Curso Teórico-Práctico

"Bases Neurobiológicas del Sueño"

Quinta edición-2017

Departamento de Fisiología - Facultad de Medicina

Aspectos farmacológicos del sueño: hipnóticos y activadores

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Noviembre 2017

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AGENDA DE LA PRESENTACIÓN

INTRODUCCIÓN:

HIPNÓTICOS: bioquímica y farmacología

ACTIVADORES: bioquímica y farmacología

USOS EN LA PRÁCTICA CLÍNICA:

DESARROLLOS FUTUROS:

CONCLUSIONES:

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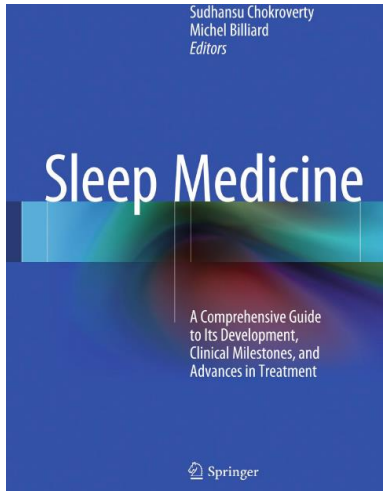
Sleep Medicine in Latin America

As it has been the case in North America and even more in Europe, basic animal and human research has preceded the development of sleep medicine in Latin America. In the 1960s, pioneering research in those fields was conducted by Raul Hernandez Peon (Neurophysiology) in Mexico and Jaime Monti (Pharmacology) in Uruguay. In the 1970s, Rene Drucker Colin (Neurophysiology) in Mexico, Daniel Cardinali (Neuroendocrinology) in Argentina, Sergio Tufik (Psychobiology) in Brazil, and Ricardo Velluti (Neurophysiology) in Uruguay conducted similar research



S. Chokroverty, M. Billiard (eds.), *Sleep Medicine*, Springer 2015


LA SOCIEDAD
24/7

Stress and Sleepiness in the 24-h Society

The Context

The "24-h Society" is a step ahead toward a social organization where time constraints are no longer "restricting" the humans, who feel free to have rest, work, and leisure at whatever time they want.

The natural light-dark cycle, which was only marginally affected by the fire discovery, has been progressively suppressed by electricity and electronics. This has also changed the space and time relationships with the environment and among the humans.

The "24-h Society" is characterized by increasing conflicts between the physiological "circadian" (*circa diem*: about 24 h) structure of the biological functions and the social constraints associated with both work and leisure activities, where the sleep/wake cycle is more and more losing its strict association with the dark/light alternation

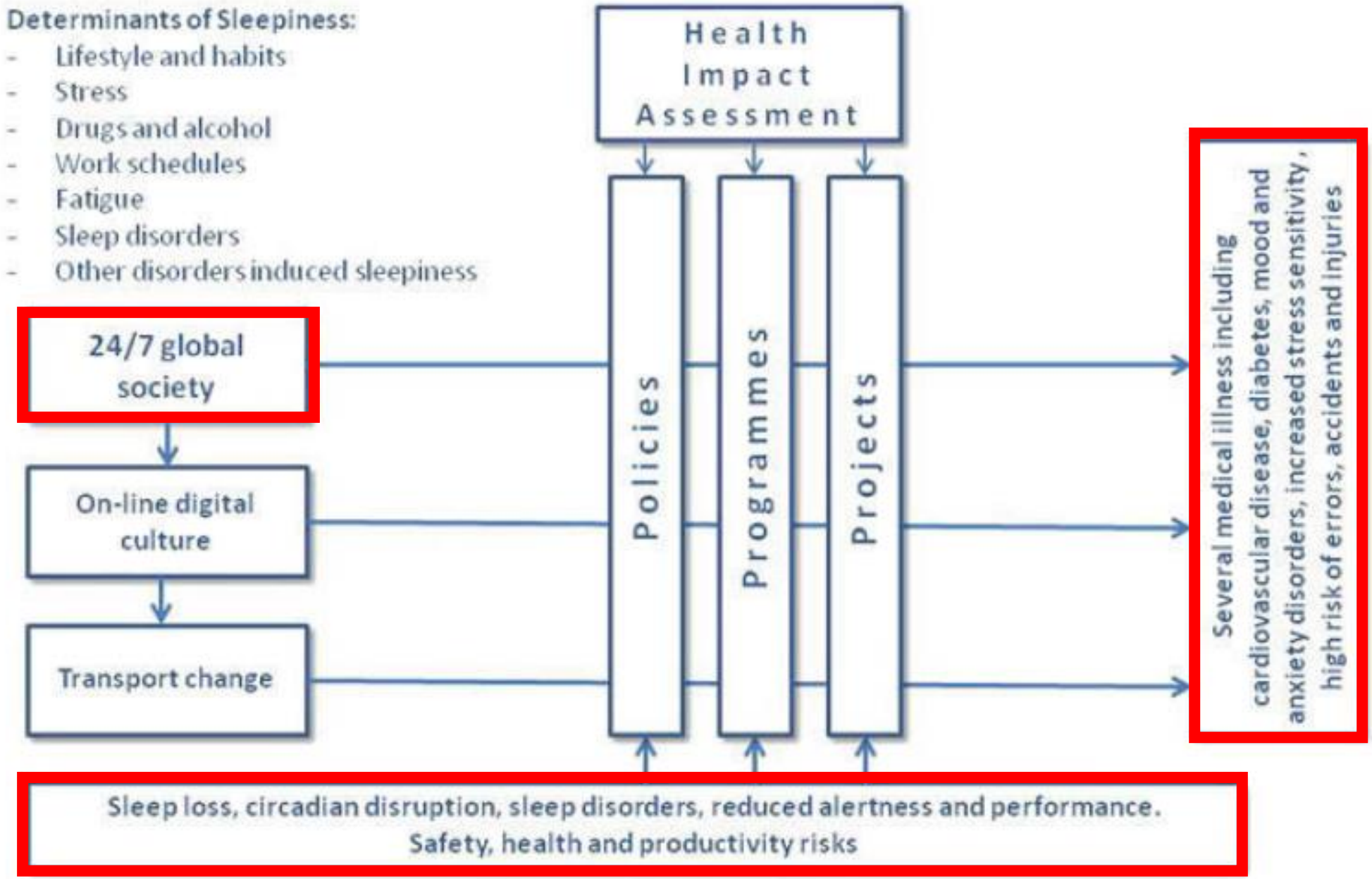
S. Garbarino et al. (eds.), *Sleepiness and Human Impact Assessment*, Springer-Verlag Italia 2014

Stress and Sleepiness in the 24-h Society

There is an increasing evidence of reduced rest and sleep periods not only related to irregular working hours (e.g., shift and night work), but also due to a misuse of free/spare time connected with an incessant and very tempting offer of amusements, musical events, sport performances, TV programs, internet world.

