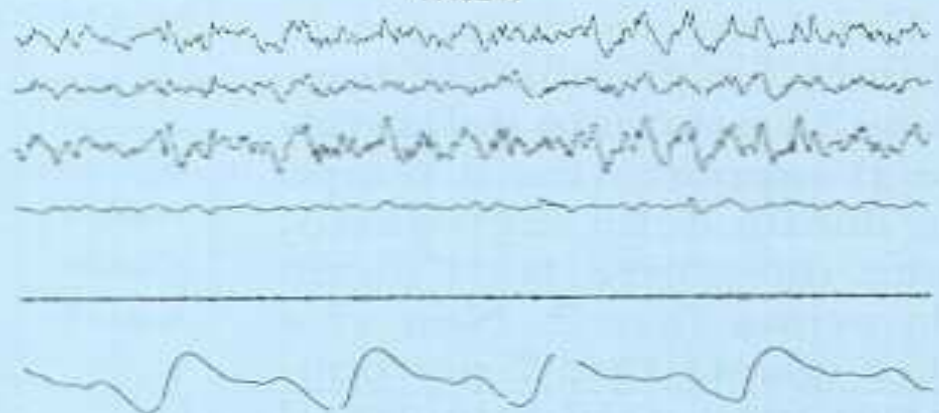
FASE 2

FASE 3

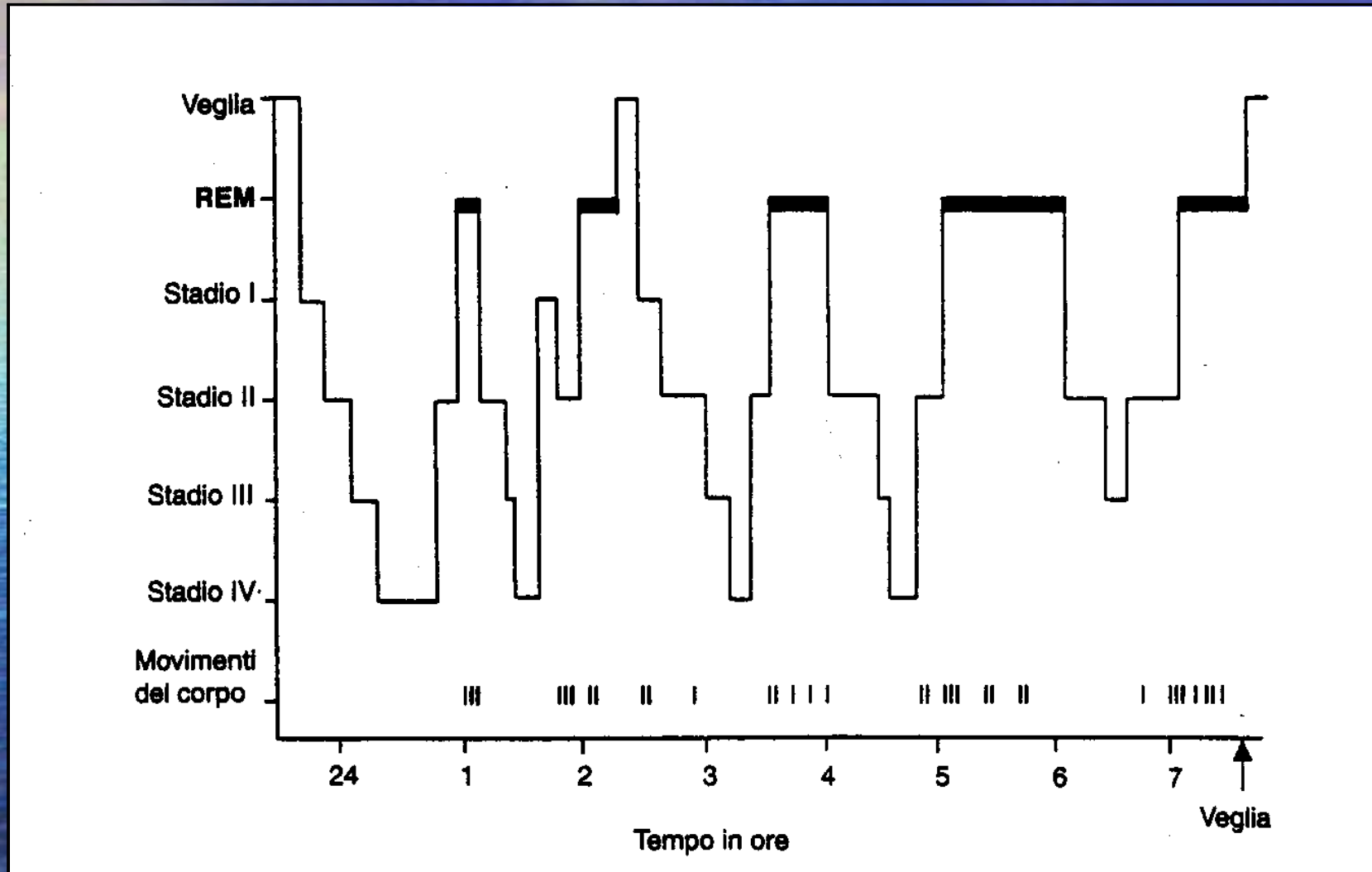


FASE 4

FASE REM



# IPNOGRAMMA



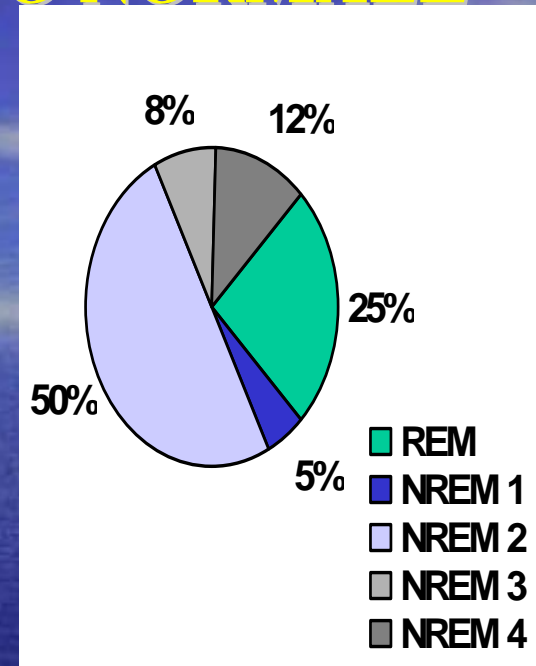
# ARCHITETTURA DEL SONNO NORMALE

## ADULTI:

- sonno non REM o sonno ortodosso:

