



**INSONNIA
ANSIA
DEPRESSIONE...**

Quanto ti diverti Mr Parkinson?!

Disturbi del sonno nella malattia di Parkinson

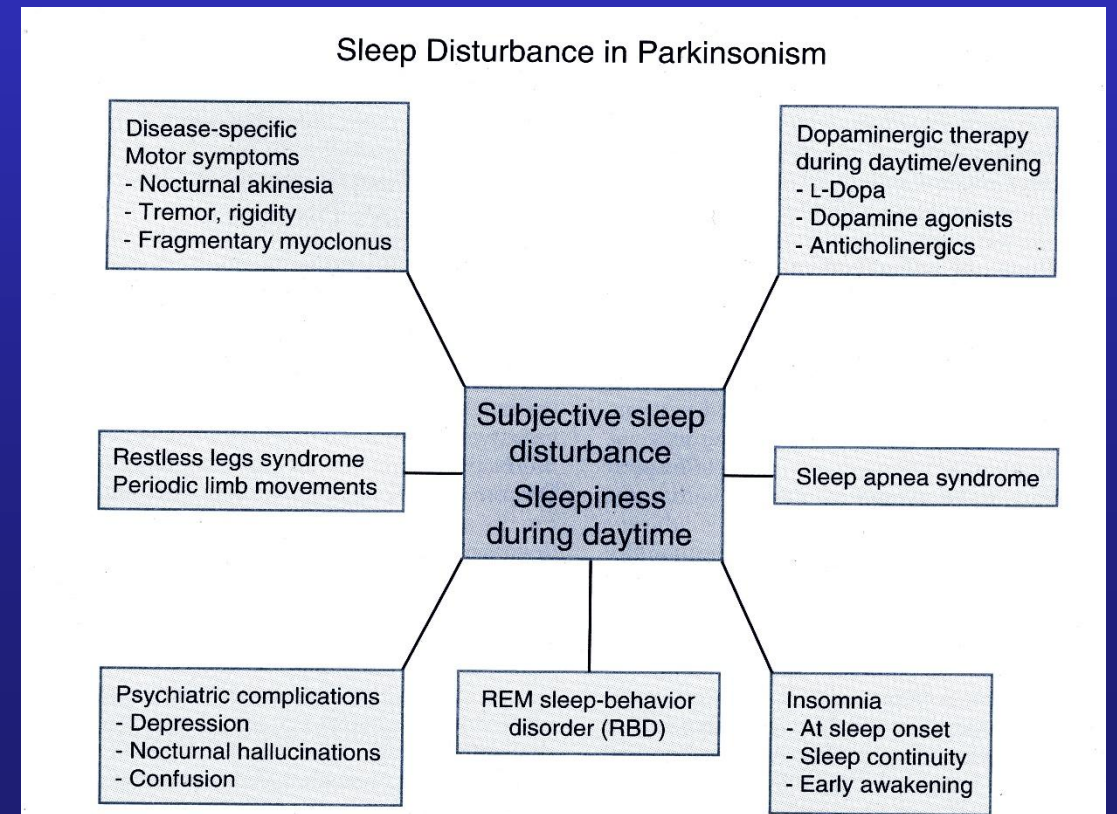
Alessandro Cicolin

**Centro Riferimento Regionale per i Disturbi del Sonno
AOU Città della Salute e della Scienza - Molinette**

Disturbi del sonno e M. di Parkinson



Authors	Years	Numbers of patients	Prevalence of sleep disorders	Characteristics
Nausieda <i>et al.</i> [1]	1982	100	74%	Sleep fragmentation
Lees AJ <i>et al.</i> [5]	1988	220	98%	Inability to turn over in bed 76%; nocturia in 80%
Factor <i>et al.</i> [4]	1990	78	89%	Sleep initiation problems in 67%; daytime napping in 49% vs. 26% controls
Smith <i>et al.</i> {Smith MC, Ellgring H, <i>et al.</i> 1997 ID: 120}	1997	153	25% male; 41% female	
Tandberg <i>et al.</i> [3]	1998	245	60%	Higher prevalence than DM (45%) or controls (33%)
Stocchi <i>et al.</i> {Stocchi F, Brusa L, <i>et al.</i> 2001 ID: 354}	2001	100	72%	52% reported EDS



Fabbisogno di sonno e sue funzioni



Sistema nervoso centrale:

- **funzioni cognitive (memoria, attenzione, emozioni)**
- **neuroprotezione (eliminazione sostanze neurotossiche)**

Sistema endocrino-metabolico:

- **ormoni (GH, cortisolo)**
- **metabolismo lipidico (leptine, ghreline)**

Sistema cardiovascolare:

- **pressione arteriosa e frequenza cardiaca**

Sistema immunitario:

- **immunocompetenza**

Fabbisogno di sonno e sue funzioni

Sistema nervoso centrale:

- funzioni cognitive (memoria, attenzione, emozioni)
- neuroprotezione (eliminazione sostanze neurotossiche)

Sistema endocrino-metabolico:

- ormoni (GH, cortisolo)
- metabolismo lipidico (leptine, ghrelina)

Sistema cardiovascolare:

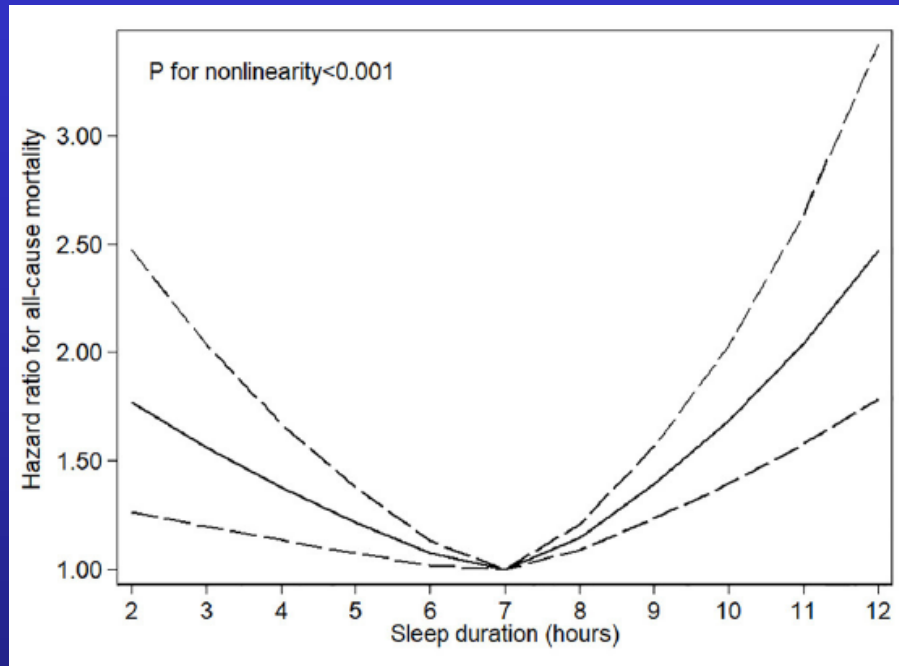
- pressione arteriosa e frequenza cardiaca

Sistema immunitario:

- immunocompetenza



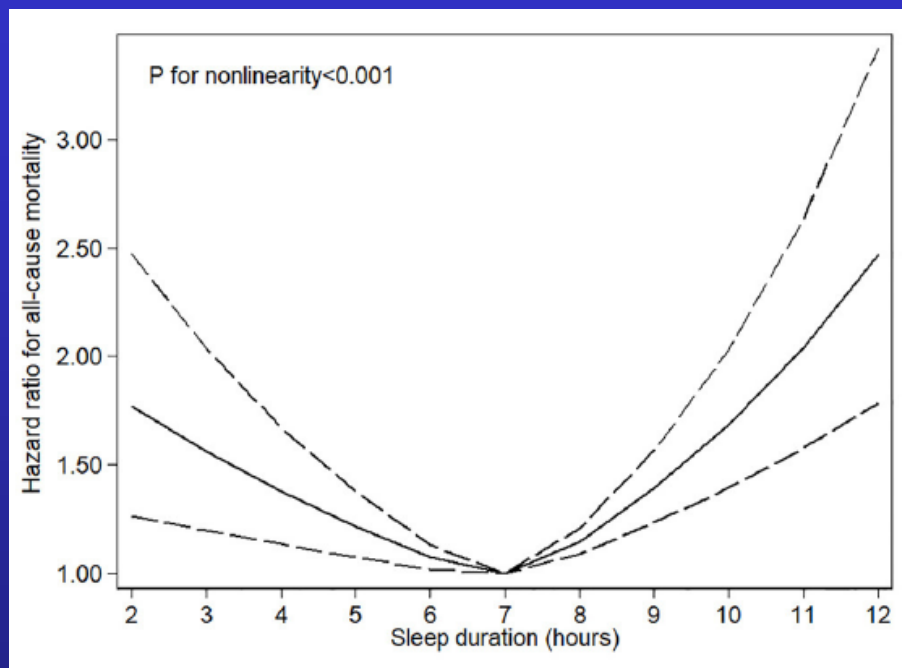
Conseguenze della deprivazione di sonno





Conseguenze della deprivazione di sonno

“INSUFFICIENT” SLEEP



Eccessiva sonnolenza diurna

Compromissione funzione cognitive

Alterazioni del tono dell'umore

Compromissione della salute a lungo termine:

- **aumento pressione arteriosa**
- **intolleranza glicidica**
- **elevati valori di cortisolo**
- **incremento parametri infiammatori**
- **incremento ponderale**

Architettura e profilo del sonno



■ NREM

■ REM



■ N 1

■ N 2

■ N 3 (SWS)