S. Garbarino et al. (eds.), *Sleepiness and Human Impact Assessment*, Springer-Verlag Italia 2014

Sleepiness and 24-h Society



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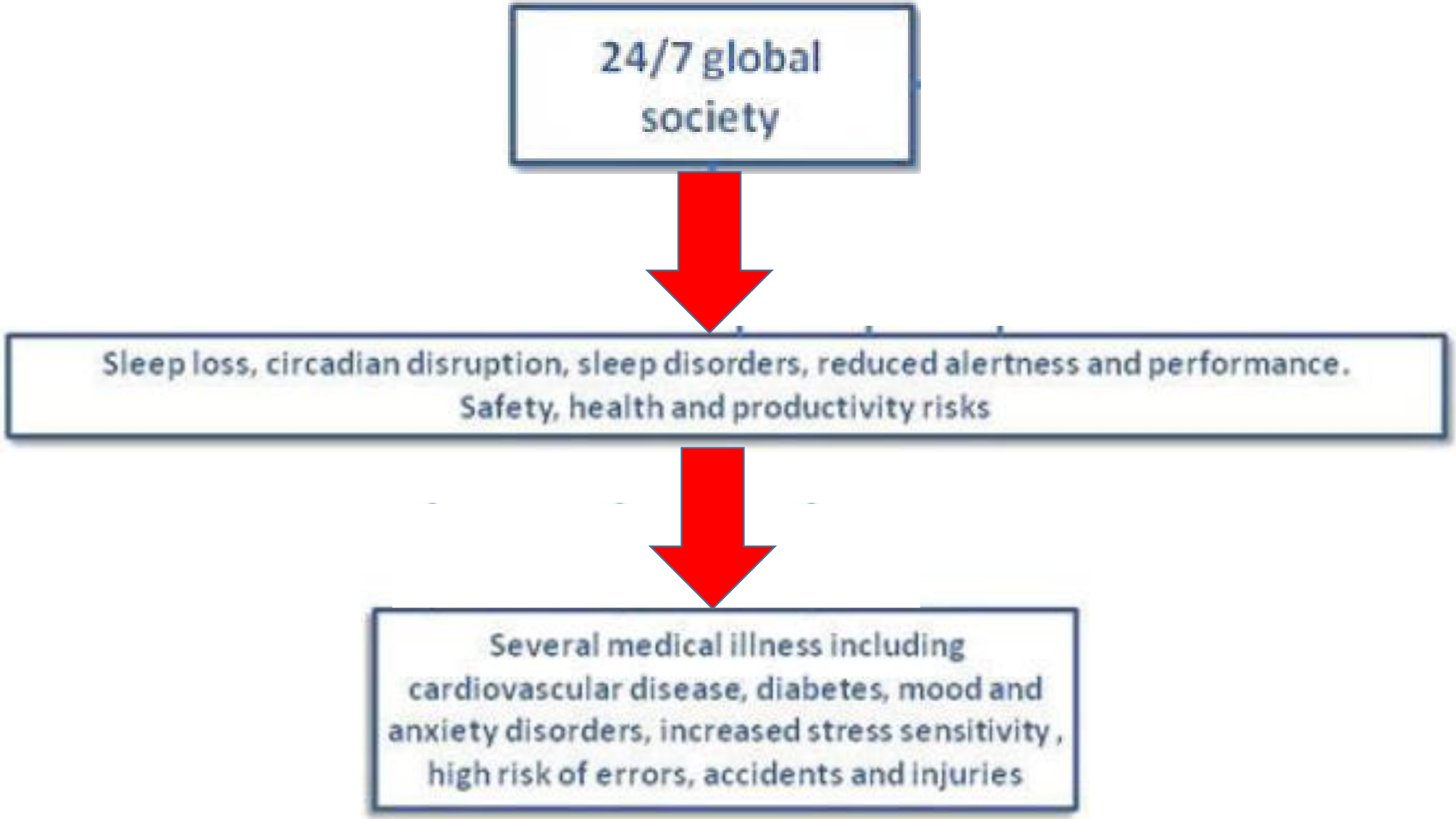

24/7 global society
Sleep loss, circadian disruption, sleep disorders, reduced alertness and performance.
Safety, health and productivity risks
Several medical illness including cardiovascular disease, diabetes, mood and anxiety disorders, increased stress sensitivity , high risk of errors, accidents and injuries

Evolution of circadian rhythms: from bacteria to human

- In higher animals such as **humans**, the periodicity of circadian rhythms is most prominently expressed as the **sleep–wake cycle**.
- Continued long-term disturbances in a sleep–wake cycle of higher animals have been linked to several disorders ranging from reduced cognitive ability to a higher incidence of cancers.

Sleep Medicine (2017)

EXPOSICIÓN A LA LUZ EN LA EVOLUCIÓN HUMANA

- **Professor George Brainard, director of the Light Research Program at Philadelphia's Jefferson Medical College said: "Humans evolved on a planet without electric light over thousands and thousands of generations.**
- **The body is designed to be alert and awake during daytime hours and to sleep at night.**
- **Now we have a 24/7 society that isn't in harmony with our biological design."**

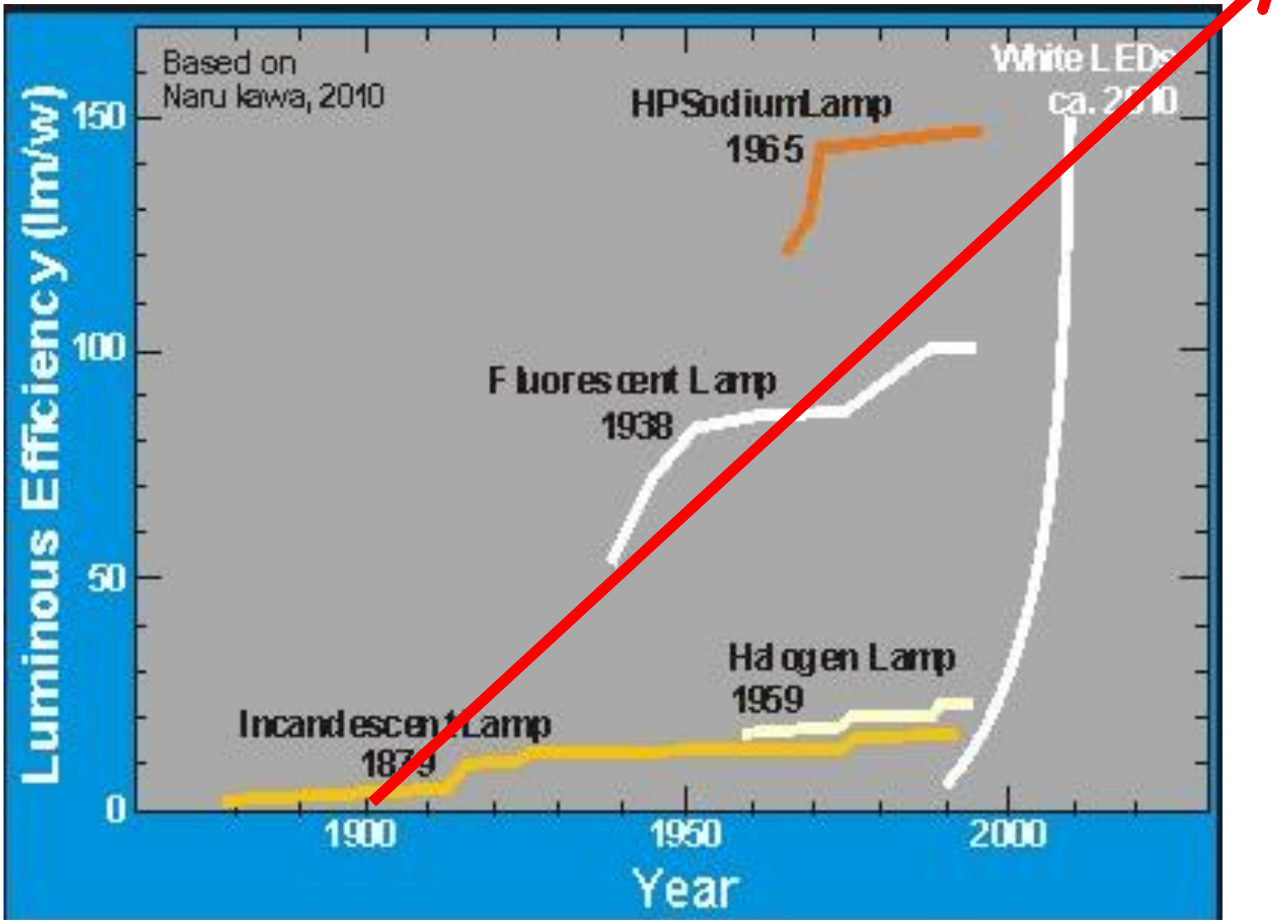
B. Mizon, *Light Pollution: Responses and Remedies*, Springer Science+Business Media New York 2012

EXPOSICIÓN A LA LUZ EN LA EVOLUCIÓN HUMANA

- **For humans, temporal organization of physiology is equally important for health and wellness.**
- **Over the past century, the boundaries of day and night have been obscured by the widespread adoption of electric light at night.**
- **Circadian disruption has become prevalent among humans.**
- **A growing body of ecological research points to nighttime lighting near urban areas as a major disruption to human life.**