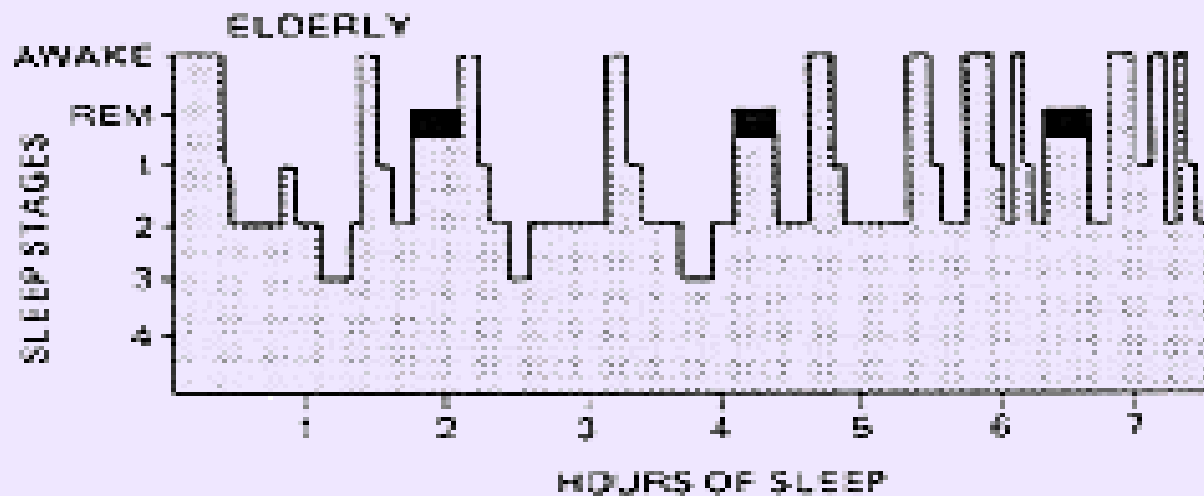
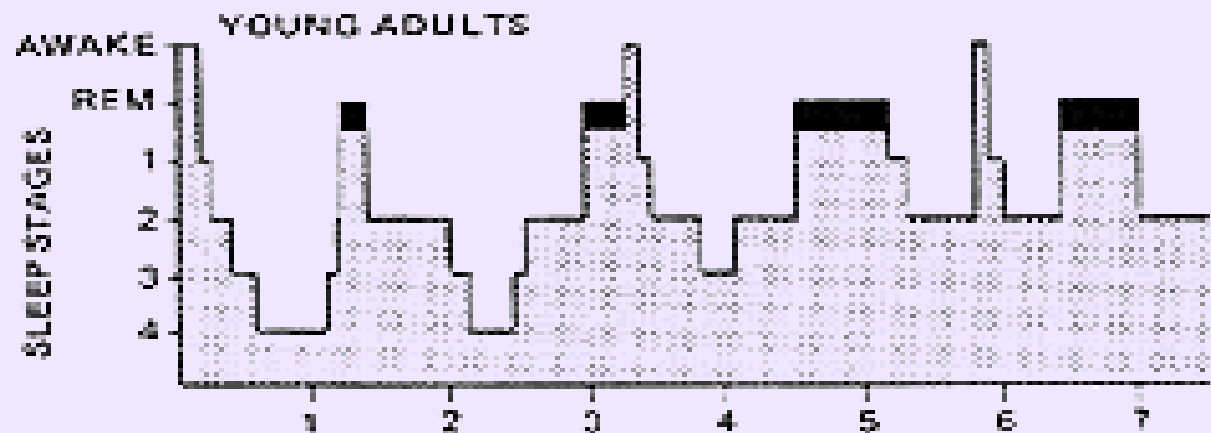
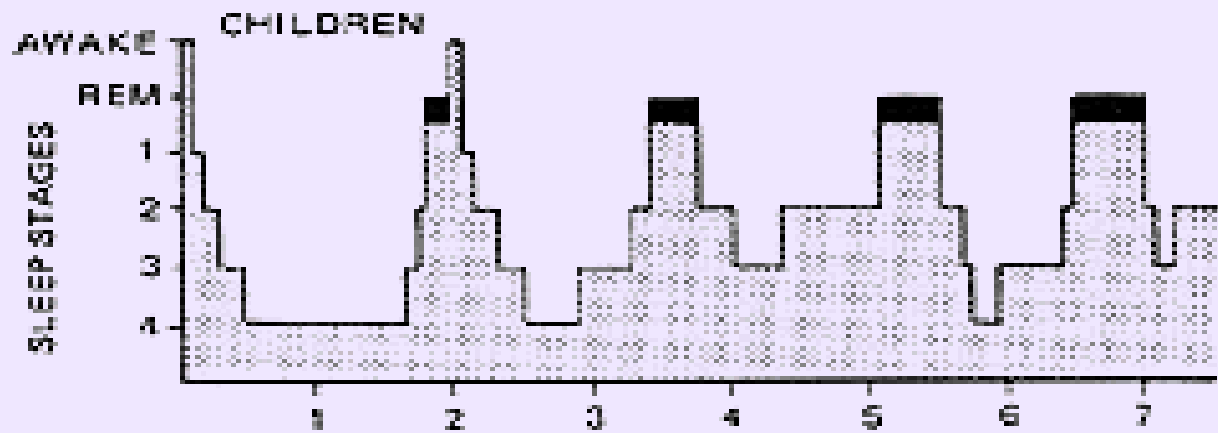
- stadio 1 = addormentamento (circa 5%)
- stadio 2 = sonno leggero (circa 50%)
- stadio 3+4 = sonno profondo o sonno lento o sonno delta (20-25%)

- sonno REM o paradosso (circa 20-25%)



## ANZIANI:

RIDUZIONE DEGLI STADI 3+4 E DEL REM  
AUMENTO DEL NUMERO DI RISVEGLI



# Insonnia

- Indicatori di insonnia

*difficoltà all'addormentamento*

*risvegli frequenti*

*risveglio precoce*

*sonno non ristoratore*

+

- Conseguenze diurne

*stanchezza*

*irritabilità*

*sonnolenza*

*disturbi della concentrazione*

# "Poor sleepers" e insonni

*Leger D et al. J Sleep Res 2000*

<b>Criteri</b>	<b>totale</b>	<b>M</b>	<b>F</b>
<b>Nell'ultimo mese :</b>			
<b>• Almeno 1 indicatore</b>	<b>73%</b>	<b>68%</b>	<b>78%</b>
<b>• 1 indicatore 3 volte alla settimana</b>	<b>29%</b>	<b>25%</b>	<b>34%</b>
<b>• Come sopra + cons.diurne</b>	<b>19%</b>	<b>14%</b>	<b>23%</b>
<b>• 2 indicatori + cons.diur. (insonnia grave)</b>	<b>9%</b>	<b>6%</b>	<b>12%</b>

# Studio osservazionale MORFEO



Sleep Medicine 5 (2004) 67–75

SLEEP  
MEDICINE

[www.elsevier.com/locate/sleep](http://www.elsevier.com/locate/sleep)

Original article

## Studio Morfeo: insomnia in primary care, a survey conducted on the Italian population<sup>☆</sup>

Mario Giovanni Terzano<sup>a,\*</sup>, Liborio Parrino<sup>a</sup>, Fabio Cirignotta<sup>b</sup>, Luigi Ferini-Strambi<sup>c</sup>,  
Gianluigi Gigli<sup>d</sup>, Giuseppa Rudelli<sup>e</sup>, Sergio Sommacal<sup>e</sup>, on behalf  
of the Studio Morfeo Committee<sup>1</sup>

<sup>a</sup>*Sleep Disorders Center, University of Parma, Via del Quartiere 4, Parma 43100, Italy*

<sup>b</sup>*Sleep Center, Unit of Neurology, S. Orsola-Malpighi Hospital, Bologna, Italy*

<sup>c</sup>*Sleep Disorders Center, Università Vita Salute, Scientific Institute H S. Raffaele, Milano, Italy*

<sup>d</sup>*Sleep Disorders Center, Department of Neurosciences, S. Maria della Misericordia, Udine, Italy*

<sup>e</sup>*Medical Department, Sanofi-Synthelabo, Italy*

Received 28 February 2003; received in revised form 19 August 2003; accepted 3 September 2003

## **Insonnia di Livello I:**

alterata qualità del sonno  
senza residui negativi diurni

## **Insonnia di Livello II:**

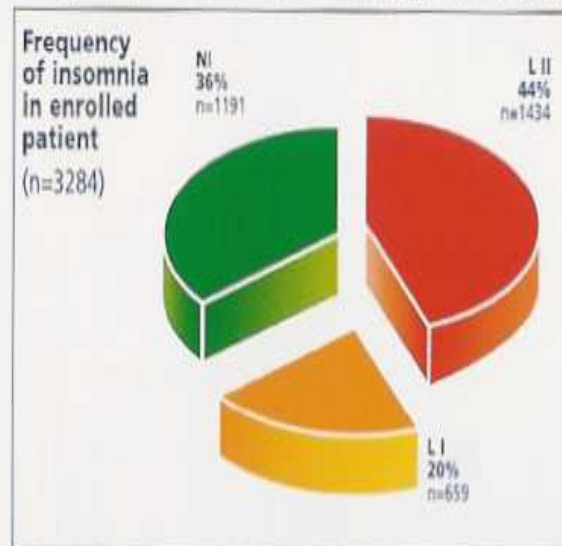
alterata qualità del sonno  
con residui negativi diurni