■ REM





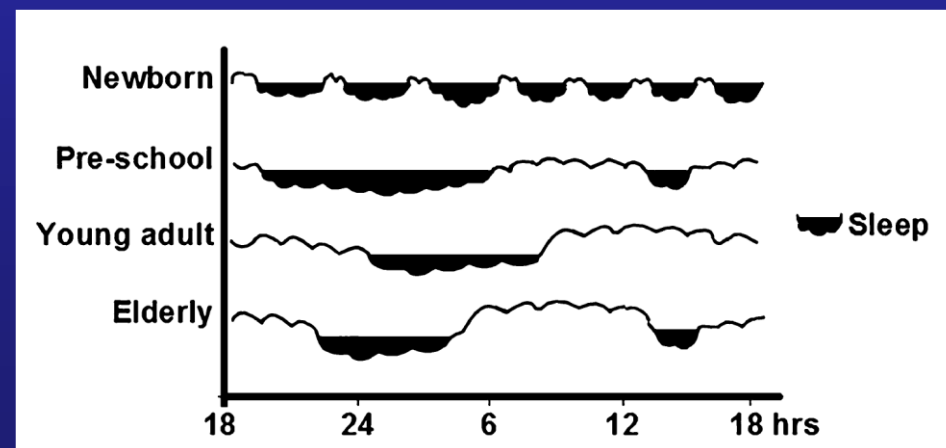
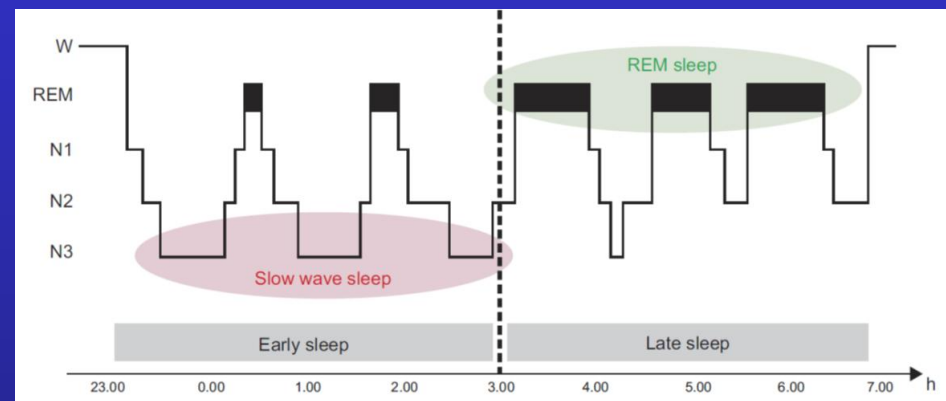
Architettura e profilo del sonno

■ NREM

■ REM



■ N 1
■ N 2
■ N 3 (SWS)
■ REM





Regolazione del sonno

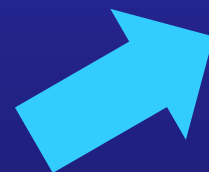
**OSCILLATORE
CIRCADIANO**

**OSCILLATORE
ULTRADIANO**

SONNO
(corteccia cerebrale)

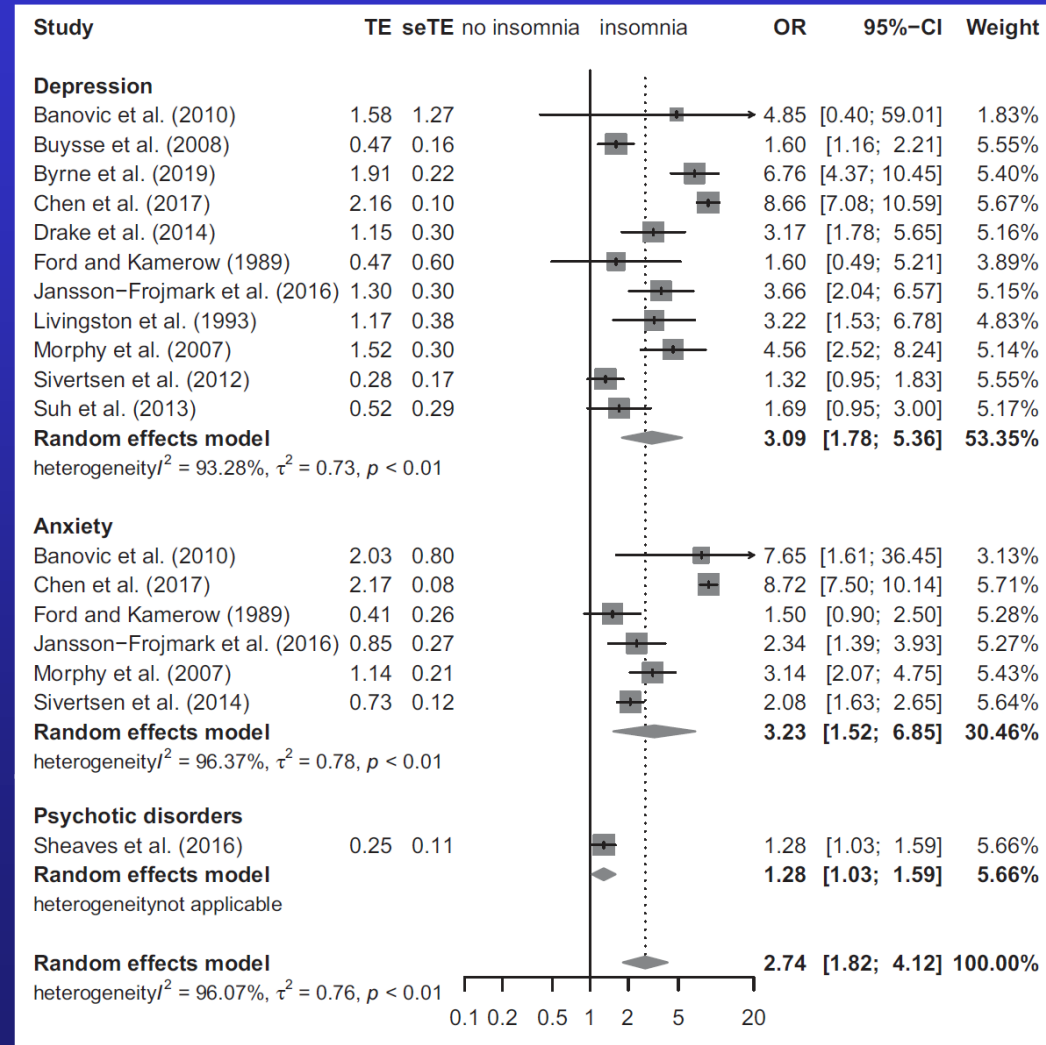
**SISTEMA
OMEOSTATICO**

**SISTEMA
DELL' AROUSAL**

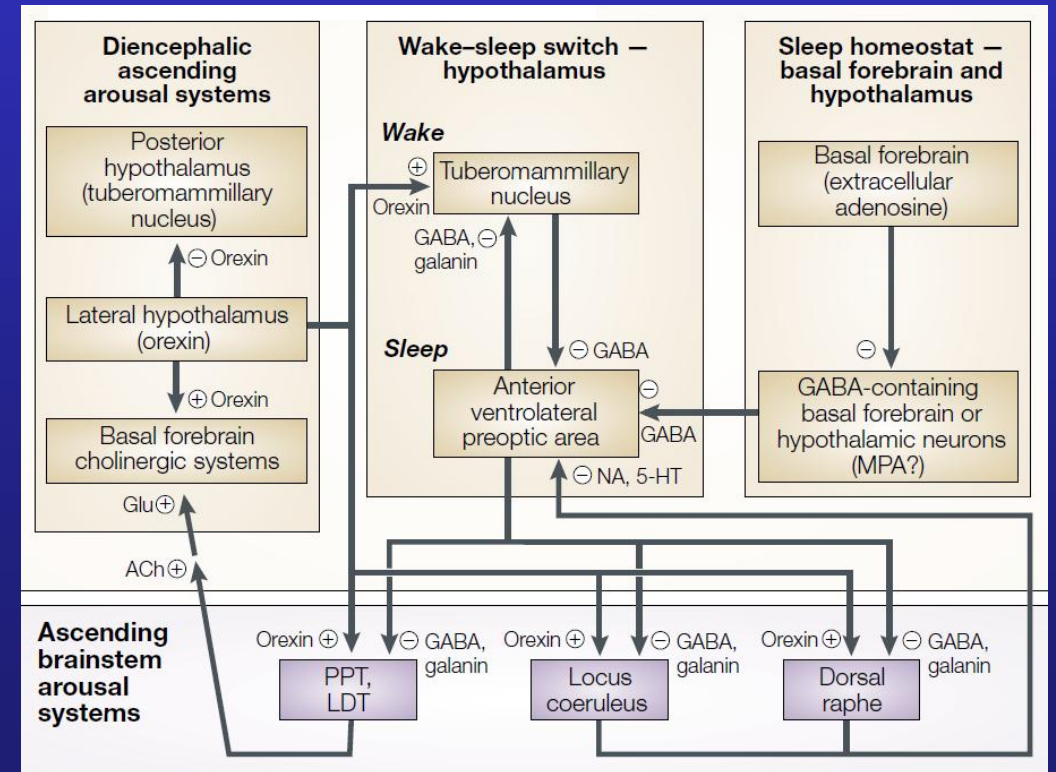
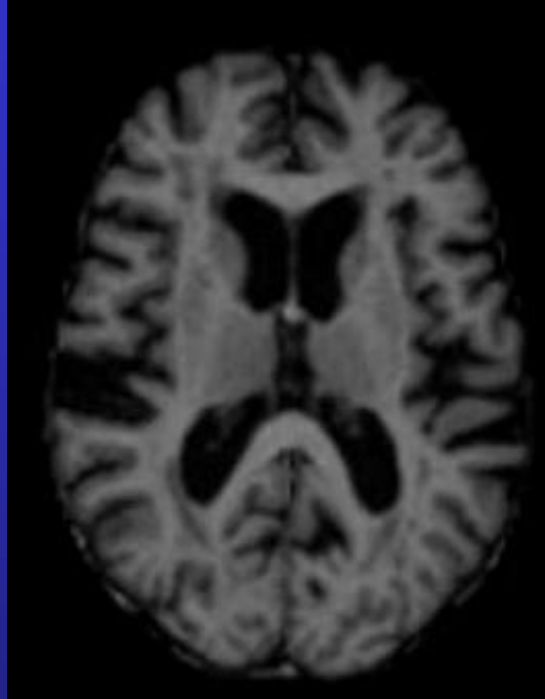
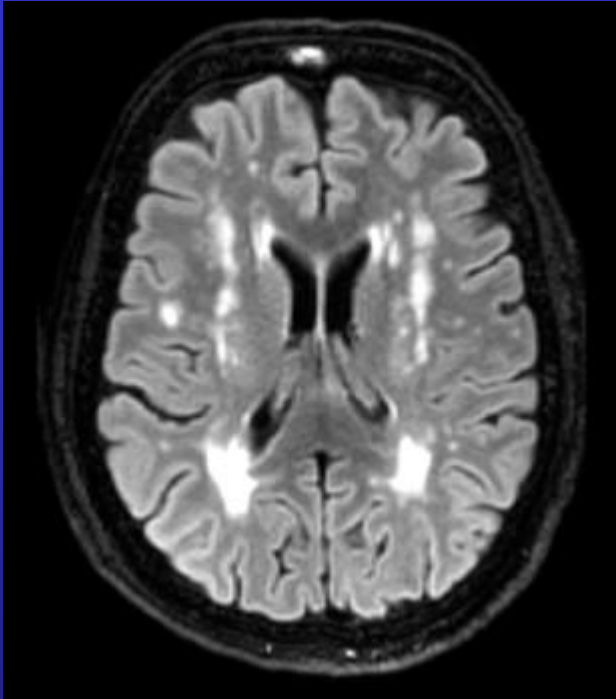