B. Mizon, *Light Pollution: Responses and Remedies*, Springer Science+Business Media New York 2012

EL SER HUMANO ESTÁ EXPUESTO A UNA CRECIENTE INTENSIDAD LUMÍNICA



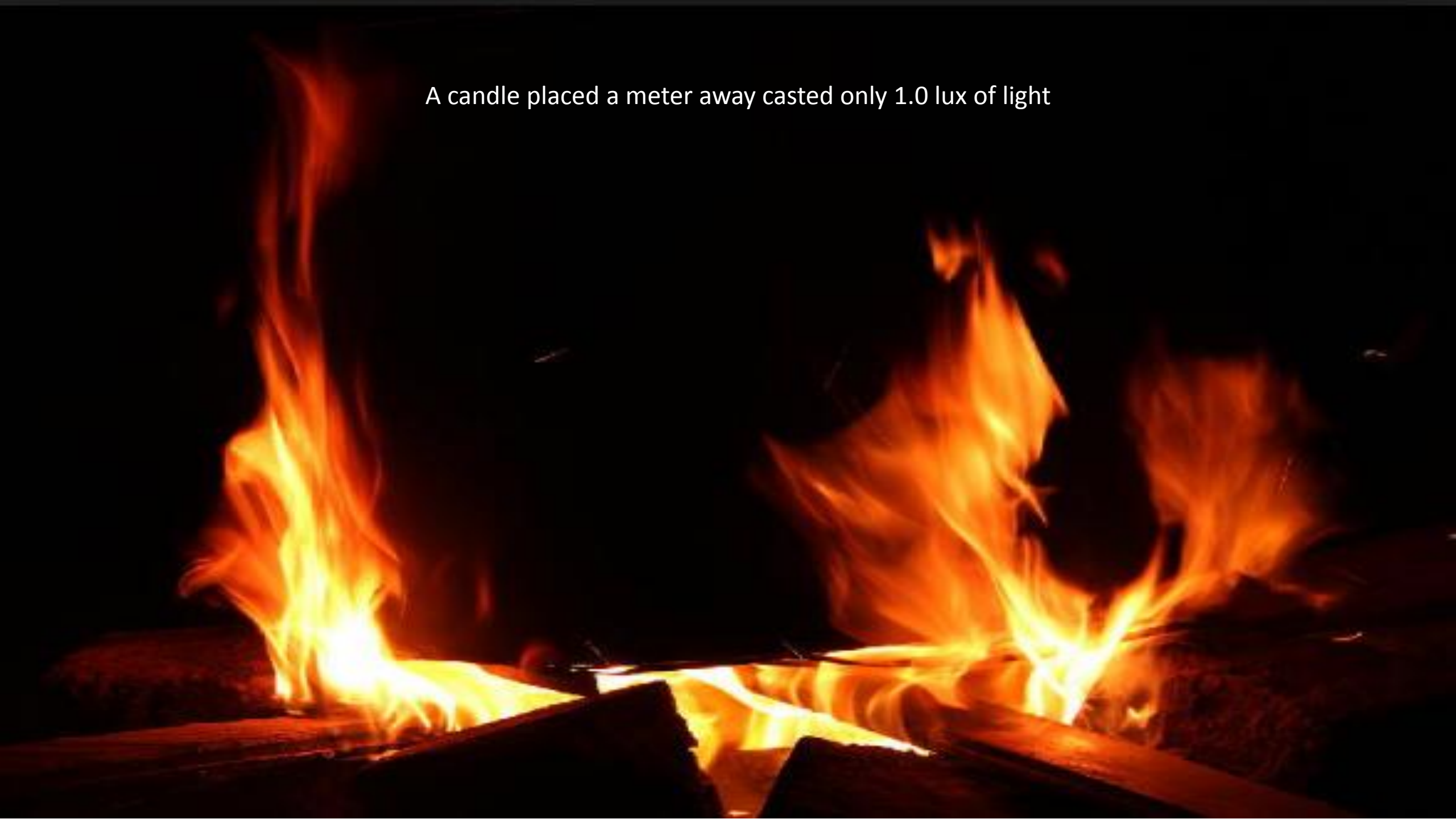
Examples of nighttime light sources and their approximate intensities

Light source	*Intensity (lux)* 1 lux =1 lumen/m²
Overcast night sky	0.00003–0.0001
Clear starry night	0.001
Full moon	0.1–0.3
Urban sky glow	0.15
Residential side street	5
Lighted parking lot	10
Main road street lighting	15
9.7 Inch tablet computer	40
Smartphone	>40 blux[a]
ICU step-down unit	1.3–47.3
24 Inch LED computer screen	~100
Intensive care unit (ICU)	190.5
Most homes	100–300

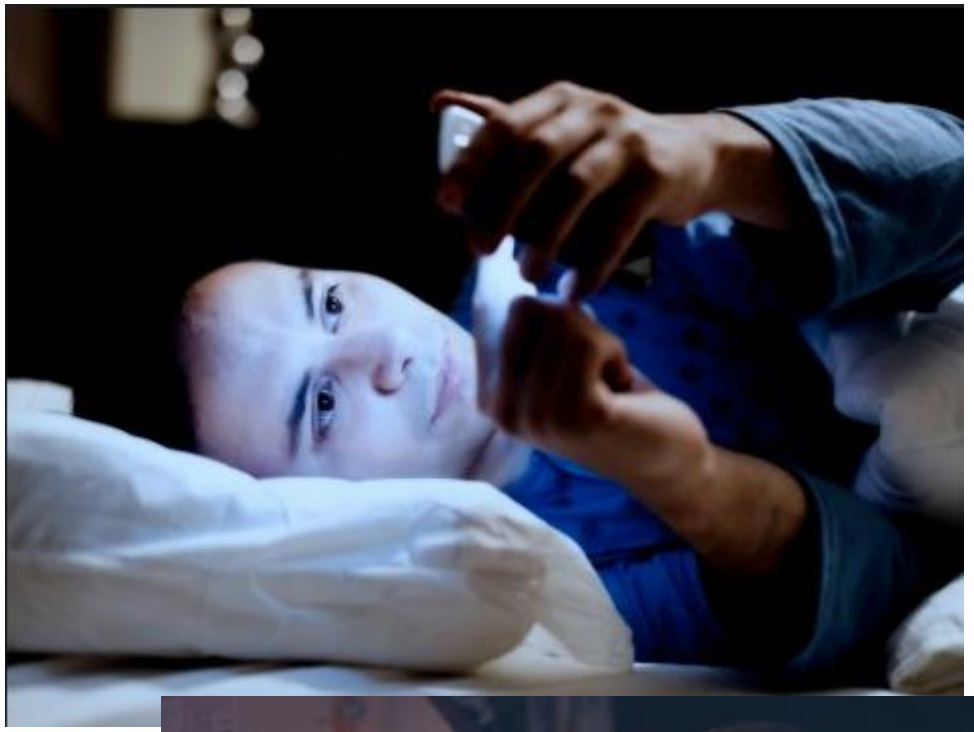
>1 millón

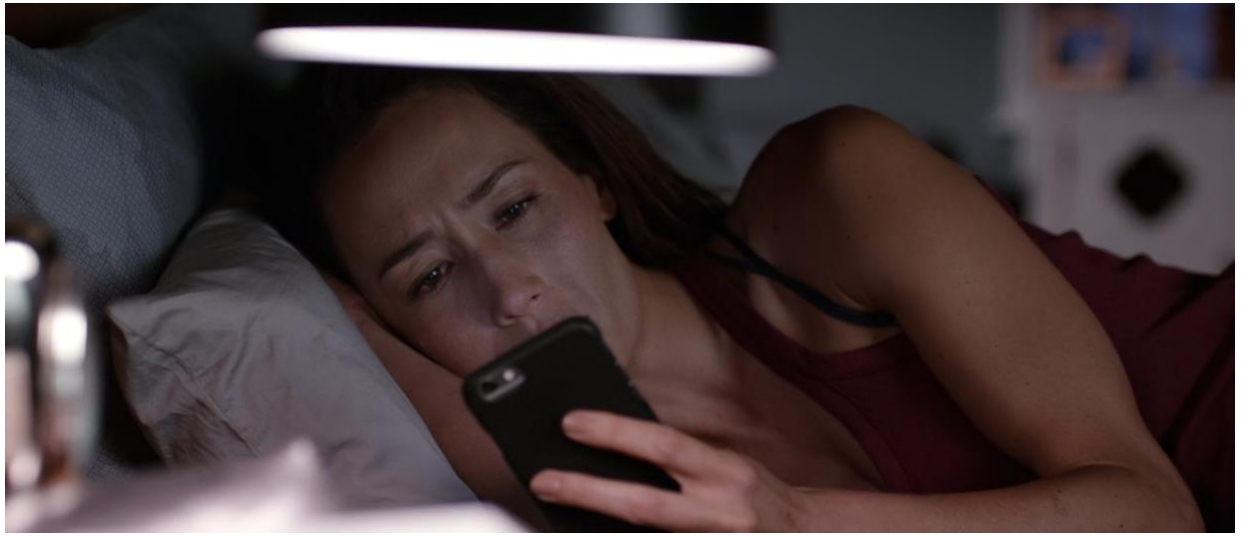
[a]Blux is a weighted measure of light intensity based on circadian-responsive wavelengths.