## Distribuzione dei soggetti in funzione dell'insonnia (n=3.284)

**Non insonni**  
**36%**

**Livello I**  
**20%**

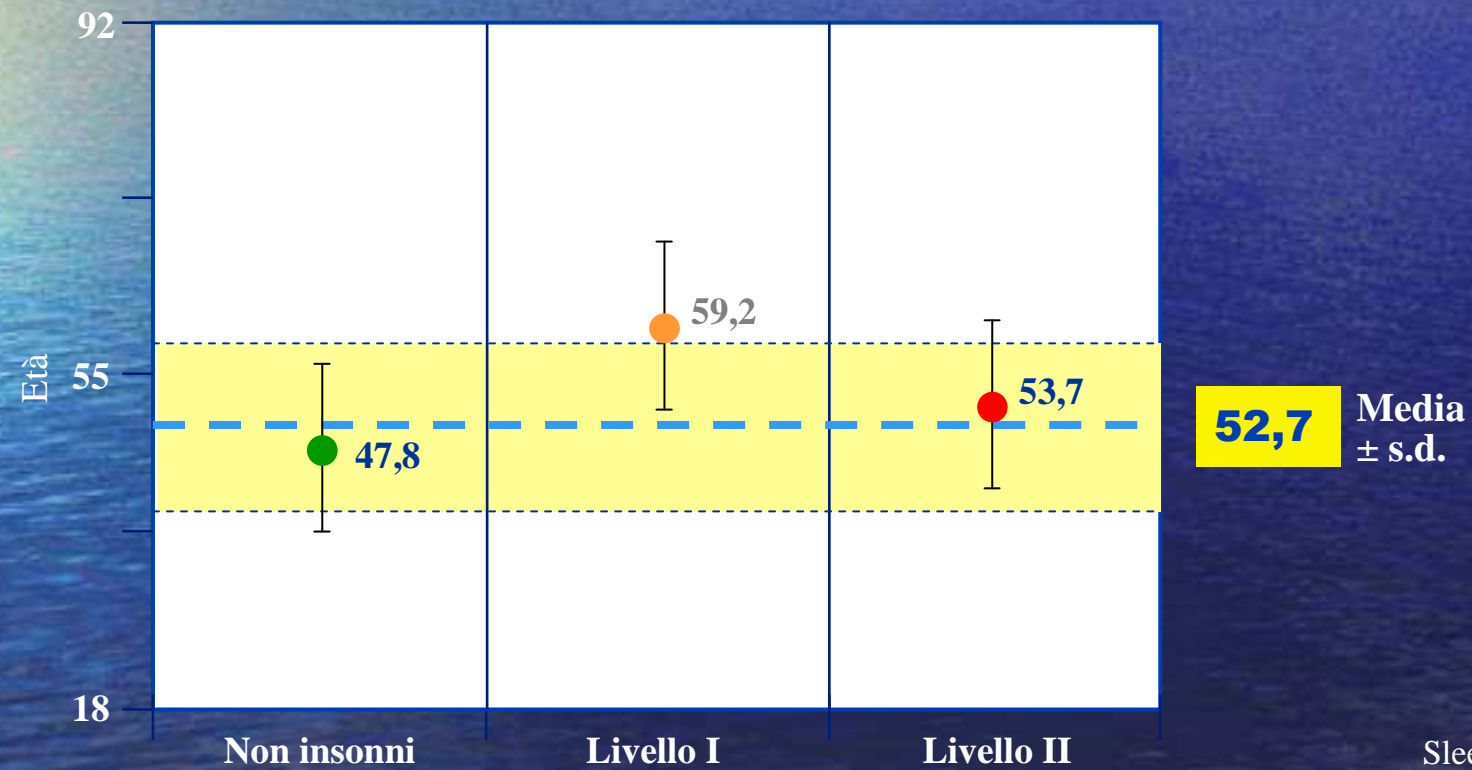
Fig. 3 - Insomnia was reported by 64% of all the interviewed patients with 20% classified as level I and 44% as level II. Insomnia was observed in 60% of male patients and in 66% of females. Compared to non-insomniacs, insomnia affected more frequently housewives and retired or unemployed people. Fifty-four percent of employed people suffered from insomnia (14.2% of level I, 39.7% of level II).



**Livello II**  
**44%**

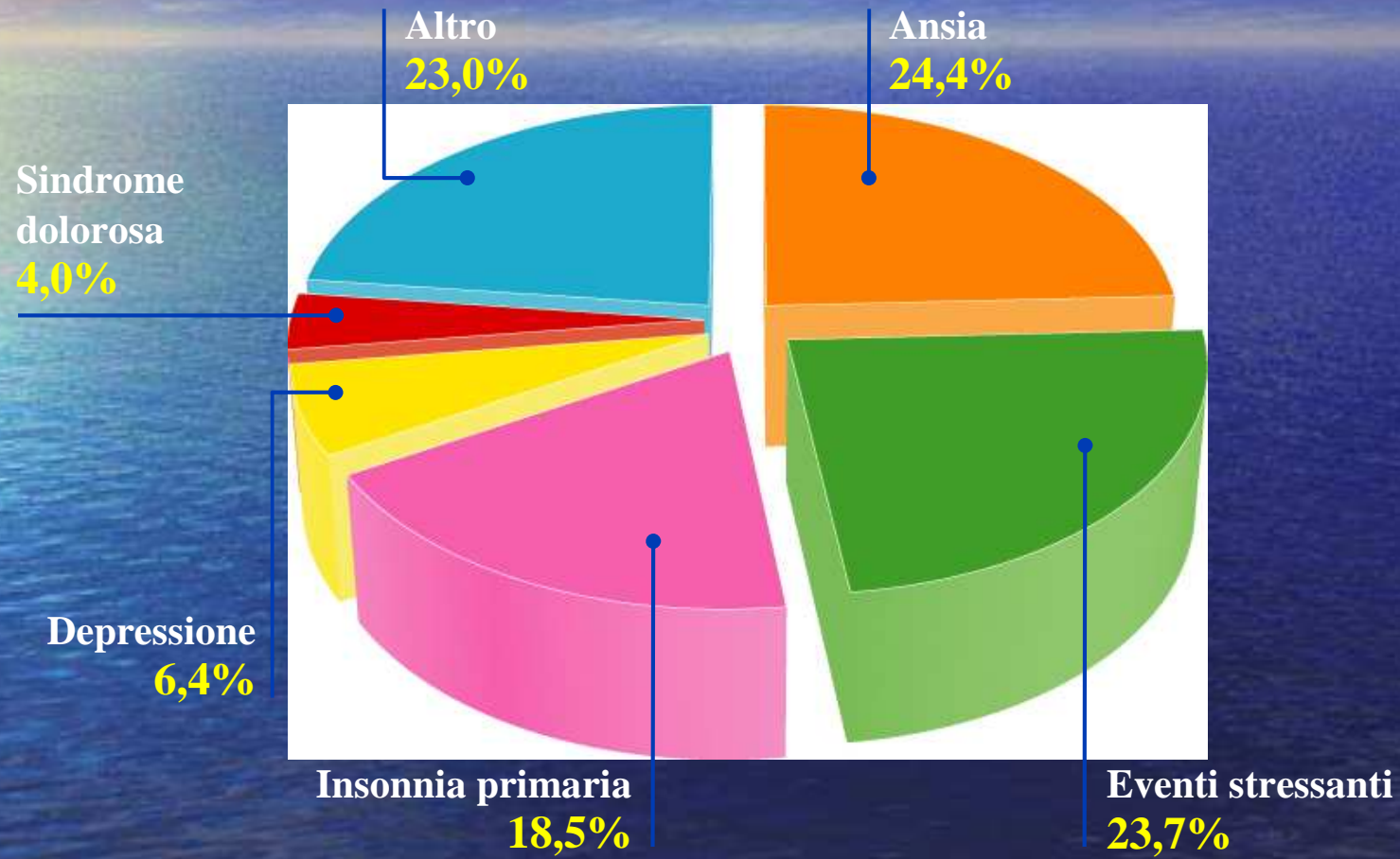
# Qual è l'età media degli insonni?

Età media



Terzano et al,  
Sleep Medicine, 2004

## Motivo principale dell'insonnia (n=2.755)



# L'insonnia aumenta il rischio di sviluppare patologie concomitanti?

## Patologie concomitanti psichiatriche

Fig. 7 – Depressive symptoms were always found more often among insomniacs, with higher frequencies in level II.



Terzano et al,  
Sleep Medicine, 2004

## Per quale motivo, invece, viene trattata l'insonnia?

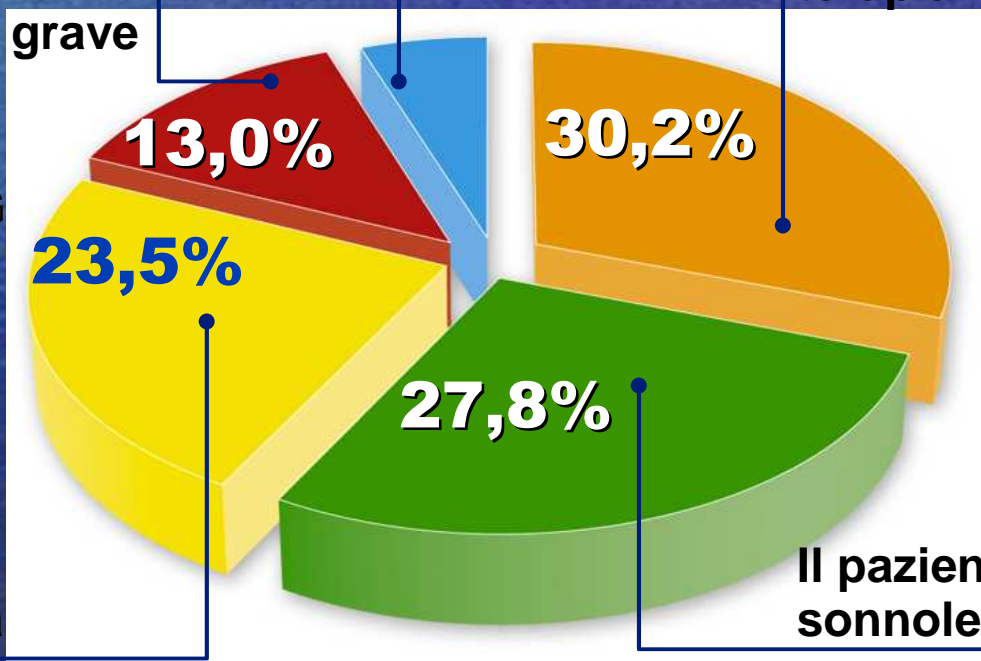
Motivo del trattamento (n=663)

**Motivo principale per il quale il MMG decide di trattare il paziente**

L'insonnia è particolarmente grave

Ansia  
5,5%

Il paziente richiede terapia



L'insonnia è peggiorata

Il paziente lamenta sonnolenza diurna

# International Classification of Sleep Disorders, 2005 (ICSD-2)

1. **INSOMNIA**
2. **SLEEP-RELATED BREATHING DISORDERS**
3. **HYPERSOMNIAS OF CENTRAL ORIGIN** (not due to a circadian rhythm sleep disorders, sleep related breathing disorders, or other causes of disturbed nocturnal sleep)
4. **CIRCADIAN RHYTHM SLEEP DISORDERS**
5. **PARASOMNIAS**
6. **SLEEP RELATED MOVEMENT DISORDERS**
7. **ISOLATED SYMPTOMS, APPARENTLY NORMAL VARIANTS AND UNRESOLVED ISSUES**
8. **OTHER SLEEP DISORDERS**