Insomnia, ansia e depressione



Processi neurodegenerativi e sonno





Comorbidità

Mental	Medical	Neurological	Substance use/dependence
Depressive disorders	Cardiovascular disorders	Neurodegenerative diseases	Alcohol
Bipolar disorders	Diabetes mellitus	Cerebrovascular diseases	Nicotine
Anxiety disorders	Chronic kidney diseases	Traumatic brain injury	Caffeine
Borderline personality disorder	Chronic obstructive pulmonary diseases	Multiple sclerosis	Tetrahydrocannabinol /marihuana
Posttraumatic stress disorder	Rheumatic disorders	RLS/PLMD	Opioids
Schizophrenia	Chronic pain	Fatal familial insomnia	“Designer” drugs
Substance use disorders	Any kind of malignant disorder		Cocaine
	SRBD/OSA		Amphetamines



Insomnia: diagnosi

- **Short-Term Insomnia Disorder**
- **Chronic Insomnia Disorder**
- **Other Insomnia Disorder**

Diagnostic Criteria (criteria A-E must be met)

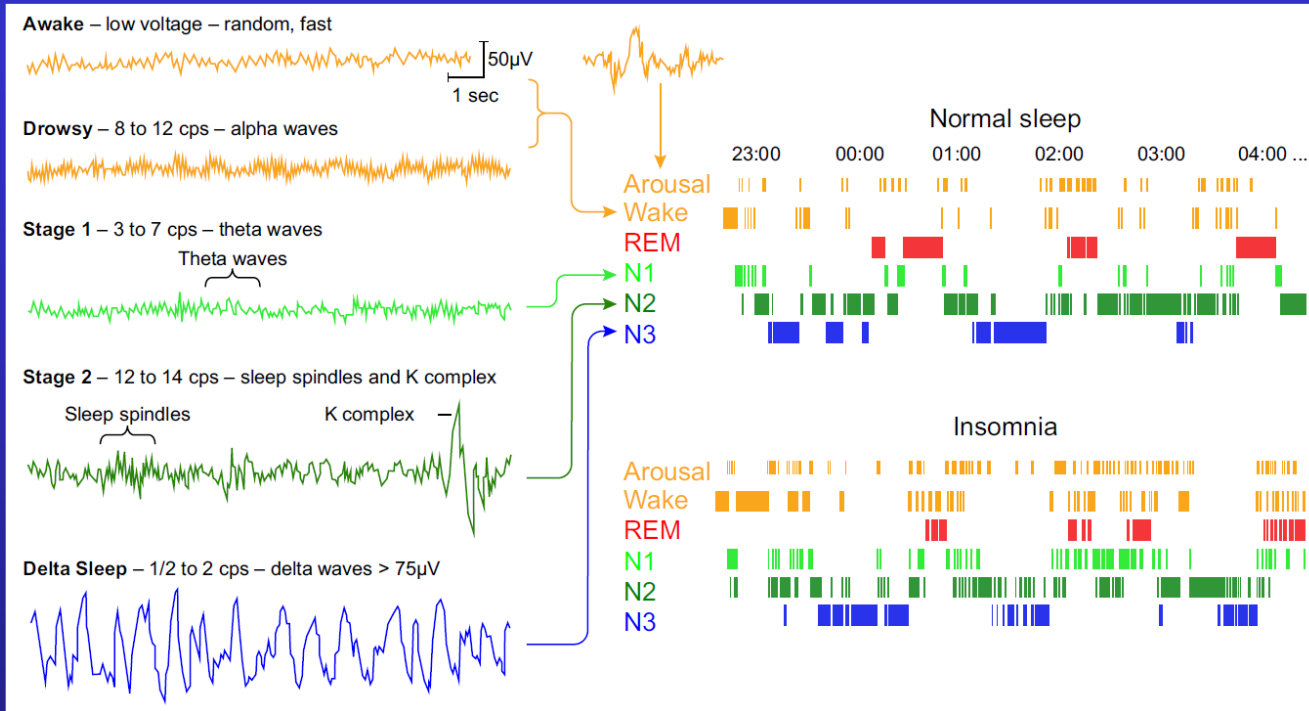
A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:

difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance to going to bed on appropriate schedule, difficulty sleeping without parent or caregiver intervention.

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

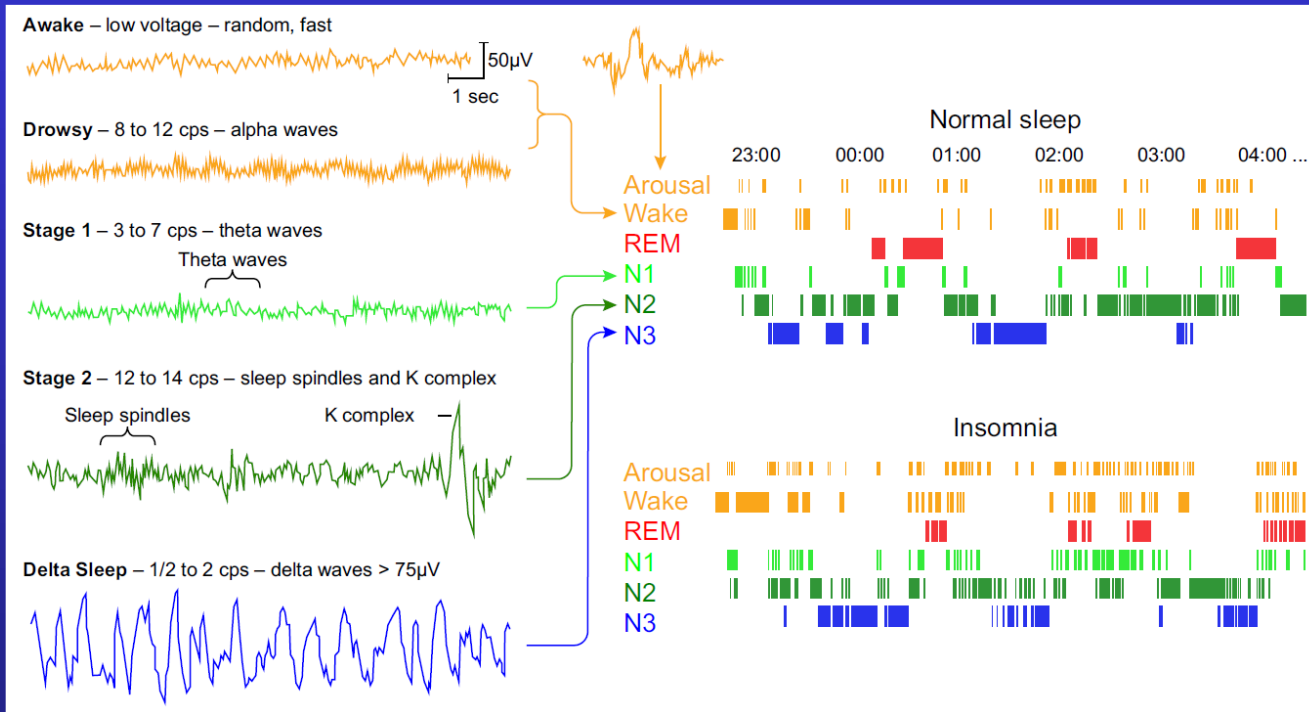
fatigue/malaise, attention, concentration, or memory impairment, impaired social, family, vocational, or academic performance, mood disturbance/irritability, daytime sleepiness, behavioral problems (e.g., hyperactivity, impulsivity, aggression), reduced motivation/energy/initiative, proneness for errors/accidents, concerns about or dissatisfaction with sleep.