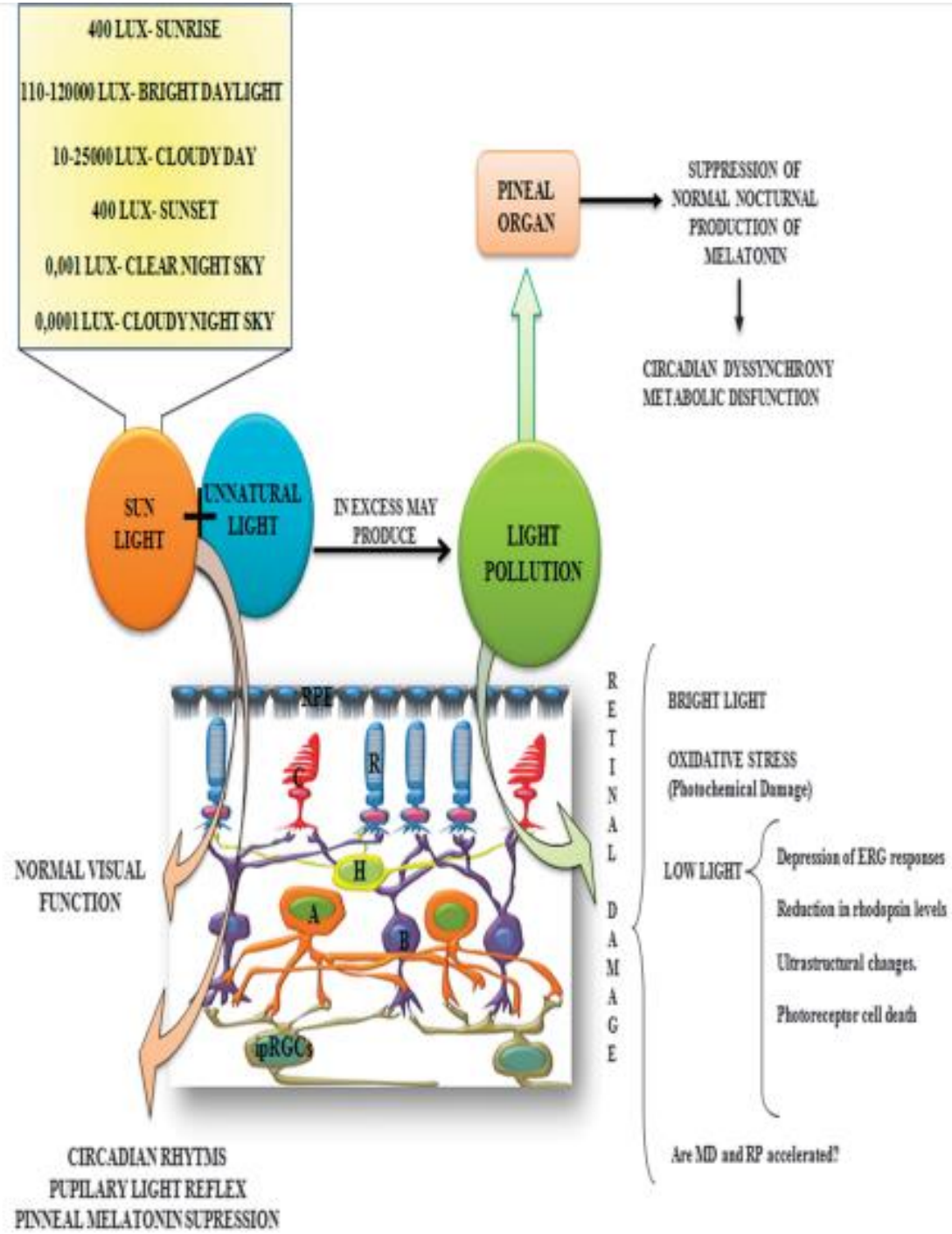
Translational Psychiatry (2017) **7**


A candle placed a meter away casted only 1.0 lux of light


Light Pollution

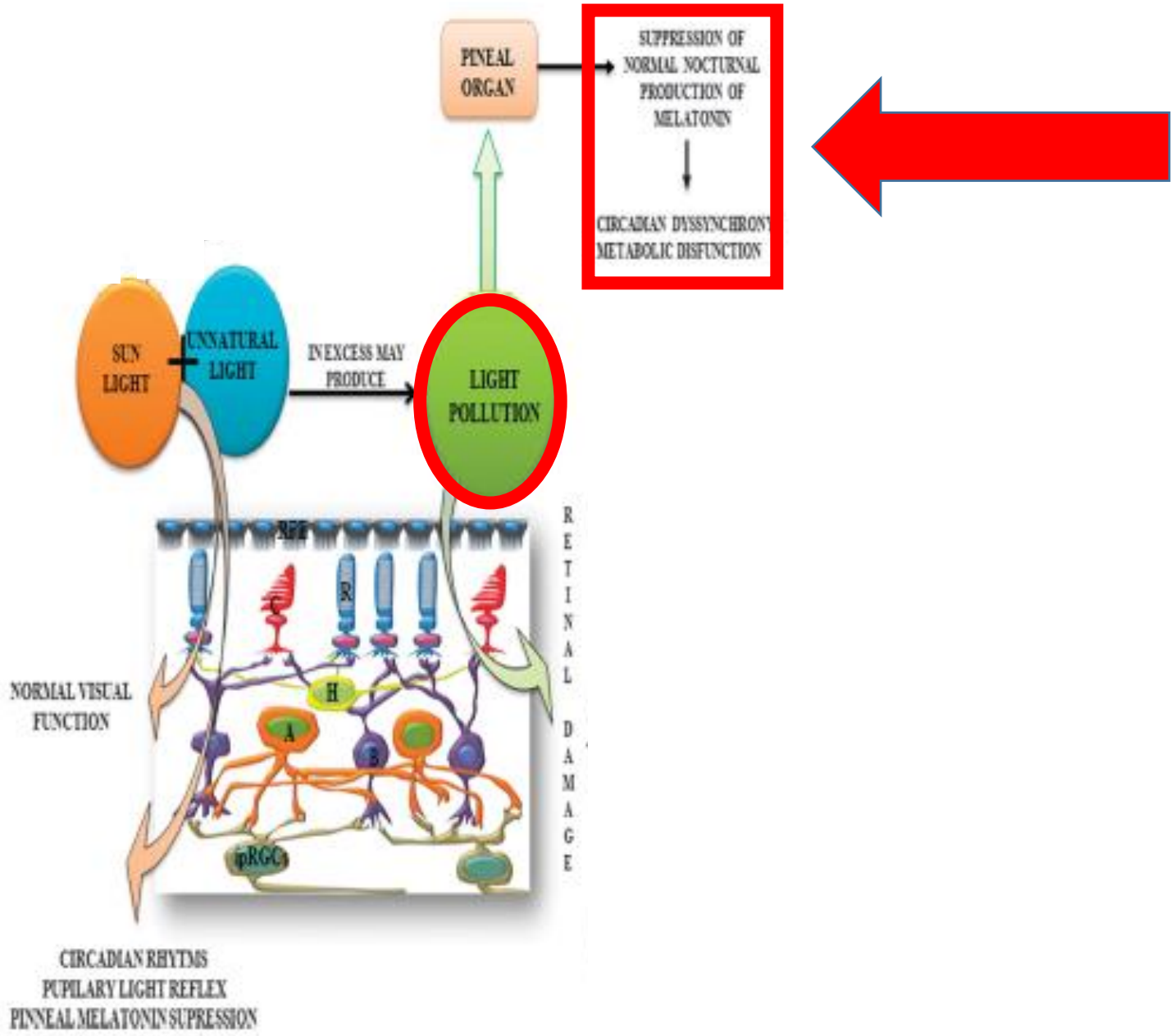






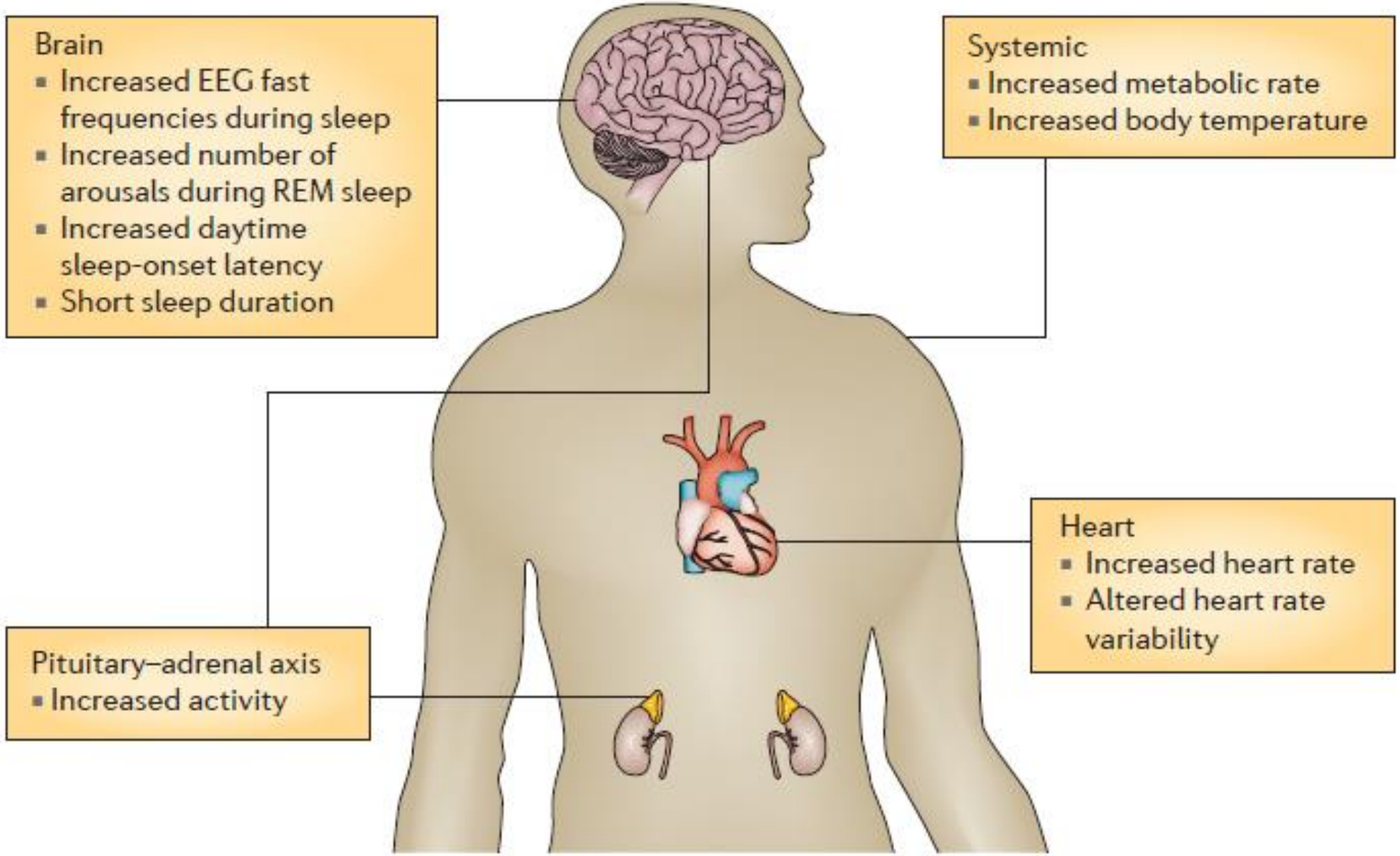
Eye (2016) 30, 255–263

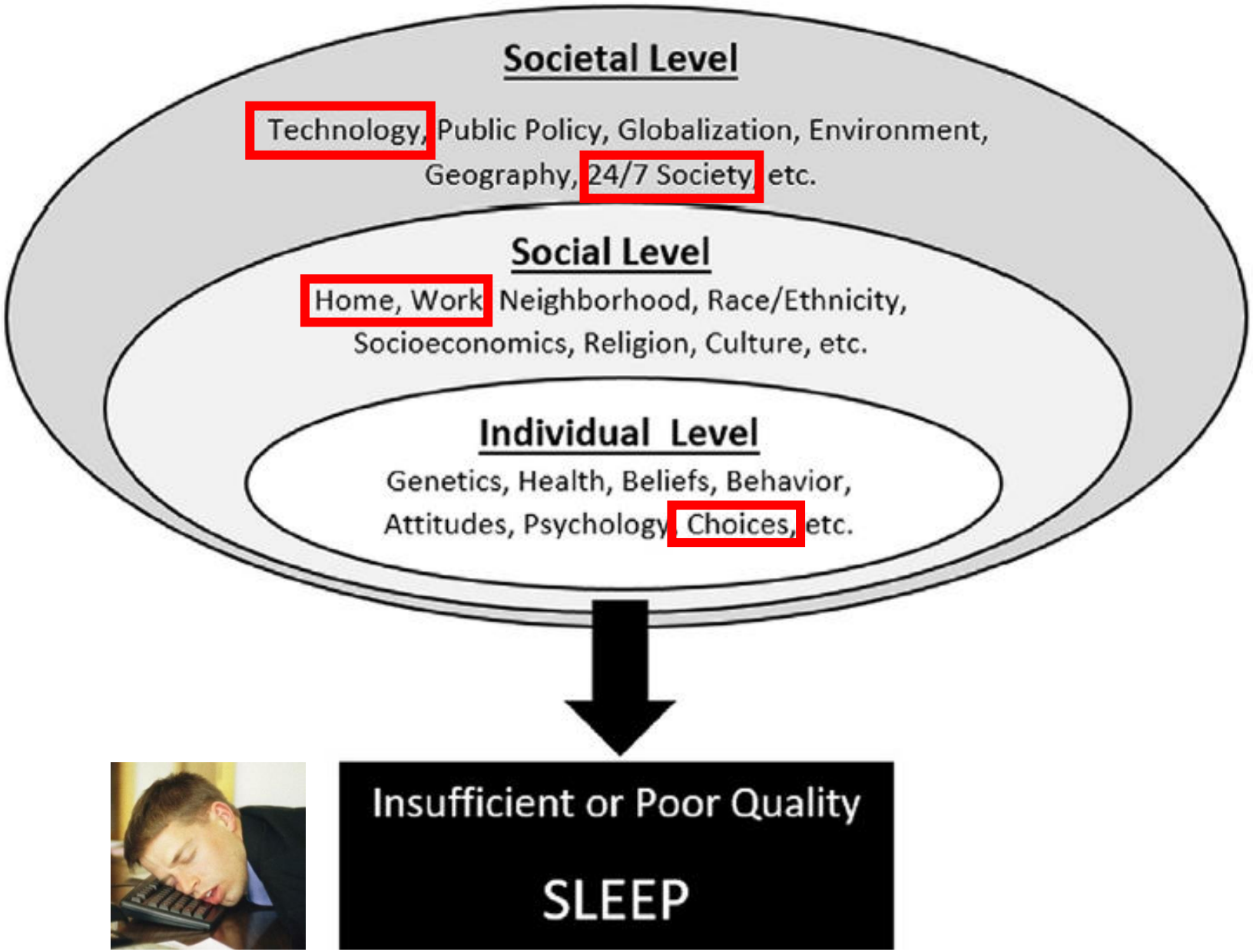
Light pollution