# International Classification of Sleep Disorders, 2005 ICSD-2

- INSOMNIA:

*Adjustment Insomnia (Acute Insomnia)*

*Psychophysiological Insomnia*

*Paradoxical Insomnia*

*Idiopathic Insomnia*

*Insomnia due to Mental Disorder*

*Inadequate Sleep Hygiene*

*Behavioral Insomnia of Childhood*

*Insomnia due to Drug or Substance*

*Insomnia due to Medical Condition*

*Primary  
Insomnia*

# CRITERI ESSENZIALI PER LA DIAGNOSI CLINICA di SINDROME DELLE GAMBE SENZA RIPOSO (RLS)

**Impellente necessità di muovere le gambe, spesso accompagnata da varie sensazioni sgradevoli e di fastidio.**

**Irrequietezza motoria dell'arto colpito.  
Il sollievo dai sintomi perdura finchè gli arti interessati sono mantenuti in movimento.**



**I sintomi peggiorano di sera e di notte.**

**I sintomi iniziano/peggiorano con il riposo e migliorano con il movimento—specialmente camminando.**

# TIPO D'INSONNIA

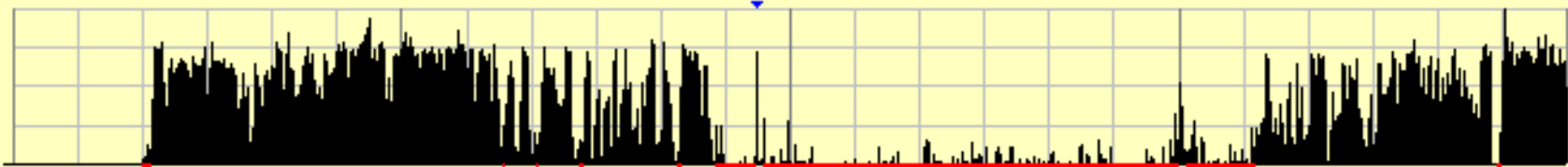
A SECONDA DEL PERIODO DELLA NOTTE IN CUI L'INSONNIA SI MANIFESTA:

- 1) INSONNIA DI TIPO INIZIALE (DIFFICOLTÀ NELL'INDUZIONE DEL SONNO)
- 2) INSONNIA CENTRALE (RISVEGLI DURANTE IL SONNO)
- 3) INSONNIA TERMINALE (RISVEGLIO PRECOCE SENZA POSSIBILITÀ DI RIADDORMENTAMENTO)
- 4) INSONNIA COMBINATA (es: 1+3, 2+3, ecc.)