PSG insomnia



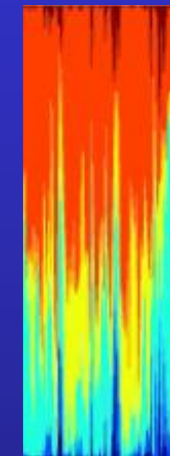
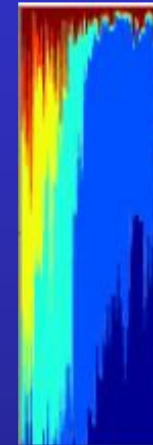


PSG insomnia

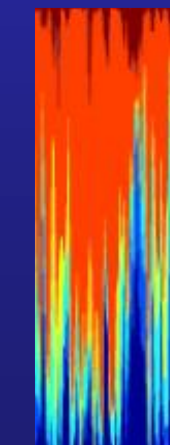
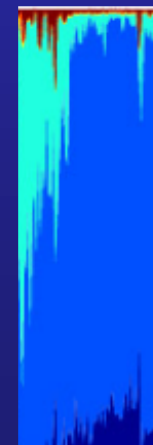


SWS

REM



ctrl



insomnia



ESRS guidelines 2023: therapies

Non farmacologica (CBTi)

Farmacologica



Non farmacologica (CBTi)

psicoeducazione

igiene del sonno

rilassamento

restrizione di sonno

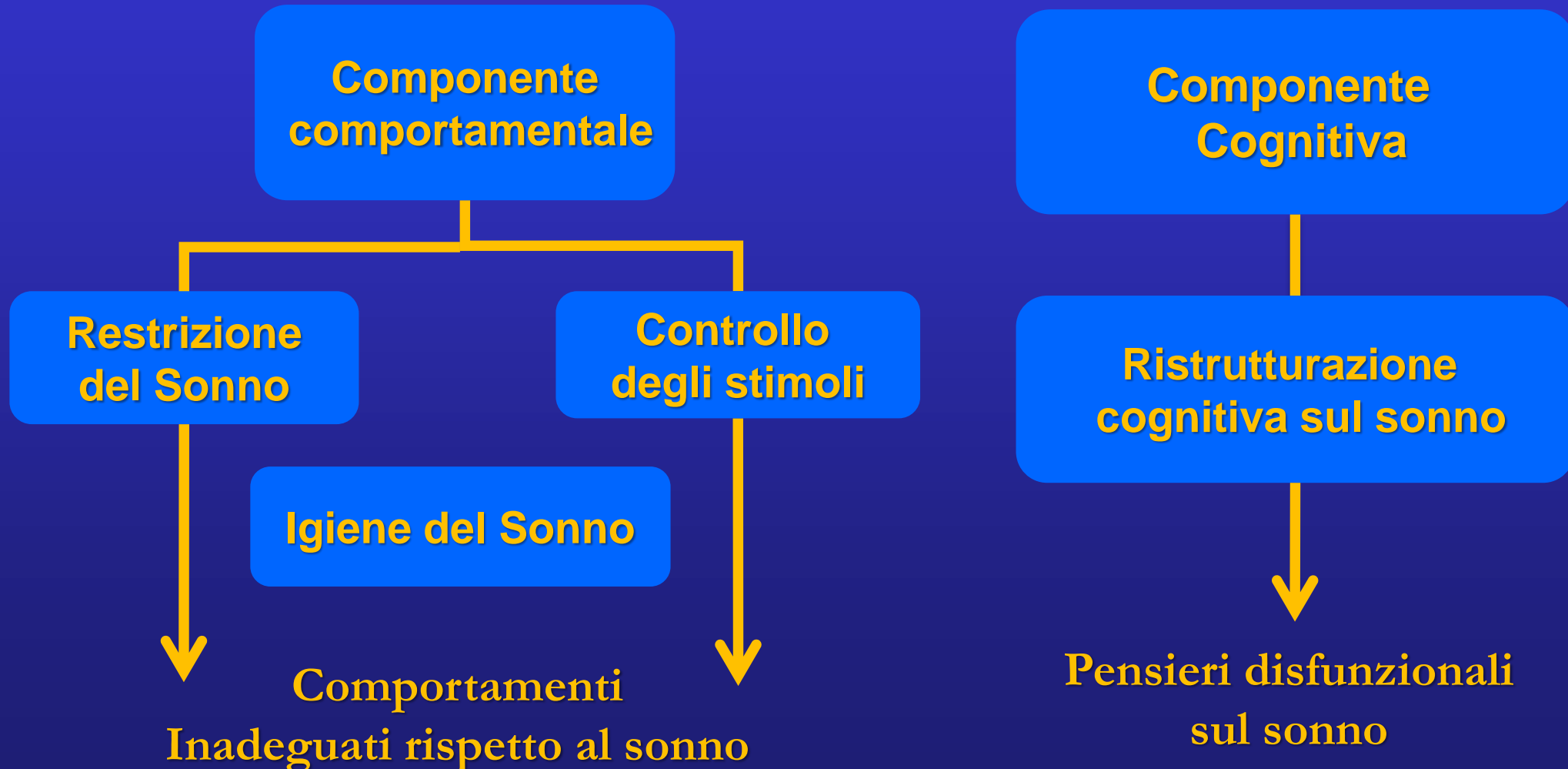
controllo dello stimolo

terapia cognitiva

Farmacologica

Cognitive-behavioural therapy for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age (including patients with comorbidities), either applied in-person or digitally (A).

Light therapy and exercise interventions may be useful as adjunct therapies to cognitive-behavioural therapy for insomnia (B).





Non farmacologica (CBTi)

When cognitive-behavioural therapy for insomnia is not sufficiently effective, a pharmacological intervention can be offered (A). Benzodiazepines (A), benzodiazepine receptor agonists (A), daridorexant (A) and low-dose sedating antidepressants (B) can be used for the short-term treatment of insomnia (≤ 4 weeks).

Longer-term treatment with these substances may be initiated in some cases, considering advantages and disadvantages (B). Orexin receptor antagonists can be used for periods of up to 3 months or longer in some cases (A). Prolonged-release melatonin can be used for up to 3 months in patients ≥ 55 years (B). Antihistaminergic drugs, antipsychotics, fast-release melatonin, ramelteon and phytotherapeutics are not recommended for insomnia treatment (A).

Farmacologica

benzodiazepine

non-BDZ

melatonine

daridorexant

antidepressivi

neurolettici

antistaminici

antiepilettici



GABA_A R-agonists : effectiveness

Benefit outcomes							
Individual drugs	oSOL	oTST	oWASO	sSOL	sTST	sWASO	Sleep quality
Estazolam	NA	NA	NA	26.23 (-1.85 to 54.32)	NA	15.50 (-7.90 to 38.90)	-0.62 (-1.17 to 0.06)
Temazepam	11.35 (-3.78 to 26.48)	63.65 (36.34 to 90.96)	-15.99 (-44.06 to 12.08)	-6.87 (-17.28 to 3.53)	21.41 (-0.71 to 43.53)	-8.04 (-23.21 to 7.12)	NA
Lormetazepam	-11.33 (-34.84 to 12.18)	8.86 (-41.29 to 59.01)	NA	-4.80 (-27.85 to 18.25)	12.00 (-46.94 to 70.94)	NA	-0.48 (-1.05 to 0.09)
Brotizolam	NA	NA	NA	25.83 (6.95 to 44.72)	18.28 (-3.93 to 40.49)	-12.00 (-26.98 to 2.98)	NA
Triazolam	9.55 (-4.01 to 23.11)	-3.22 (-23.20 to 16.77)	-22.17 (-46.11 to 1.77)	-13.33 (-30.15 to 3.48)	20.56 (-22.11 to 63.23)	26.66 (0.61 to 52.71)	-0.13 (-0.60 to 0.35)
Flurazepam	NA	NA	NA	3.67 (-8.28 to 15.61)	-23.86 (-61.66 to 13.94)	NA	-0.69 (-1.1 to -0.27)
Alprazolam	NA	NA	NA	-26.00 (-58.56 to 6.56)	42.00 (-0.37 to 84.37)	NA	NA
Nitrazepam	NA	-38.15 (-72.39 to -3.91)	NA	-29.63 (-56.47 to -2.78)	NA	NA	0.24 (-0.32 to 0.80)
Quazepam	NA	NA	NA	-72.43 (-171.05 to 26.19)	19.56 (-40.11 to 79.23)	-14.54 (-35.86 to 6.77)	NA
Midazolam	NA	NA	NA	-8.70 (-31.86 to 14.45)	20.21 (-27.01 to 67.43)	NA	NA
Loprazolam	NA	NA	NA	NA	NA	NA	NA
Flunitrazepam	NA	NA	NA	NA	NA	NA	NA

Benefit outcomes							
Individual drugs	oSOL	oTST	oWASO	sSOL	sTST	sWASO	Sleep quality
Eszopiclone	-16.64 (-25.33 to -7.95)	12.00 (-6.64 to 30.65)	-9.31 (-29.31 to 10.69)	-11.29 (-19.02 to -3.57)	34.83 (20.11 to 49.54)	-16.38 (-22.82 to -9.93)	-0.43 (-0.68 to 0.18)
Zopiclone	-16.27 (-28.55 to -3.98)	7.85 (-17.39 to 33.09)	-0.51 (-38.32 to 37.29)	-40.87 (-64.03 to -17.72)	13.50 (-44.48 to 71.48)	NA	0.16 (-0.40 to 0.72)
Zolpidem	-4.98 (-11.97 to 2.01)	28.42 (14.41 to 42.42)	-15.40 (-25.56 to -5.24)	-5.16 (-10.46 to 0.14)	20.36 (10.38 to 30.34)	-12.67 (-18.81 to -6.53)	-0.13 (-0.24 to 0.01)
Zaleplon	NA	-1.25 (-20.27 to 17.78)	NA	-15.00 (-24.23 to -5.77)	4.06 (-14.25 to 22.37)	NA	-0.05 (-0.22 to 0.12)