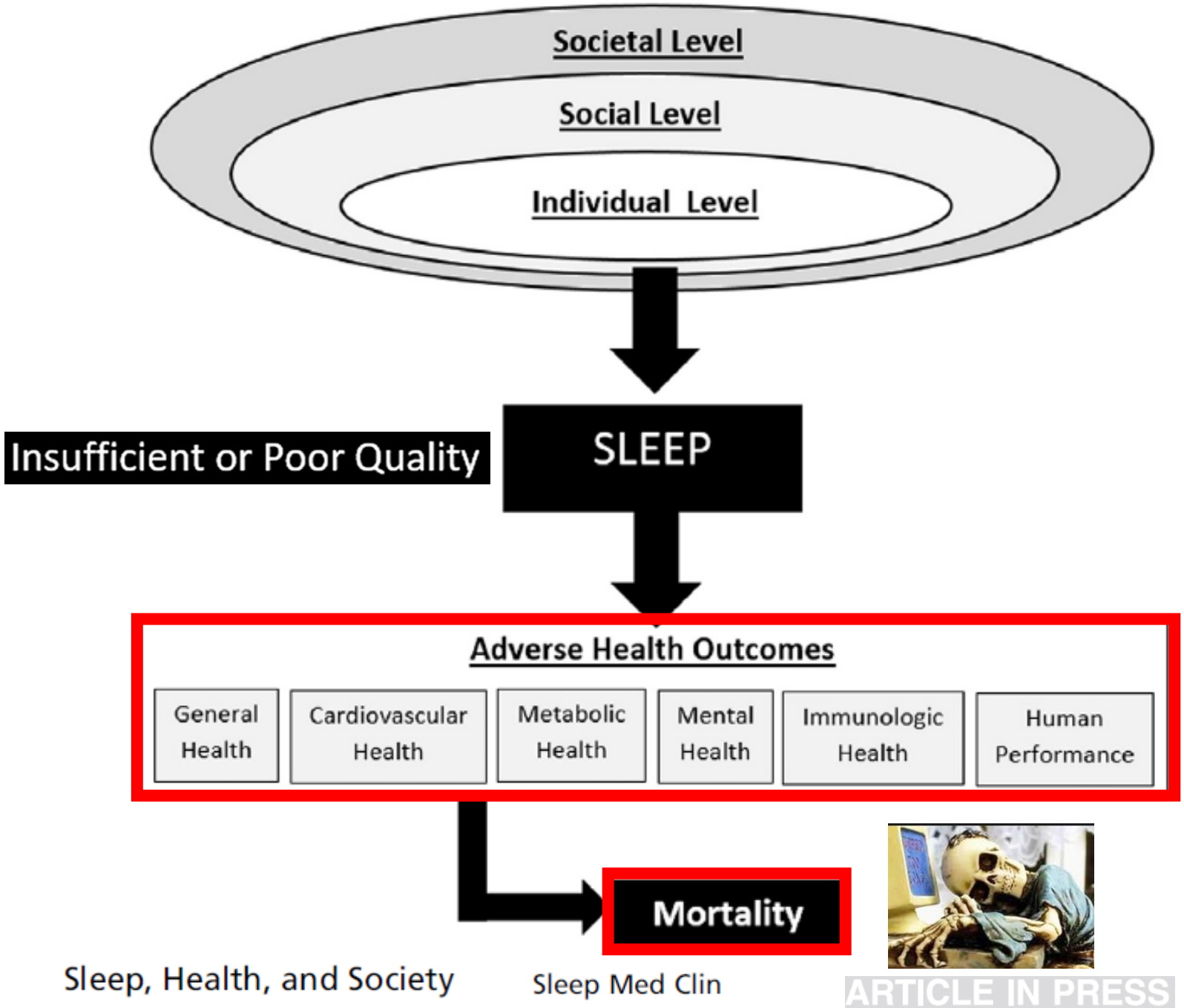
Eye (2016) 30, 255–263

Hallmarks of hyperarousal





Sleep, Health, and Society Sleep Med Clin



Sleep, Health, and Society

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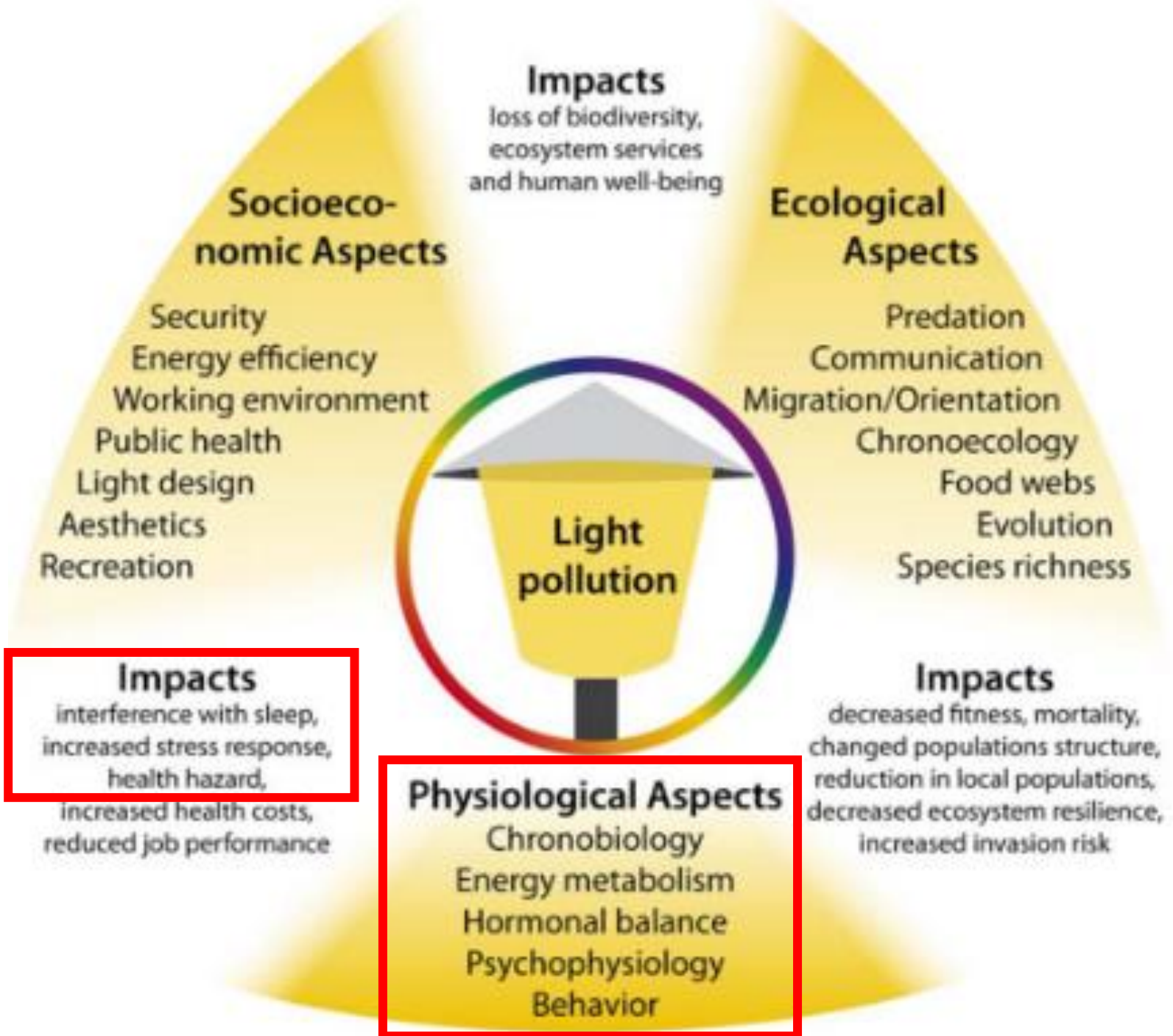
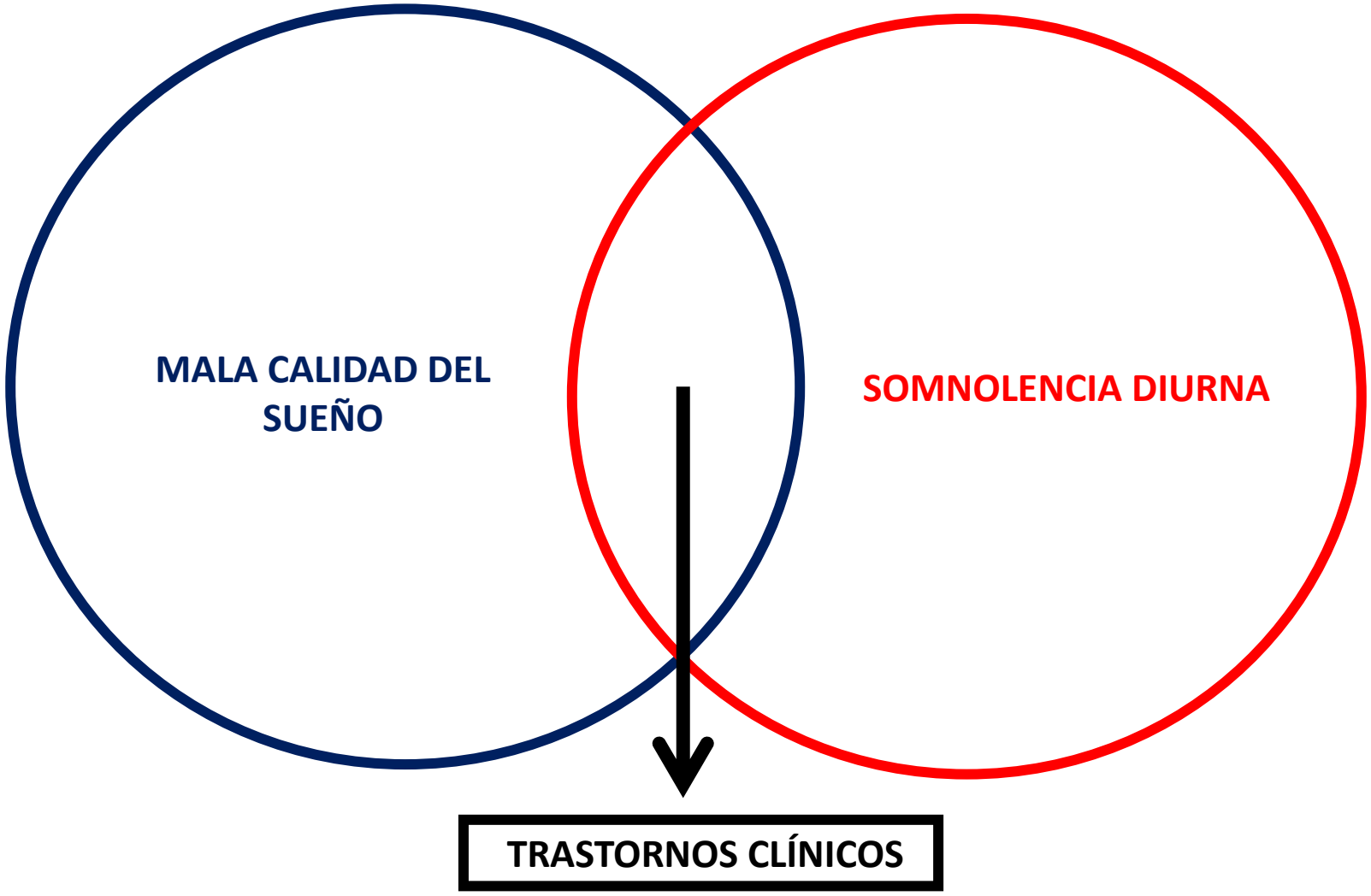
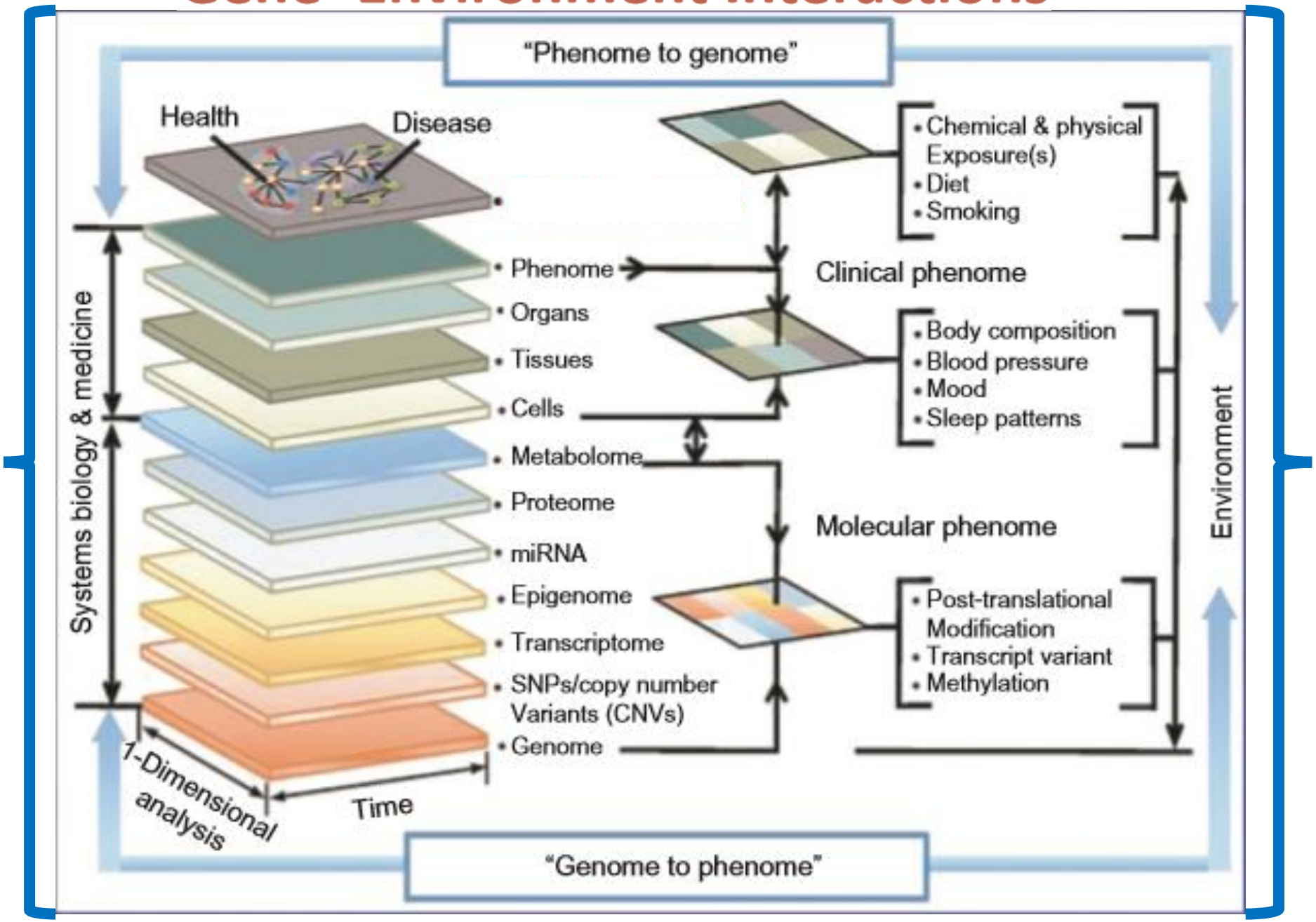

Impacts
loss of biodiversity, ecosystem services and human well-being
Socioeco-nomic Aspects
Security
Energy efficiency
Working environment
Public health
Light design
Aesthetics
Recreation
Ecological Aspects
Predation
Communication
Migration/Orientation
Chronoecology
Food webs
Evolution
Species richness
Light pollution
Impacts
interference with sleep, increased stress response, health hazard, increased health costs, reduced job performance
Impacts
decreased fitness, mortality, changed populations structure, reduction in local populations, decreased ecosystem resilience, increased invasion risk
Physiological Aspects
Chronobiology
Energy metabolism
Hormonal balance
Psychophysiology
Behavior