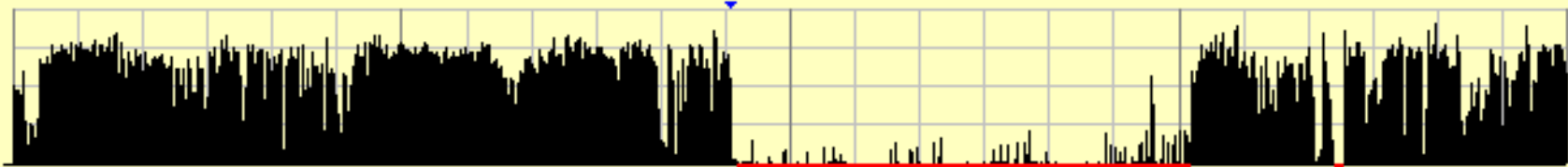
# ACTIGRAPH



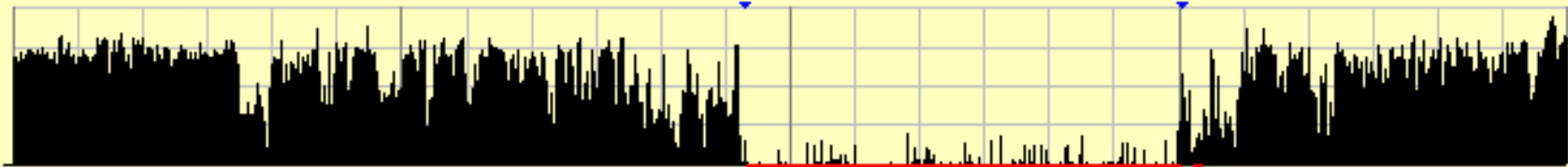
Fri 14/02/92



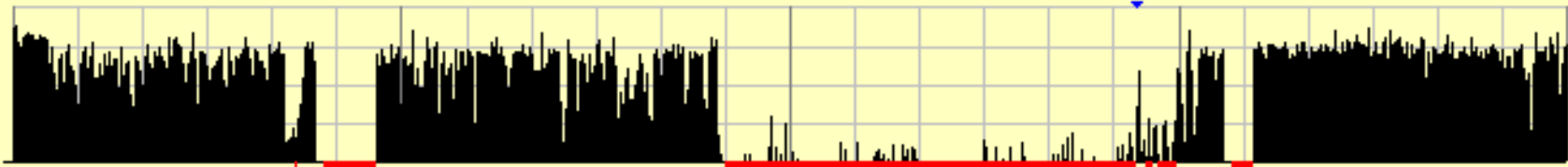
Sat 15/02/92



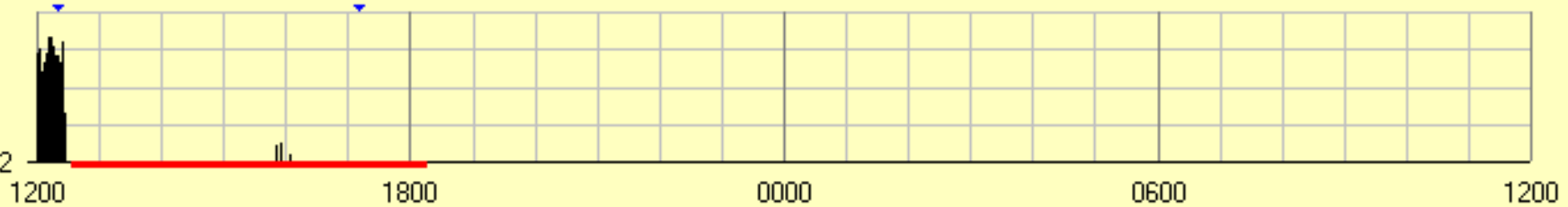
Sun 16/02/92



Mon 17/02/92



Tue 18/02/92



**SOGETTO NORMALE**



# PAZIENTE CON RLS

# TRATTAMENTO DELL'INSONNIA

## NON FARMACOLOGICO

Igiene del sonno

Restrizione del sonno

Tecniche comportamentali

- Training autogeno

- Biofeedback

- Ipnosi

Psicoterapia

Cronoterapia

Fototerapia

## FARMACOLOGICO

Ipnotici

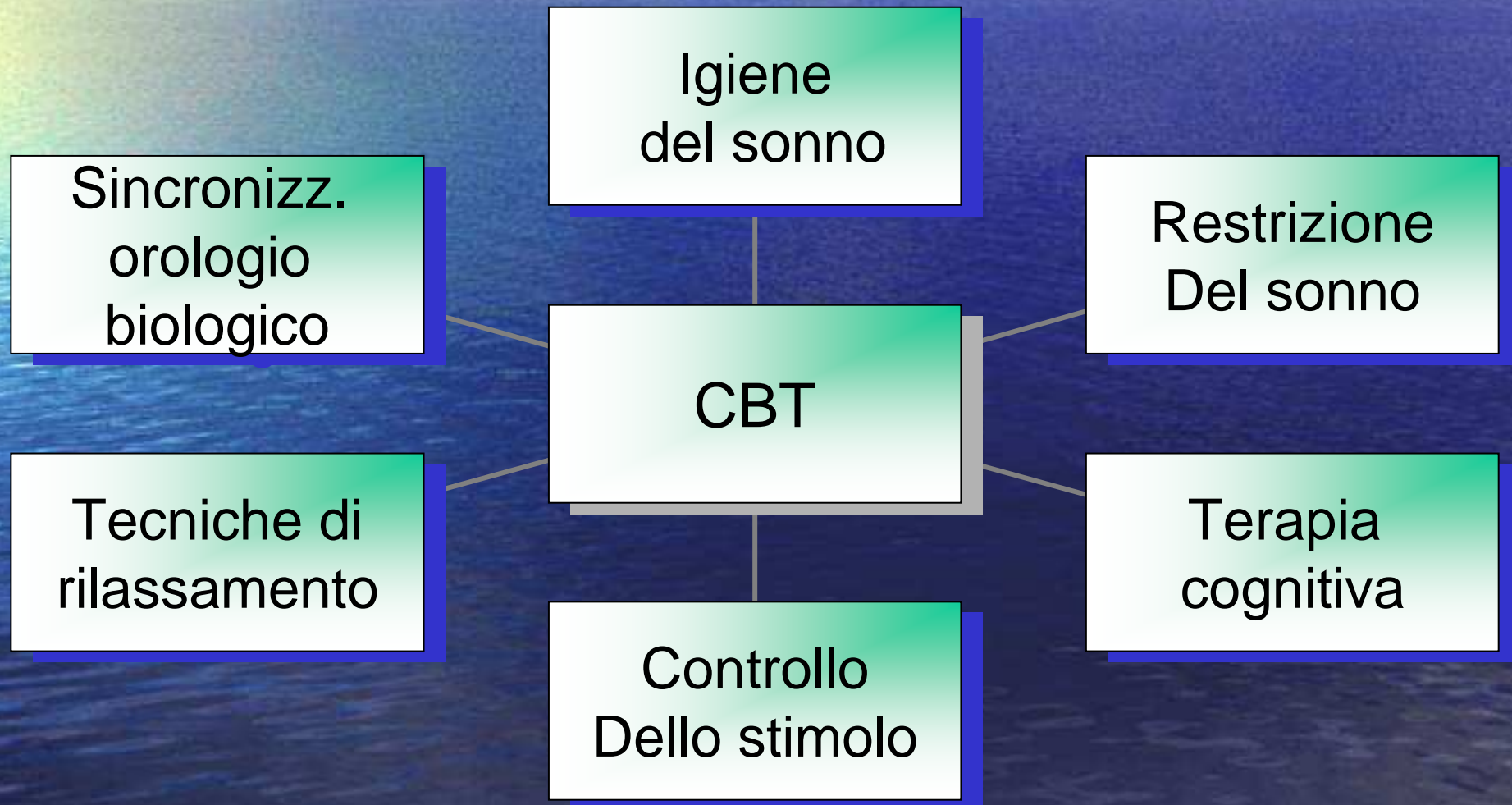
Ansiolitici

Antidepressivi

Melatonina

# Approccio cognitivo-comportamentale

- Include tutte le strategie necessarie a trattare l'insonnia



# Obiettivi CBT:

- Aumentare l'efficienza, la continuità e la qualità del sonno
- Aumentare la durata del sonno (se possibile e necessario)
- Ripristinare il senso di controllabilità del proprio sonno
- Eliminare abuso e dipendenza dagli ipnotici (**e non l'uso**)
- Ridurre il disagio emotivo, cognitivo e sociale
- **SCOPO: Ristabilire / imparare un "modo di essere"  
"compatibile" con il sonno.**

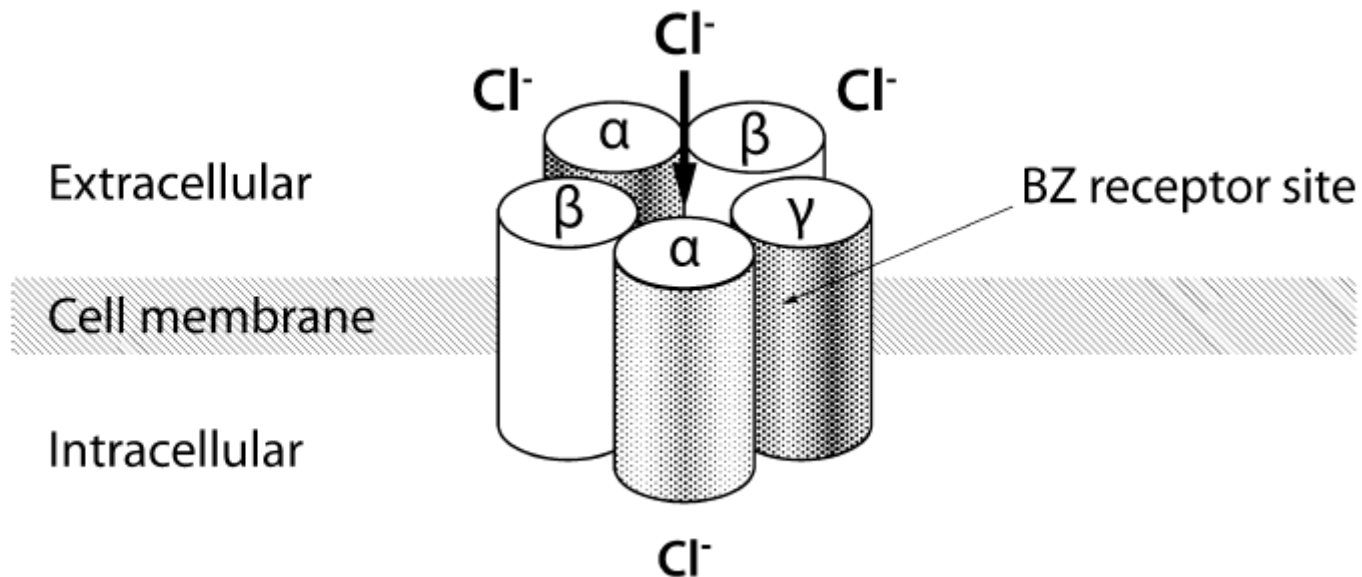
**Table II. Effects of hypnotics on sleep architecture** (↓ = decrease, ↑ = increase, ↔ = no significant effects)

Drug	Half-life	PSG in healthy individuals	ACP effects <sup>a</sup>	Rebound and residual effects <sup>b</sup>	Latency	Total sleep time	Delta sleep	REM	Sleep quality	Comments
<b>Benzodiazepine hypnotics</b>										
Triazolam	Short	°	<pathol. ACP rate	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Midazolam	Short	°	°	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Brotizolam	Short	°	°	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Loprazolam	Intermediate	°	°	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Lometazepam	Intermediate	°	°	Rebound insomnia	↓	↑	↓	↓	↑	↑ stage 2
Flunitrazepam	Intermediate	↓ slow waves	°	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
Flurazepam	Long	↓ slow waves	°	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
Nitrazepam	Long	°	°	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
Quazepam	Long	°	°	< latencies in MSLT. No rebound	↓	↑	↓	↓	↑	↑ stage 2
<b>Non-benzodiazepine hypnotics</b>										
Zolpidem	Short	No or few changes	<pathol. ACP rate	No rebound or residual effects	↓	↑	↑	↔	↑↑	↓ waking
Zopiclone	Short	No or few changes	<pathol. ACP rate	No rebound	↓	↑	↑	↔	↑↑	↓ waking
Zaleplon	Short	No changes	°	No rebound or adverse effects	↓	↑	↑	↓	°	°

<sup>a</sup> Alternating cyclic pattern; pseudo-periodic activation phenomenon of slow sleep characterised in the EEG by limited duration waves that can appear spontaneously or after waking stimuli. <ACP means that these compounds decrease the ACP index.

**Table 1—US FDA-Approved Insomnia Treatment Medications<sup>5</sup>**

Medication	Brand Name	Available Doses (mg)	Elimination Half-Life (hr)	DEA Schedule
<b>Benzodiazepine Receptor Agonists</b>				
<i>Immediate-Release Benzodiazepines</i>				
Estazolam	ProSom	1, 2	8 – 24	IV
Flurazepam	Dalmane	15, 30	48 – 120	IV
Quazepam	Doral	7.5, 15	48 – 120	IV
Temazepam	Restoril	7.5, 15, 22.5, 30	8 – 20	IV
Triazolam	Halcion	0.125, 0.25	2 – 4	IV
<i>Immediate-Release Nonbenzodiazepines</i>				
Eszopiclone	Lunesta	1, 2, 3	5 – 7	IV
Zaleplon	Sonata	5, 10	1	IV
Zolpidem	Ambien	5, 10	1.5 – 2.4	IV
<i>Modified-Release Nonbenzodiazepines</i>				
<u>Zolpidem ER</u>	Ambien CR	6.25, 12.5	2.8 – 2.9	IV
<b>Selective Melatonin Receptor Agonist</b>				
<u>Ramelteon</u>	Rozerem	8	1 – 2.6	None