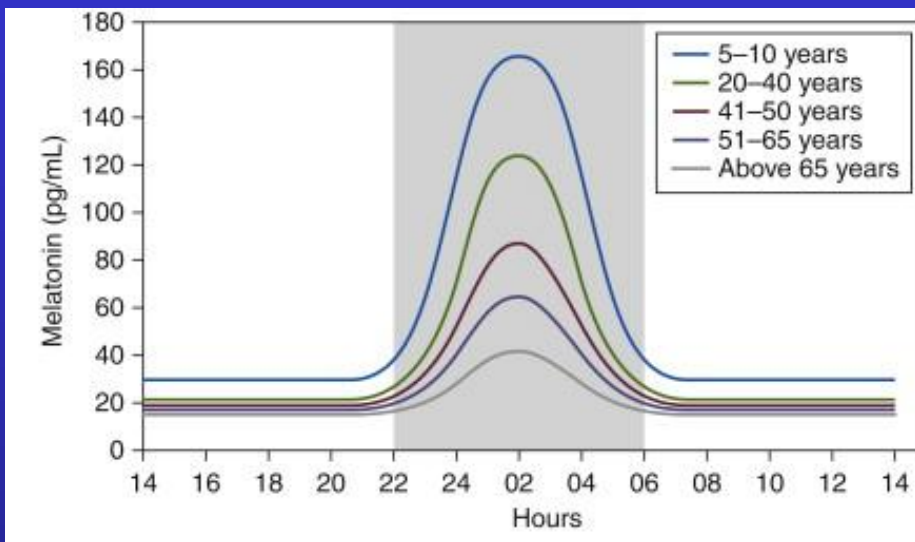


GABA_A R-agonists: safety

Individual drugs	Harm outcomes		
	Any AE	Drug-related AE	Discontinued owing to AE
Estazolam	0.74 (0.44 to 1.23)	NA	0.62 (0.21 to 1.84)
Temazepam	1.20 (0.96 to 1.49)	NA	1.65 (0.62 to 4.39)
Lormetazepam	2.28 (1.06 to 4.92)	0.33 (0.08 to 1.44)	NA
Brotizolam	1.04 (0.54 to 2.01)	NA	NA
Triazolam	1.21 (1.00 to 1.46)	NA	1.69 (0.88 to 3.27)
Flurazepam	0.90 (0.58 to 1.41)	NA	1.04 (0.42 to 2.56)
Alprazolam	NA	NA	NA
Nitrazepam	NA	NA	0.87 (0.20 to 3.71)
Quazepam	NA	NA	NA
Midazolam	NA	NA	2.48 (0.63 to 9.85)
Loprazolam	2.28 (1.06 to 4.92)	NA	0.92 (0.41 to 2.10)
Flunitrazepam	NA	NA	1.22 (0.35 to 4.22)

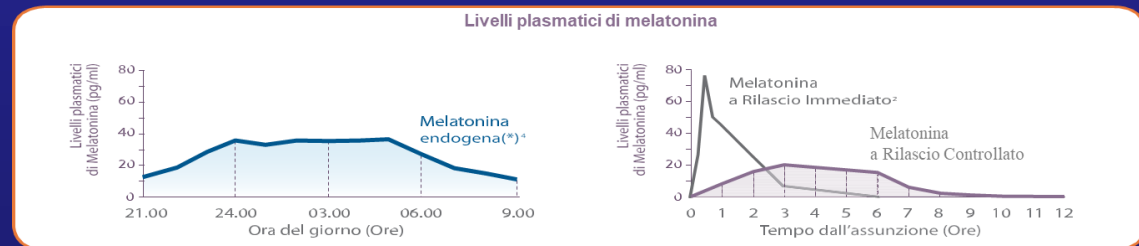
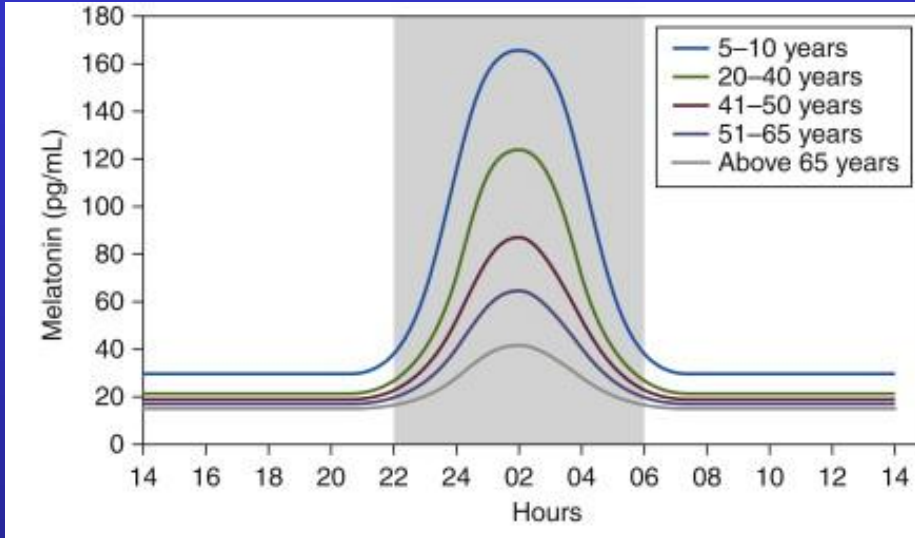
Individual drugs	Harm outcomes		
	Any AE	Drug-related AE	Discontinued owing to AE
Eszopiclone	1.11 (1.04 to 1.19)	NA	1.36 (1.03 to 1.79)
Zopiclone	1.16 (0.98 to 1.37)	NA	1.72 (1.05 to 2.81)
Zolpidem	1.11 (1.04 to 1.18)	2.05 (1.37 to 3.05)	1.44 (1.02 to 2.04)
Zaleplon	0.99 (0.92 to 1.08)	NA	1.10 (0.67 to 1.83)

Melatonina



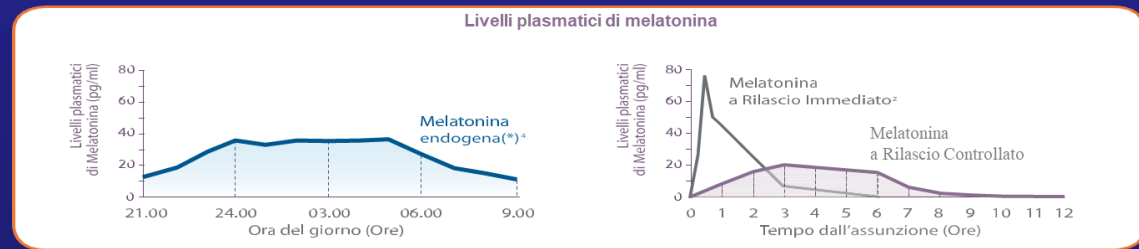
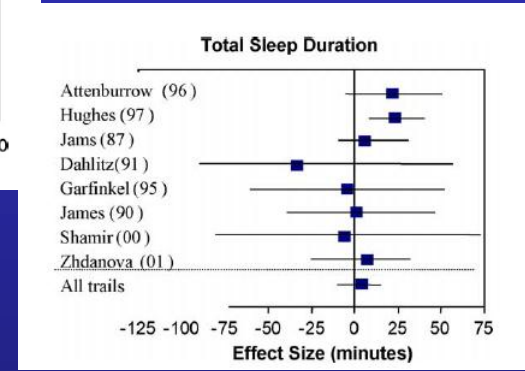
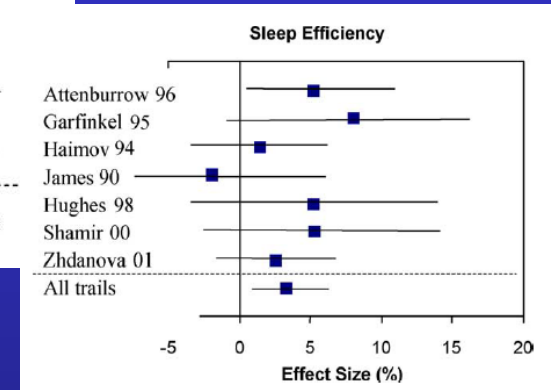
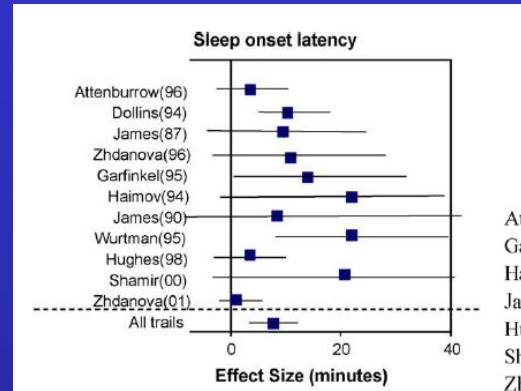
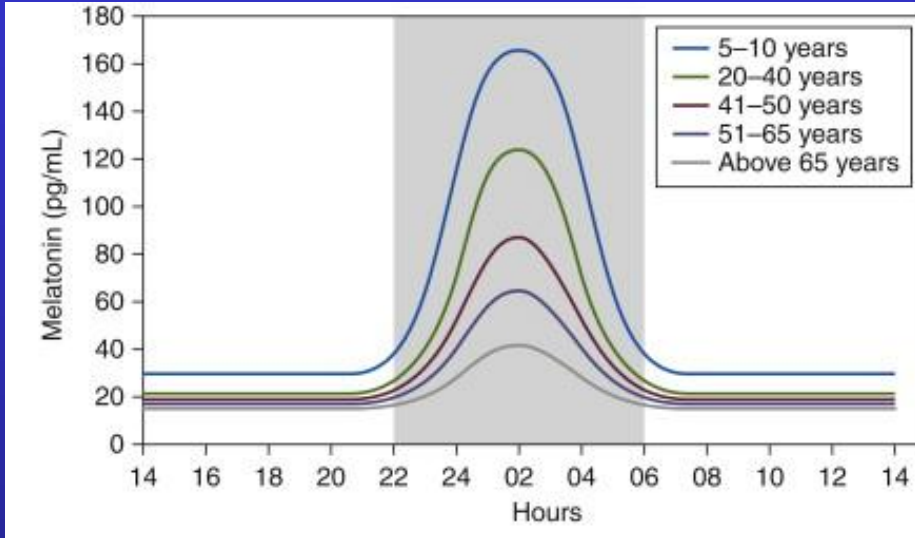