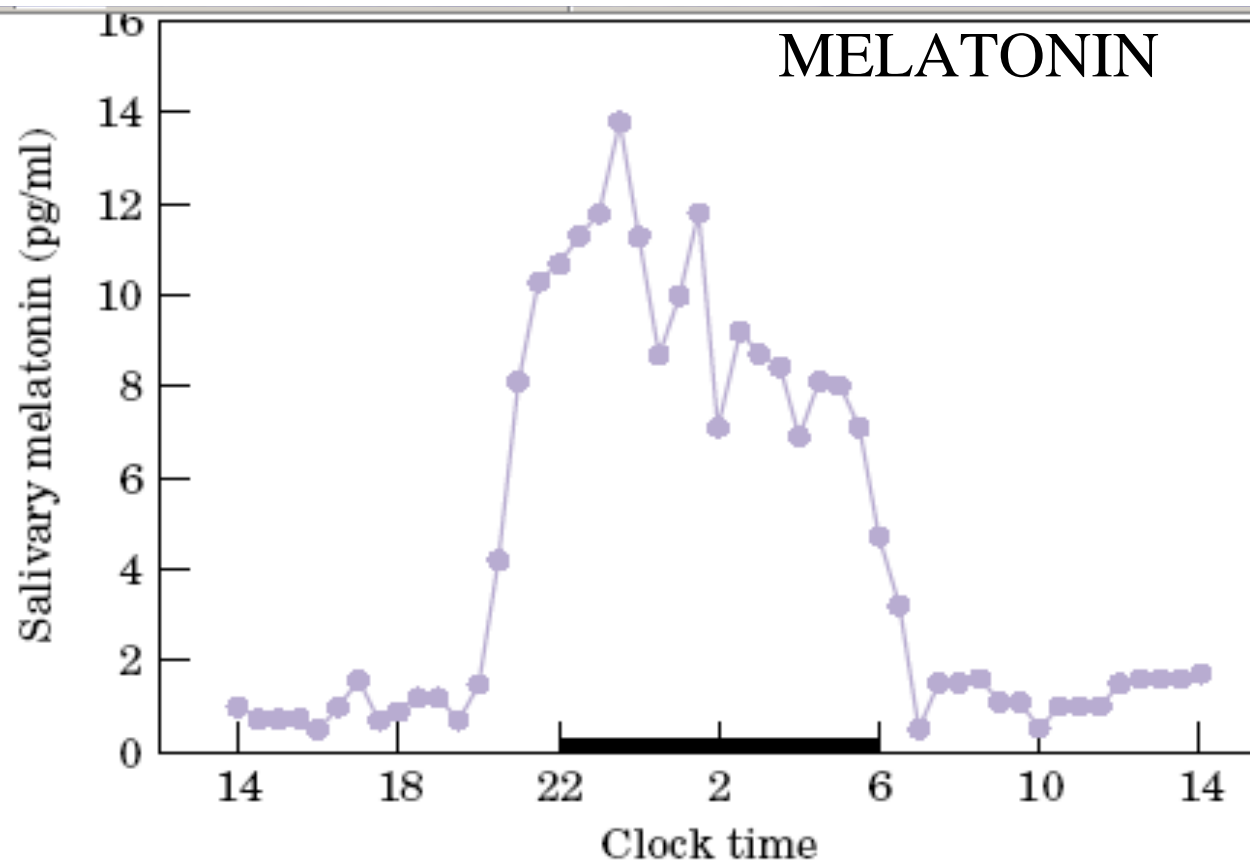
**Figure 1—Structure of the GABA<sub>A</sub> receptor<sup>6,14</sup>; BZ = benzodiazepine**

*Neubauer,  
J Clin Sleep Med 2007*

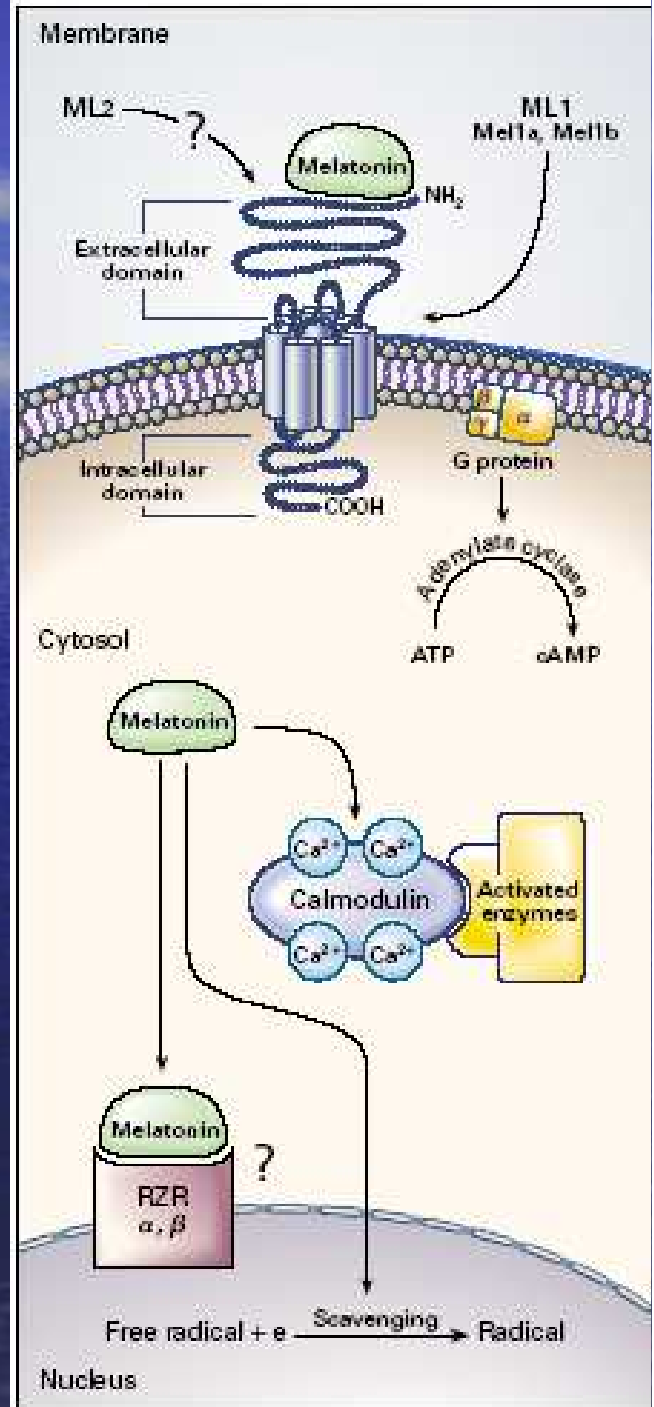
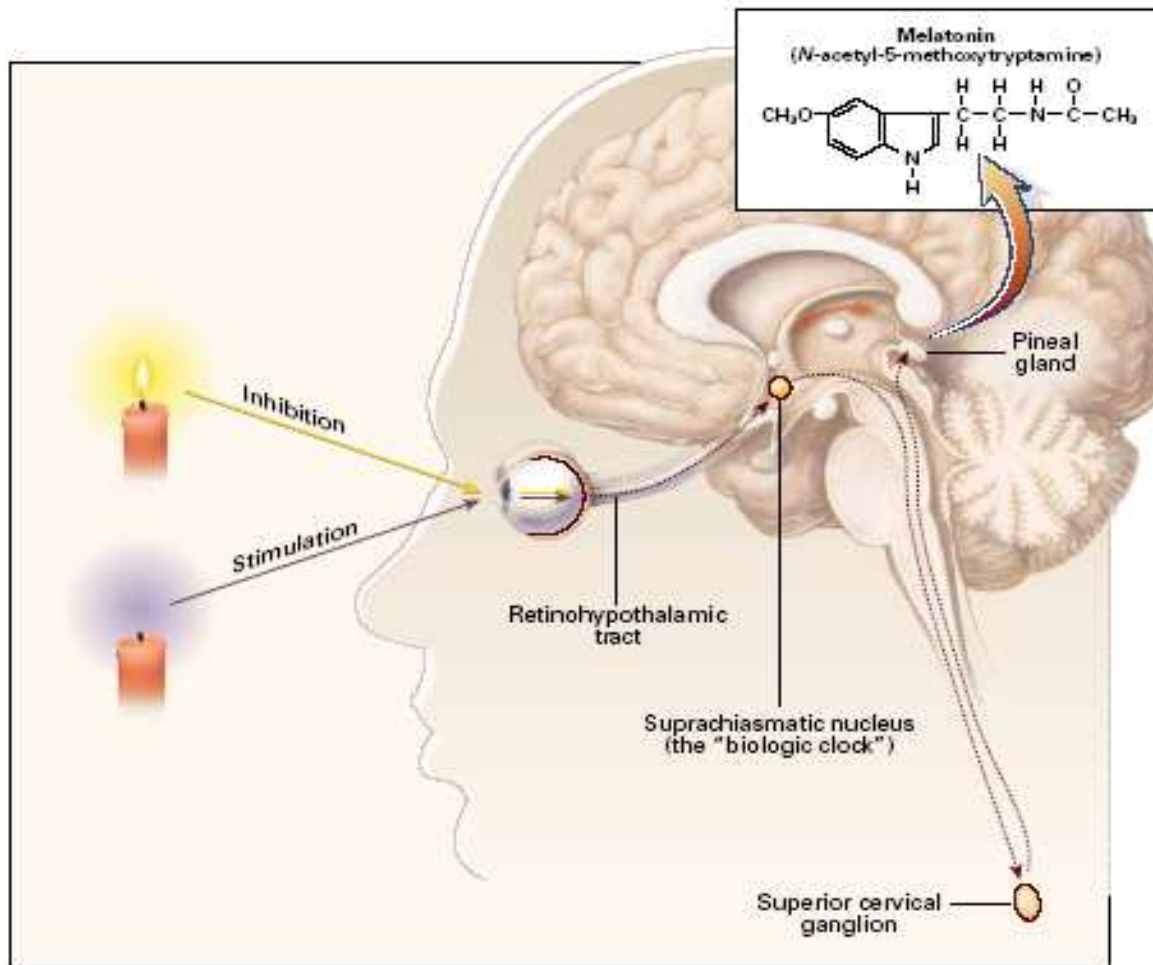
## **Nell'utilizzo di un ipnotico classico:**