Melatonina: effetti sul sonno



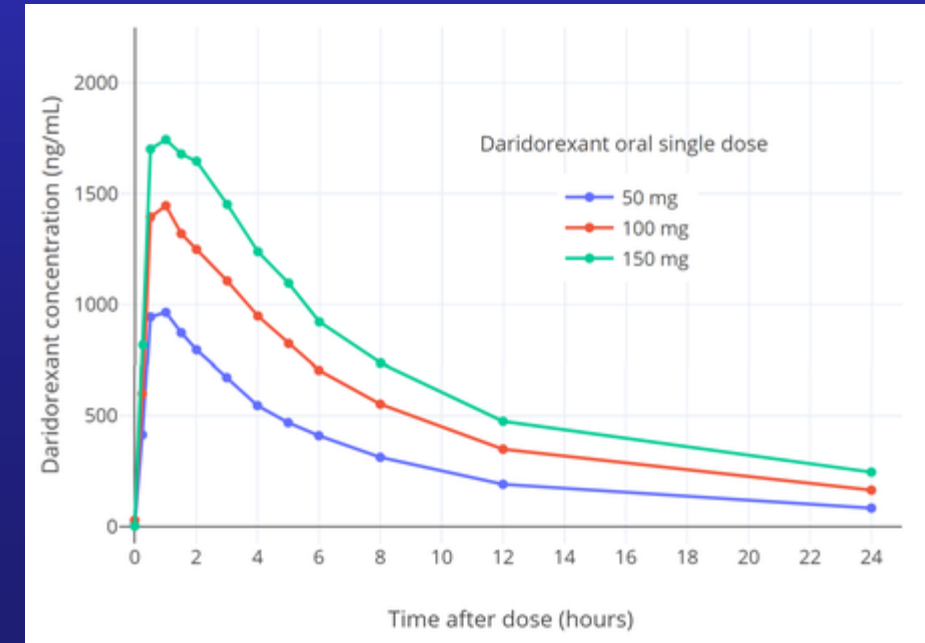
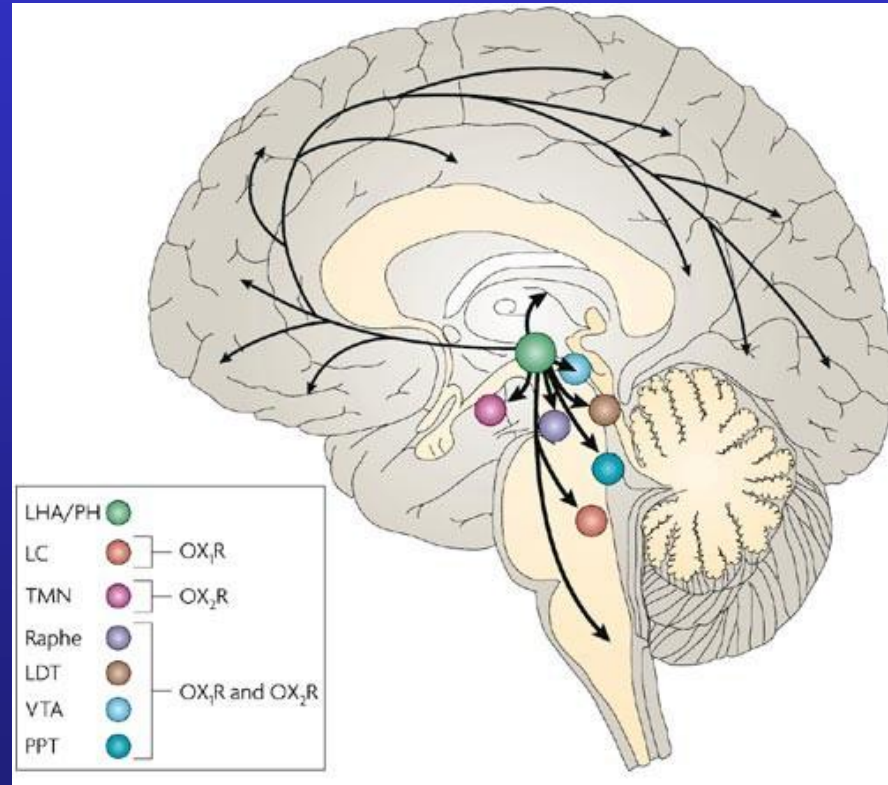
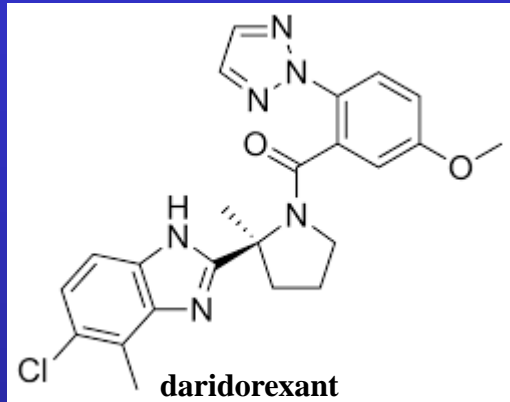


Melatonina: effetti sul sonno



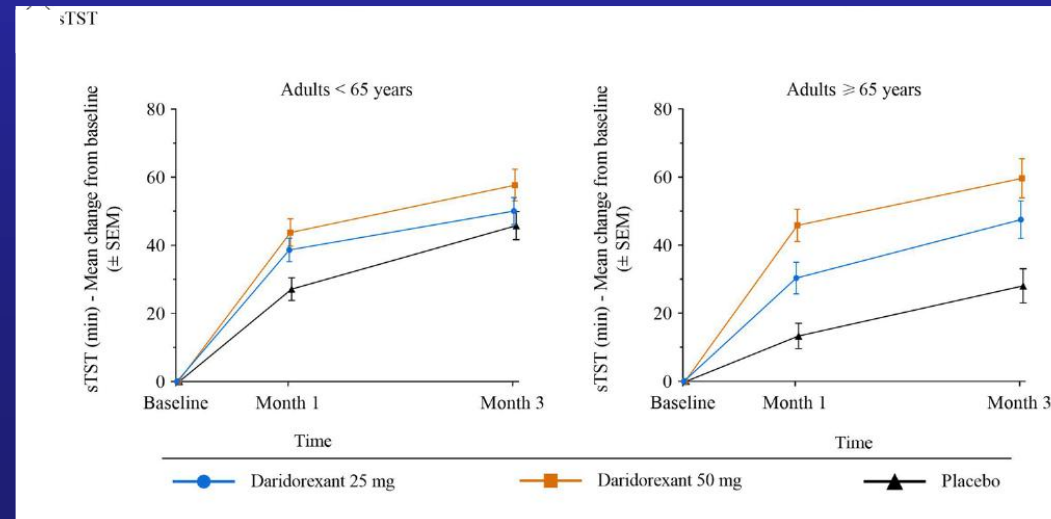
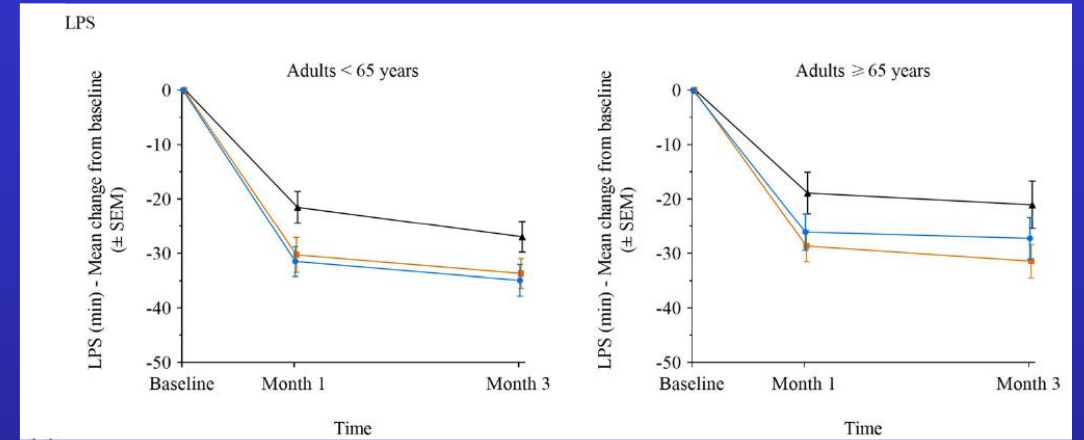
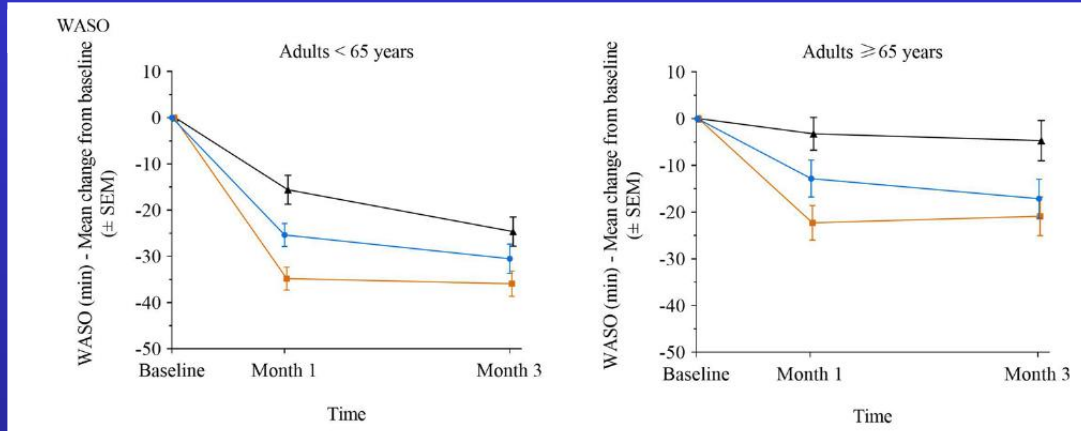