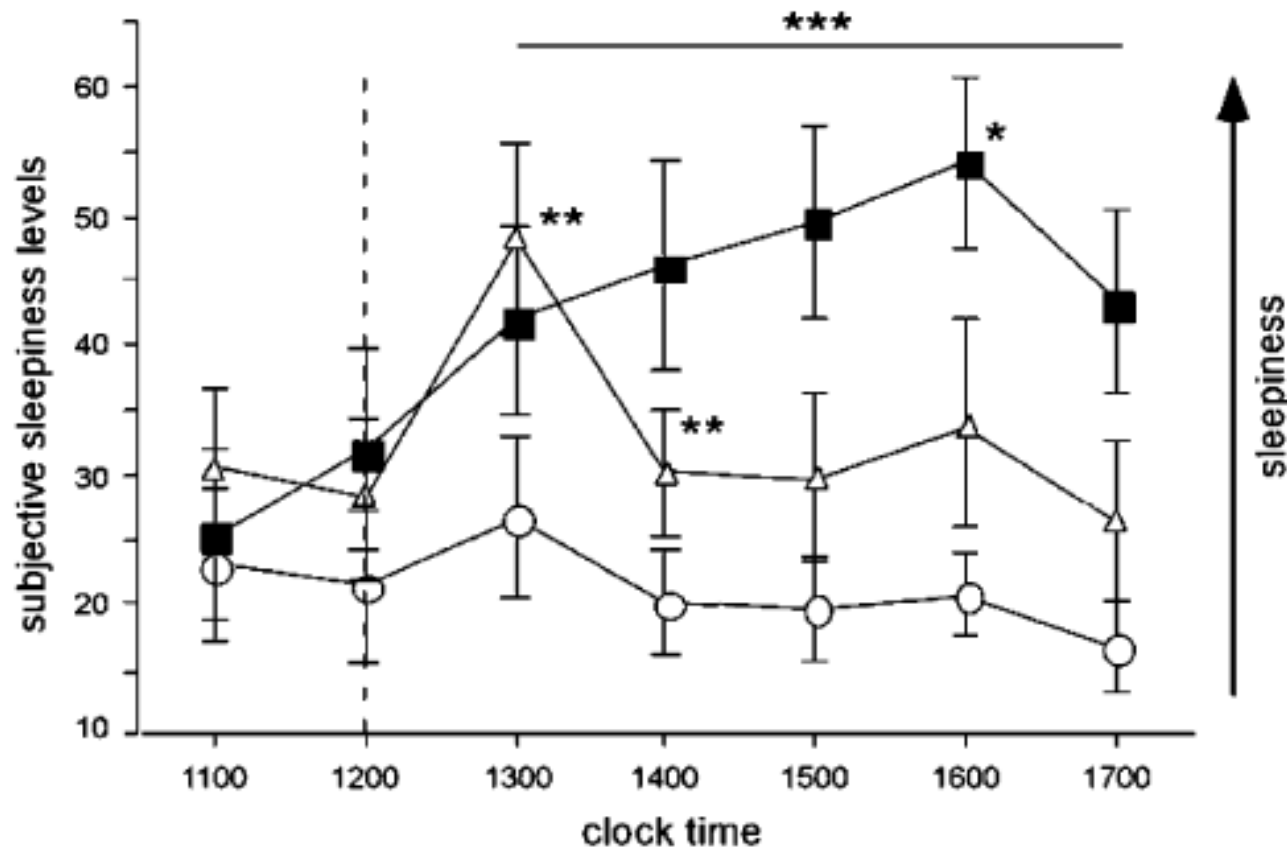
- Prescrivere la dose minima efficace
- Somministrare il farmaco in modo intermittente
- Possibilmente non prolungare la somministrazione oltre le 4 settimane
- Sospendere il farmaco gradualmente
- Cercare di ridurre al minimo gli effetti indesiderati diurni somministrando un dosaggio minore o utilizzando composti con emivita più breve

***Kupfer & Reynolds, N Engl J Med 1997***



**Figure 2** A typical 24 h profile of melatonin secretion. This individual, a 25-year-old male, slept from 10.00 p.m.–6.00 a.m. (indicated by the black bar) for one week before his melatonin profile was assessed. During the assessment, the subject remained awake in a semi-recumbent position in dim light (<10 lux) and saliva samples were collected at 30 min intervals and later assayed for melatonin [58].





**Figure 6** Effect of melatonin and temazepam on subjective sleepiness, using a visual analogue scale. ○ represents the placebo condition, ■ represents the melatonin condition, △ represents the temazepam condition. Each point represents mean  $\pm$  SEM. Administration of 5 mg melatonin, 10 mg temazepam or placebo was at 1200 h (dashed line). \*\*\* represents a significant ( $p \leq 0.05$ ) difference between the placebo and melatonin conditions; \*\* represents a significant ( $p < 0.05$ ) difference between the placebo and temazepam conditions; \* represents a significant ( $p < 0.05$ ) difference between the melatonin and temazepam conditions. Reprinted with permission from Ref. 28.