Dual OX-R antagonists: daridorexant



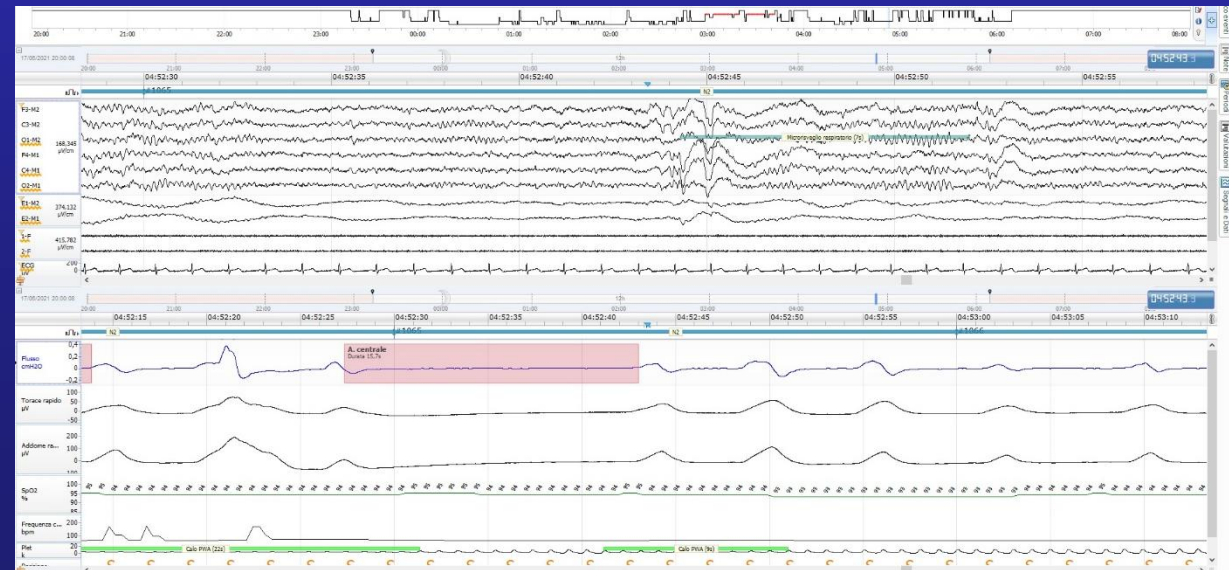
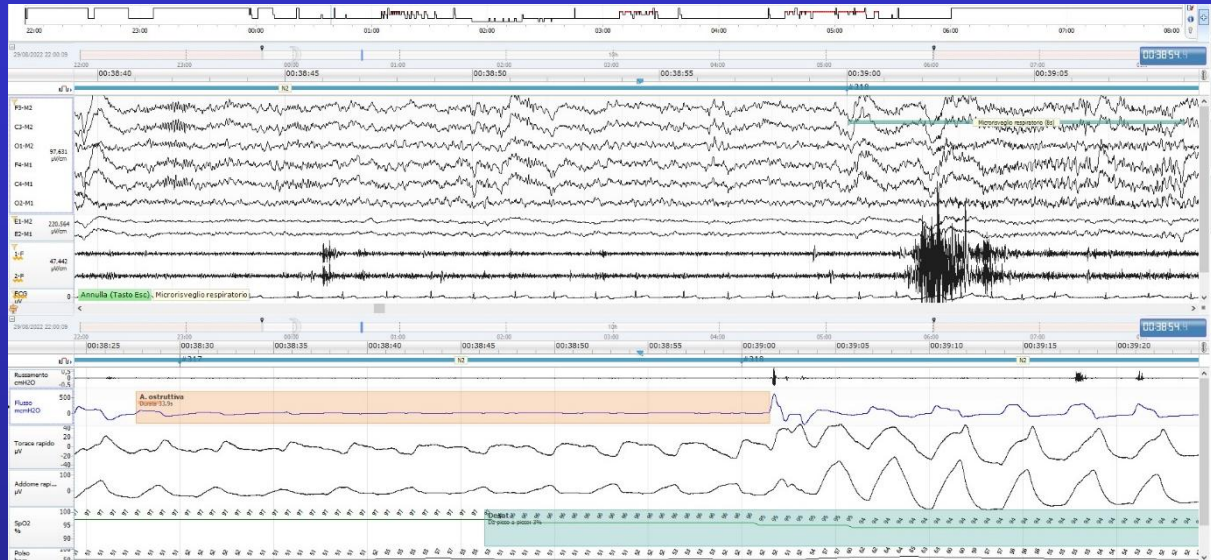


Dual OX-R antagonists



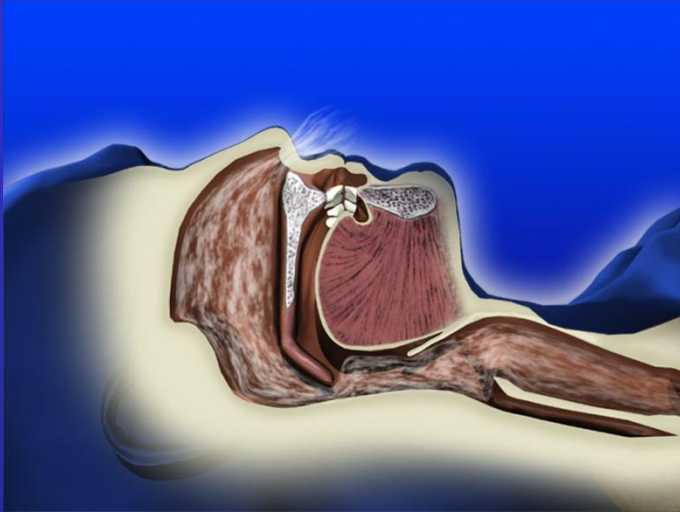


Eventi respiratori nel sonno





Fattori predisponenti/slatentizzanti OSAS



The Mallampati Score

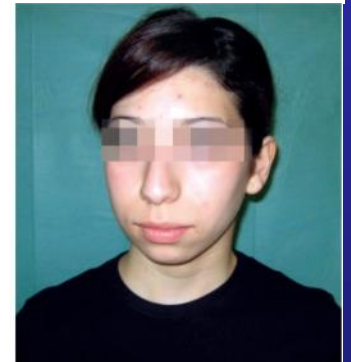


CLASS I
Complete
visualization of
the soft palate

CLASS II
Complete
visualization
of the uvula

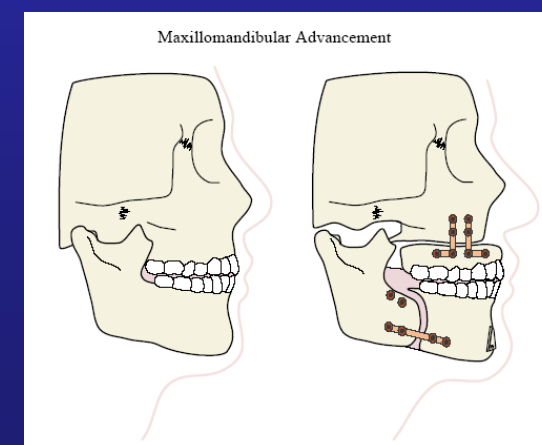
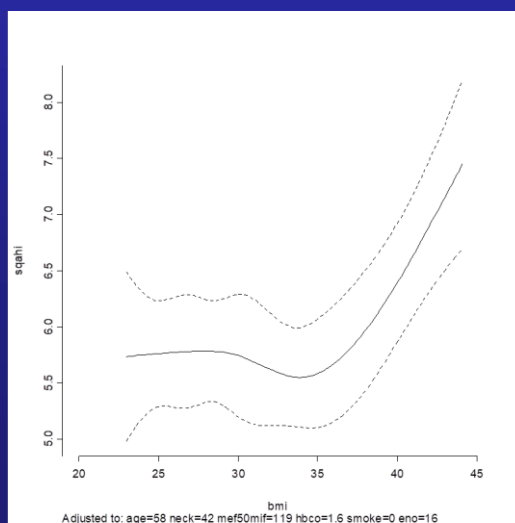
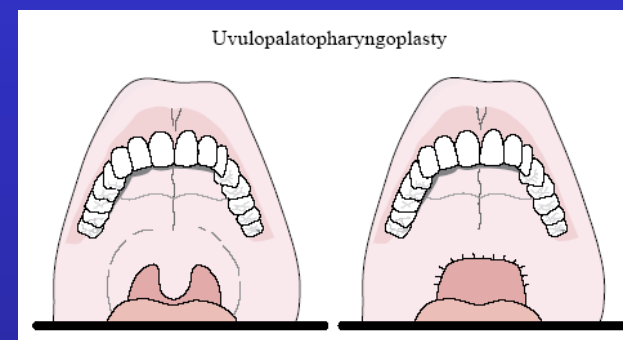
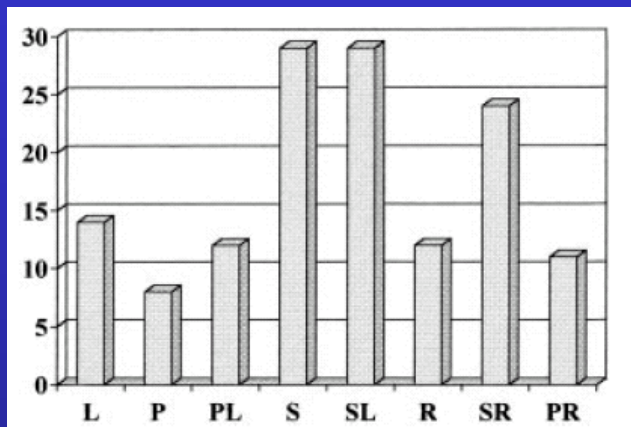
CLASS III
Visualization
of only the
base of the uvula