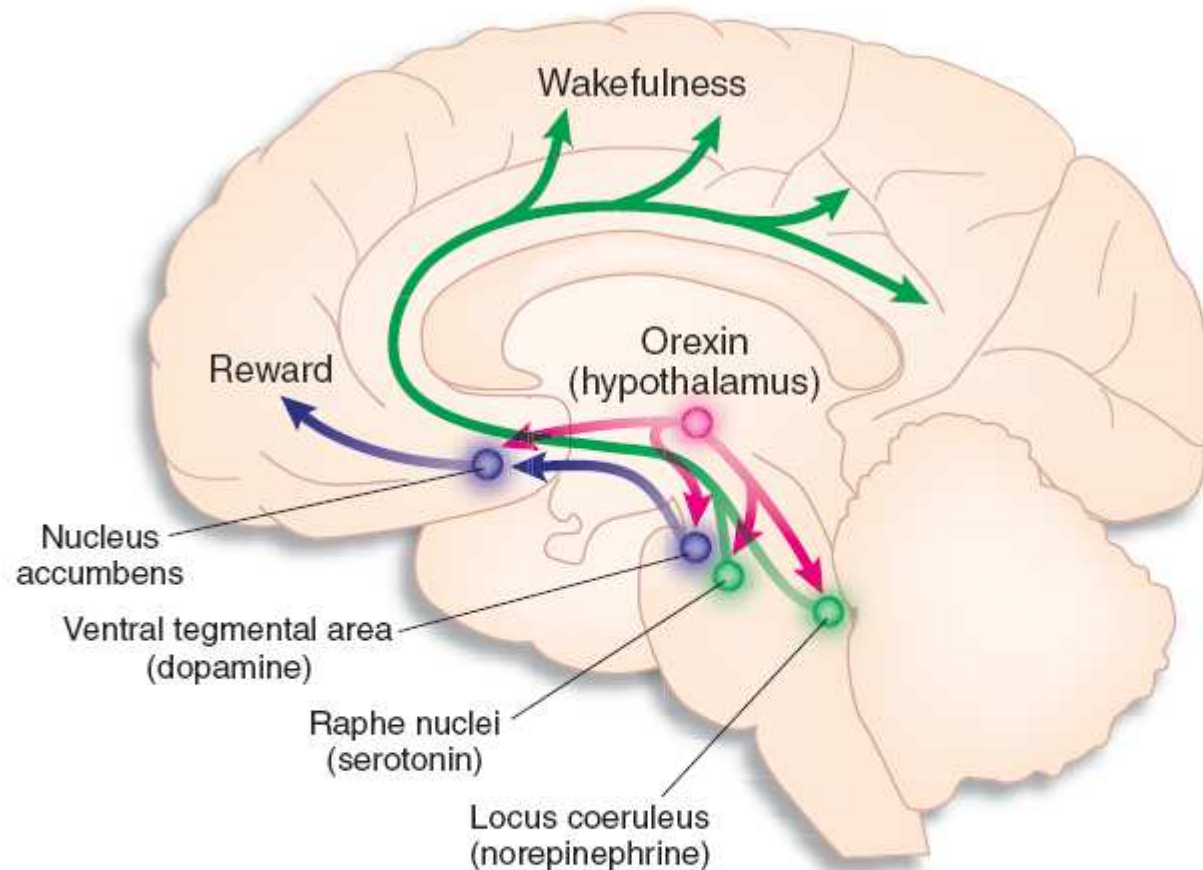
### Insomnia treatments being developed

Compound (product)	Pharma group	Mode of action	Phase
Indiplon	Neurocrine / Pfizer	GABA <sub>A</sub> agonist	Filed *
Doxepin (Silenor)	Somaxon	H1,H2 antagonist/ adrenergic reuptake blocker	Filed
<u>Melatonin</u> (Posidorm)	Alliance Pharmaceuticals	Melatonin receptor agonist	III
VEC-162	Vanda Pharmaceuticals	Melatonin receptor agonist	III
<u>Eplivanserin</u>	<b>Sanofi-Aventis</b>	<b>5HT<sub>2A</sub> receptor antagonist</b>	<b>Filed</b>
Volinanserin	Sanofi-Aventis	5HT <sub>2A</sub> receptor antagonist	III
Esmirtazapin	Schering-Plough	5HT <sub>2A</sub> antagonist/ alpha adrenergic antagonist/ H1 antagonist	III
<u>Almorexant</u>	Actelion	Orexin receptor antagonist	III
SD-649868	GSK	Orexin receptor antagonist	II (stopped)
Adipiplon	Neurogen Corp.	GABA <sub>A</sub> partial agonist ; alpha-3 subunit agonist	IIb (stopped)
EVT-201	Evotec	GABA <sub>A</sub> modulator	II
PD-200390	Pfizer	Voltage-gated calcium channel alpha(2)delta subunit modulator	II
Pimavanserin	Acandia	5HT <sub>2A</sub> receptor inverse agonist, dopamine D <sub>2</sub> /D <sub>3</sub> receptor partial agonist	II
APD-125	Arena Pharmaceuticals	5HT <sub>2A</sub> receptor inverse agonist	II
Pruvanserin	Lilly	5HT <sub>2A</sub> receptor inverse agonist	II
HY 10275	Lilly	5HT <sub>2A</sub> receptor antagonist/ H1 receptor antagonist	II
PD-6735	Phase 2 discovery	Melatonin receptor agonist	II
TIK-301	Tivah pharmaceuticals	?	II
MK-8998	Merck&Co	?	I

(\**) Indiplon has suffered a regulatory setback and more trials are needed to obtain FDA approval. Note that this chemical family appears to be encountering problems in clinical trials as in July 2008, Neurogen announced that it is ending adipiplon's phase II trials due to side effects*

Source: RJEE

# OREXIN modulations in CNS



**Figure 1** Among their many functions, the orexin neurons promote wakefulness and modulate reward pathways. The orexin neurons innervate and excite many brain regions that drive arousal and attention, including the locus coeruleus and the dorsal raphe. Rewarding stimuli trigger release of dopamine from the mesolimbic projections between the ventral tegmental area and the nucleus accumbens, and orexins enhance signaling in this pathway. As Brisbare-Roch *et al.* have found, an orexin antagonist that blocks these signals can promote sleep (by reducing arousal) and possibly aid in the treatment of drug addiction (by dampening reward signals).

# Hypocretin-orexin neuropeptides

- Regulation of wakefulness and sleep
- Control of body weight and metabolism
- Regulation of motivation and addiction

# Hypocretin-orexin neuropeptides

↓  
produced by posterior lateral  
hypothalamus

↙  
promote and sustain  
wakefulness

↘  
Essential regulators  
of REM sleep

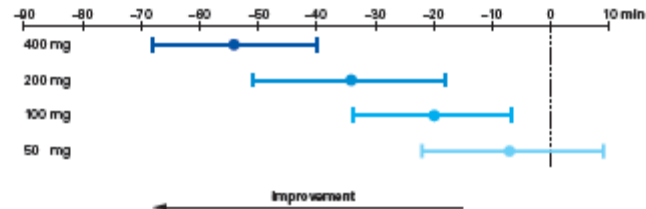
↙  
Increase excitatory drive to regions governing arousal and alertness

## *ALMOREXANT (ACT-078573)*

- **Selective blockade of orexin receptors (*OX1* and *OX2*), transient and reversible**
- Orally active and rapidly enter the brain
- Normal people taking the drug during the day feel asleep quickly

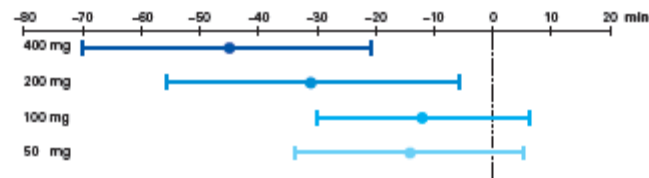
*Less effects (on animals) when administered during the day period*

**Almorexant decreased wake after sleep onset**



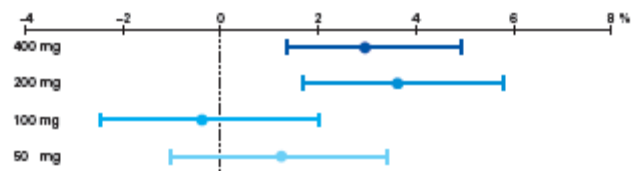
Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	39	-54.0	94.0	40.0
200 mg	38	-34.3	86.9	52.7
100 mg	38	-20.1	88.5	48.4
50 mg	32	-8.7	89.8	82.9

**Almorexant decreased latency to REM**



Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	39	-45.2	121.9	76.6
200 mg	38	-30.7	122.6	96.9
100 mg	38	-12.1	105.7	93.6
50 mg	31	-14.5	122.7	108.2

**Almorexant increased percentage of REM**

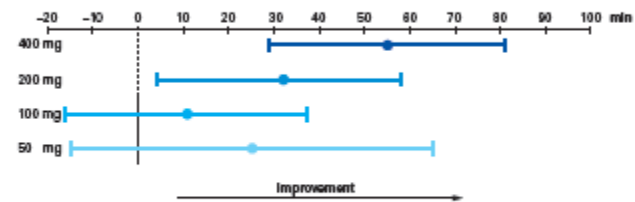


Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	39	3.1	18.2	19.2
200 mg	38	3.8	15.9	19.7
100 mg	38	-0.3	19.3	19.0
50 mg	32	1.3	15.9	17.1

**Proof-of-concept study in primary insomnia patients with almorexant (ACT-078573), a dual orexin receptor antagonist**

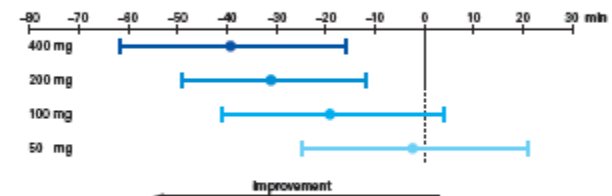
**Effects of almorexant on subjective sleep variables (mean ± 95% CI)**

**Almorexant increased subjective total sleep time**



Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	37	55.1	300.9	356.0
200 mg	37	31.4	300.3	331.6
100 mg	38	10.5	321.7	332.2
50 mg	30	25.2	303.7	328.8

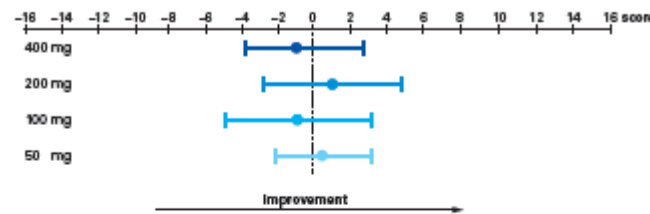
**Almorexant decreased subjective sleep latency**



Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	34	-38.6	81.5	42.8
200 mg	34	-30.6	78.3	45.7
100 mg	35	-19.0	78.8	59.7
50 mg	28	-2.4	63.0	60.7

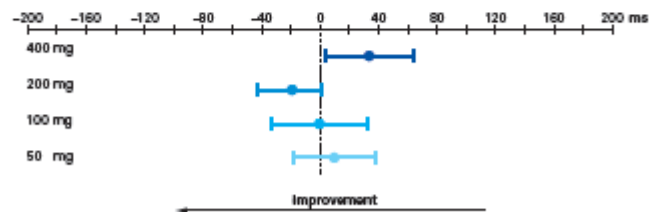
## Effects of almorexant on next-day performance (mean $\pm$ 95% CI)

Almorexant had no effect on fine motor test



Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	39	-0.7	77.2	76.5
200 mg	37	1.0	77.1	78.0
100 mg	39	-0.8	78.4	77.5
50 mg	32	0.5	75.2	75.7

Almorexant had no relevant effect on mean reaction time



Dose	n	Mean treatment effect	Mean	
			Pla	Almor
400 mg	29	34.7	844.8	879.5
200 mg	34	-19.6	830.0	811.2
100 mg	35	-0.1	898.5	898.3
50 mg	28	10.0	830.1	840.1

**Proof-of-concept study in primary insomnia patients with almorexant (ACT-078573), a dual orexin receptor antagonist**

## Conclusions

- Almorexant doses as low as 100 mg significantly increased SE in primary insomnia patients
- Almorexant increased SE, decreased WASO, decreased LPS, reduced the latency to REM, and increased the time in REM in a dose-dependent way
- Almorexant improved subjective sleep variables and had no relevant effect on next-day performance
- No safety concerns emerged during the conduct of the study
- These data show that the endogenous orexin system plays an important role in insomnia. Almorexant represents a new approach aimed at restoring physiological sleep, in contrast to existing hypnotic drugs.

## *ALMOREXANT (ACT-078573)* *potentials*

- It promote sleep and decrease of wakefulness during the night
- It can promote sleep during the day (when orexins are increased)
- It may be useful in shift workers or people with jet lag
- Does not produce cataplexy (at the moment)
- Treatment of obesity or drug addiction by reducing addictive behaviors and reward pathways)