CLASS IV
Soft palate
is not
visible at all



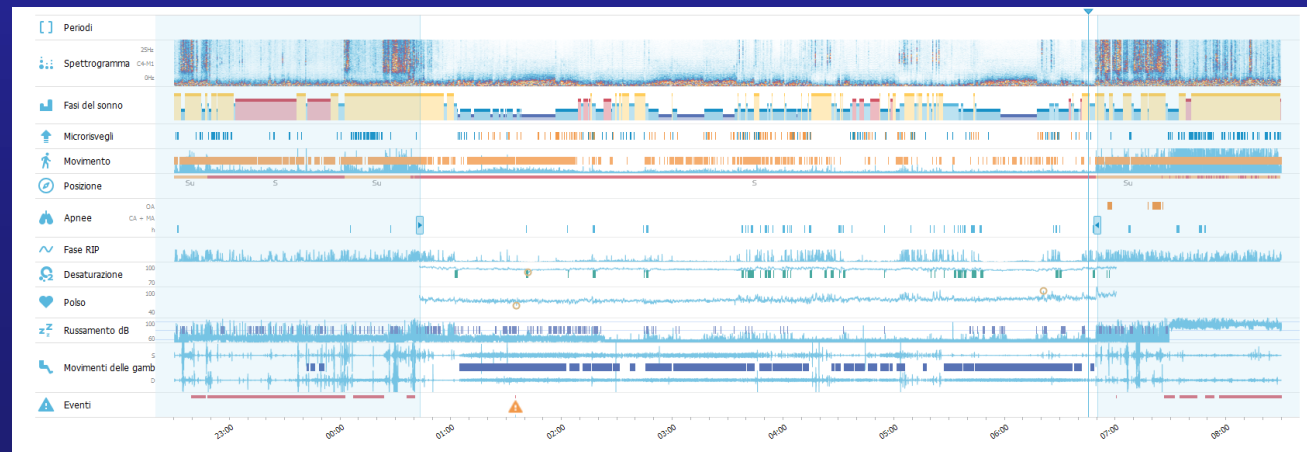
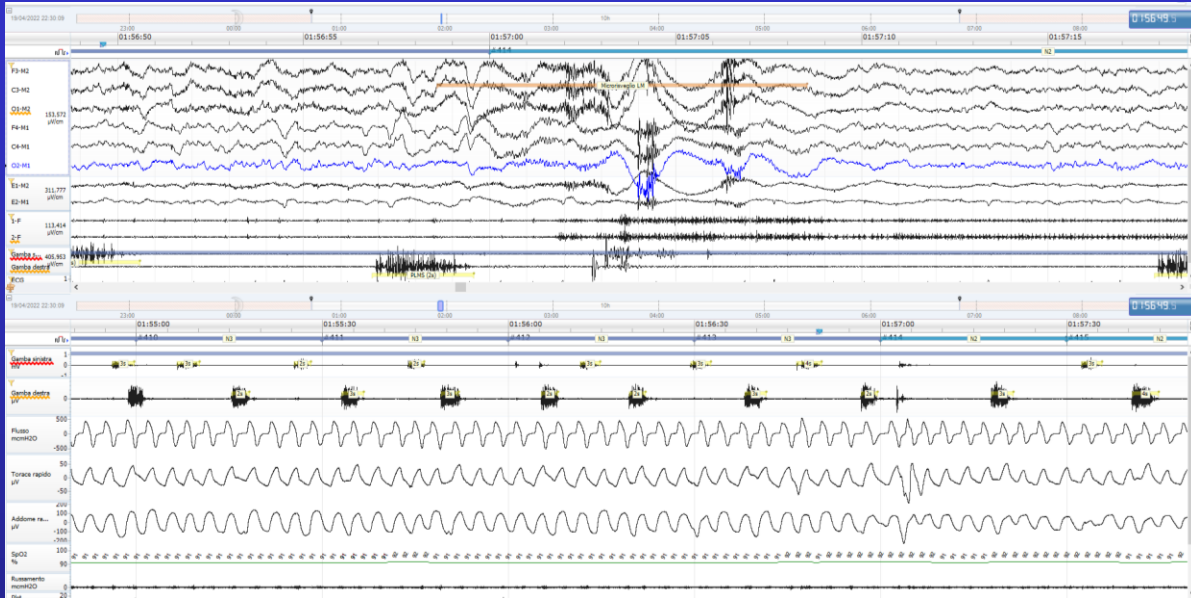


OSAS: terapia

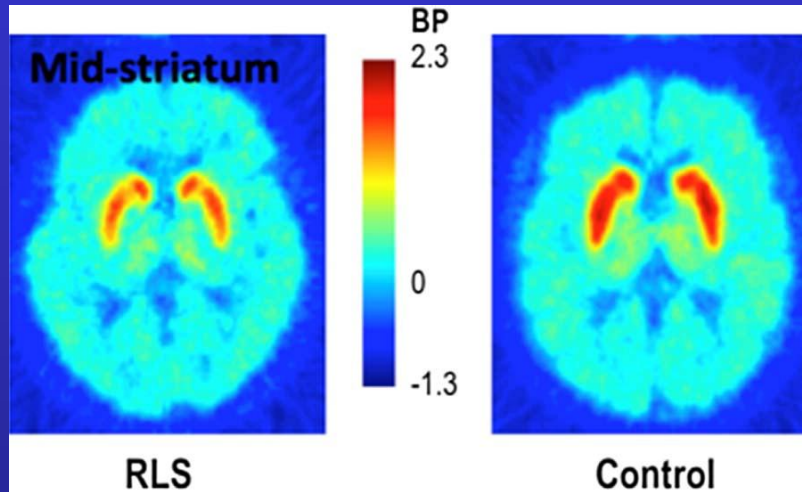




RLS and PLMD



RLS e dopamina



- ↓ legame con il recettore D2 postsinaptico striatale in studi SPECT (IBZM) o PET (raclopride)
(disfunzione dopaminergica post-sinaptica)
- ↓ lieve della captazione di ^{18}F -DOPA a livello striatale presinaptico
(disfunzione dopaminergica pre-sinaptica)



RLS e PLMD secondari

Sleep Medicine Reviews, Vol. 3, No. 2, pp 147–158, 1999

**SLEEP
MEDICINE**
reviews

REVIEW ARTICLE

Secondary periodic limb movement disorder and restless legs syndrome

R. M. Rijsman and A. W. de Weerd

Condizioni di rischio

- **insufficienza renale**
- **ipotiroidismo**
- **quadri carenziali**
- **m. di Parkinson**
- **polineuropatie**
- **radiculopatie**
- **siringomielia**

Diagnostica strumentale

- **Hb, HCT, MCV, MCH, MCHC, Fe, ferritina, Mg, Na, K, urea, creatinina, B12, ac. folico, 25OH vit D, TSH reflex**
- **PG, PSG**
- **EMG (VC)**
- **RNM**



RLS: terapia

The American Journal of Medicine (2007) Vol 120 (1A), S22–S27



THE AMERICAN
JOURNAL of
MEDICINE®

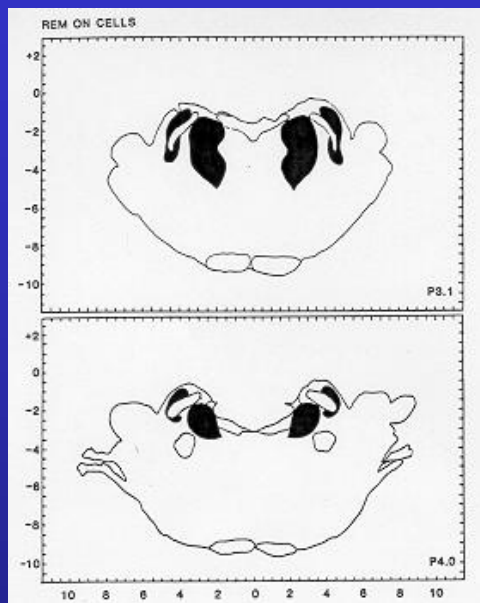
Current Guidelines and Standards of Practice for Restless Legs Syndrome

Wayne A. Hening, MD, PhD

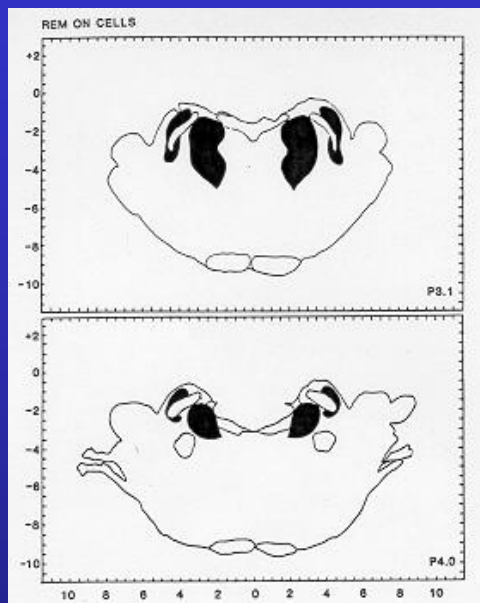
Department of Neurology, UMDNJ–Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

- Intermittent RLS symptoms
 - Medications that can be taken as needed
 - Levodopa with decarboxylase inhibitor (carbidopa or benserazide)
 - Mild- to moderate-strength opioid (codeine, propoxyphene, tramadol, hydrocodone, oxycodone)
 - Sedative-hypnotics
 - Dopamine agonist: low dose, if tolerated
- Daily RLS symptoms
 - Dopamine agonists
 - Nonergoline
 - Ropinirole (0.25–6 mg/day)
 - Pramipexole (0.125–1.5 mg/day)
 - Ergoline
 - Pergolide (0.10–1.0 mg/day)
 - Anticonvulsants
 - Gabapentin (300–2,700 mg/day)
 - Opioids
 - Tramadol (100–400 mg/day)
 - Hydrocodone (5–20 mg/day)
 - Oxycodone (5–20 mg/day)
 - Extended-release formulations
 - Benzodiazepines
 - Clonazepam (0.5–4 mg/day)

Parasomnia: RBD



Parasomnia: RBD



Sistema glinfatico e sonno



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Sleep fragmentation affects glymphatic system through the different expression of AQP4 in wild type and 5xFAD mouse models

Valeria Vasciaveo^{1,2}, Antonella Iadarola³, Antonino Casile⁴, Davide Dante², Giulia Morello^{1,2}, Lorenzo Minotta², Elena Tamagno^{1,2}, Alessandro Cicolin¹ and Michela Guglielmotto^{1,2*}