EN LA PRÁCTICA CLÍNICA DIARIA



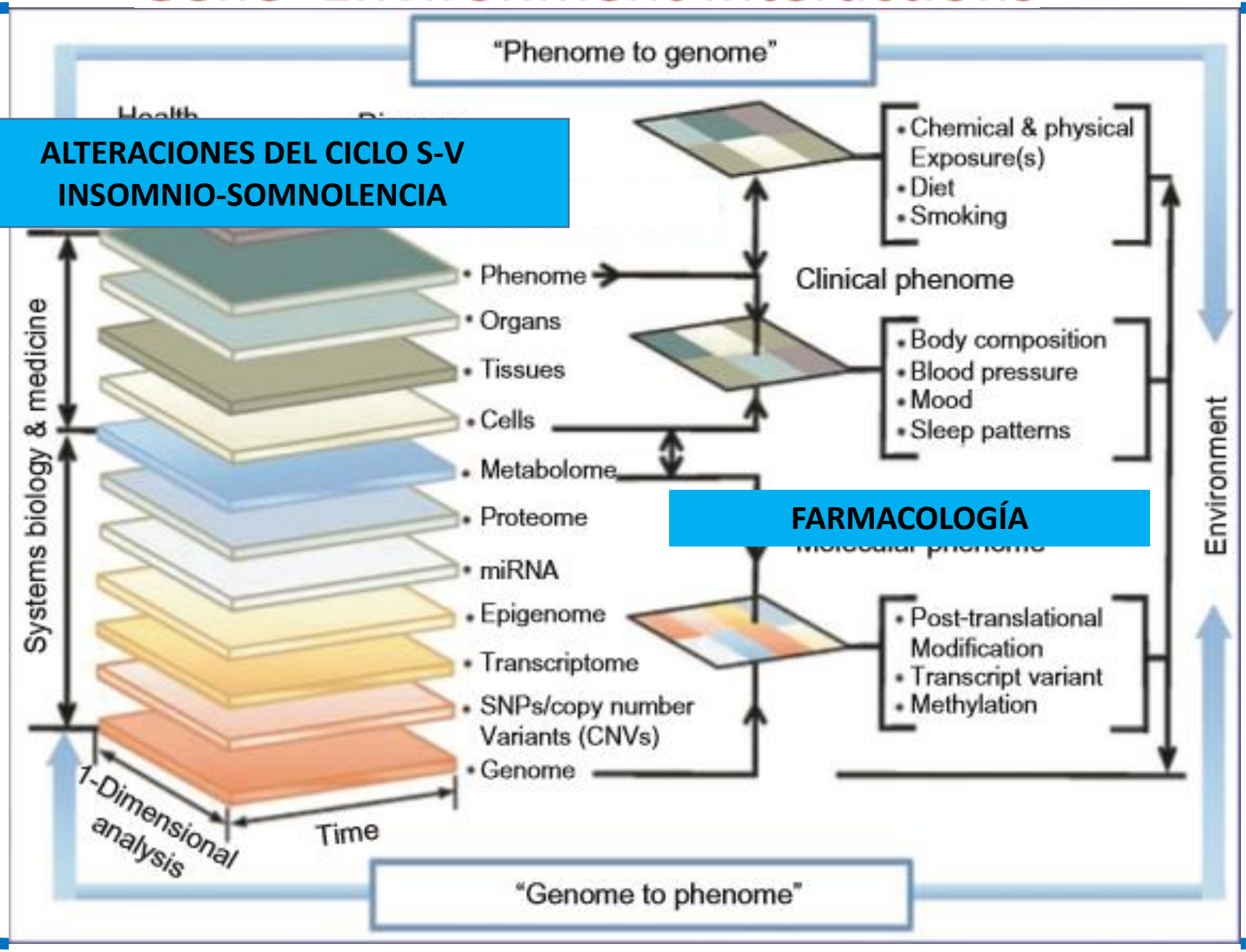
Gene–Environment Interactions



Genomic and Personalized Medicine, 2nd edition 2013, Elsevier Inc.

Gene–Environment Interactions

ALTERACIONES DEL CICLO S-V
INSOMNIO-SOMNOLENCIA



FARMACOLOGÍA

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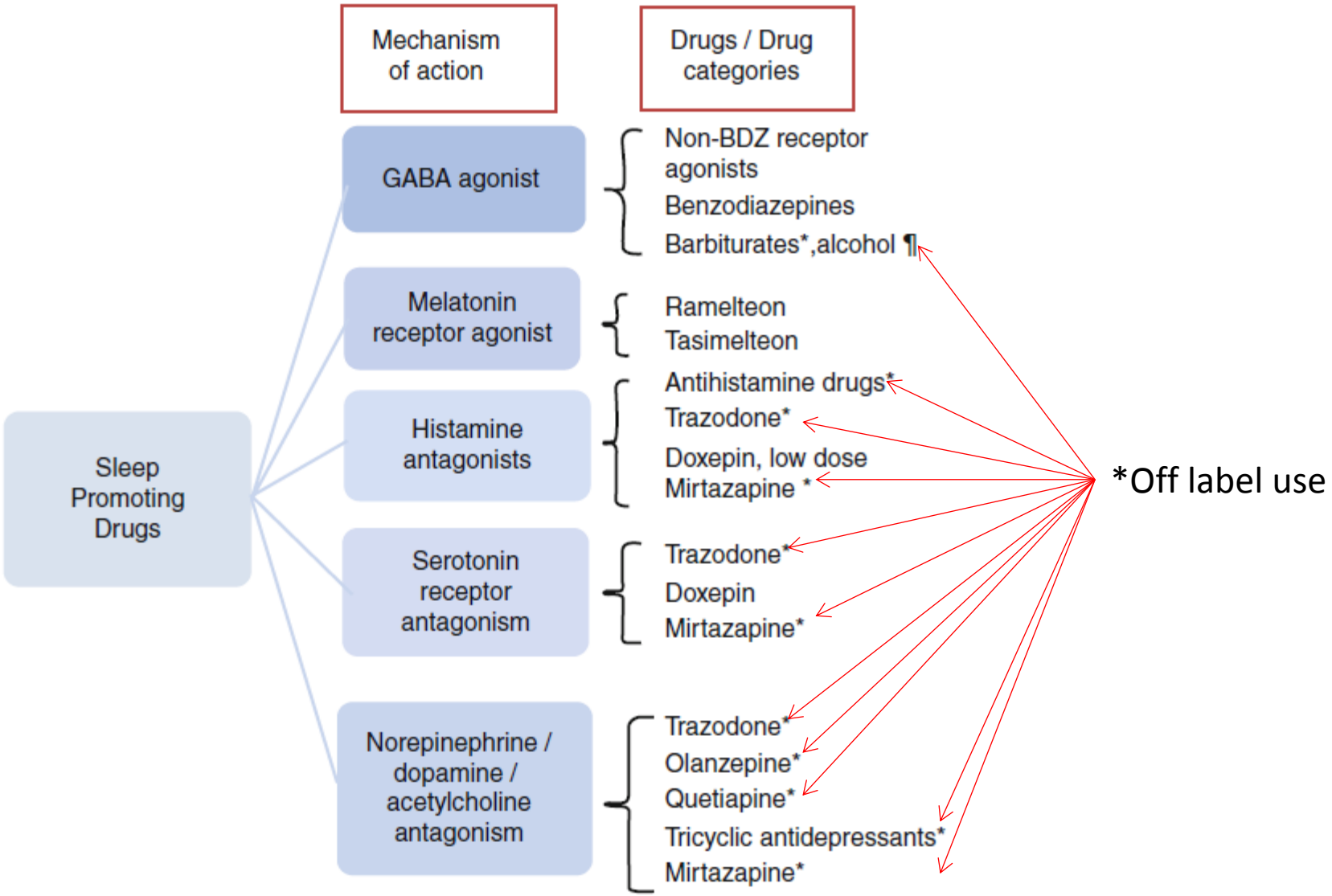
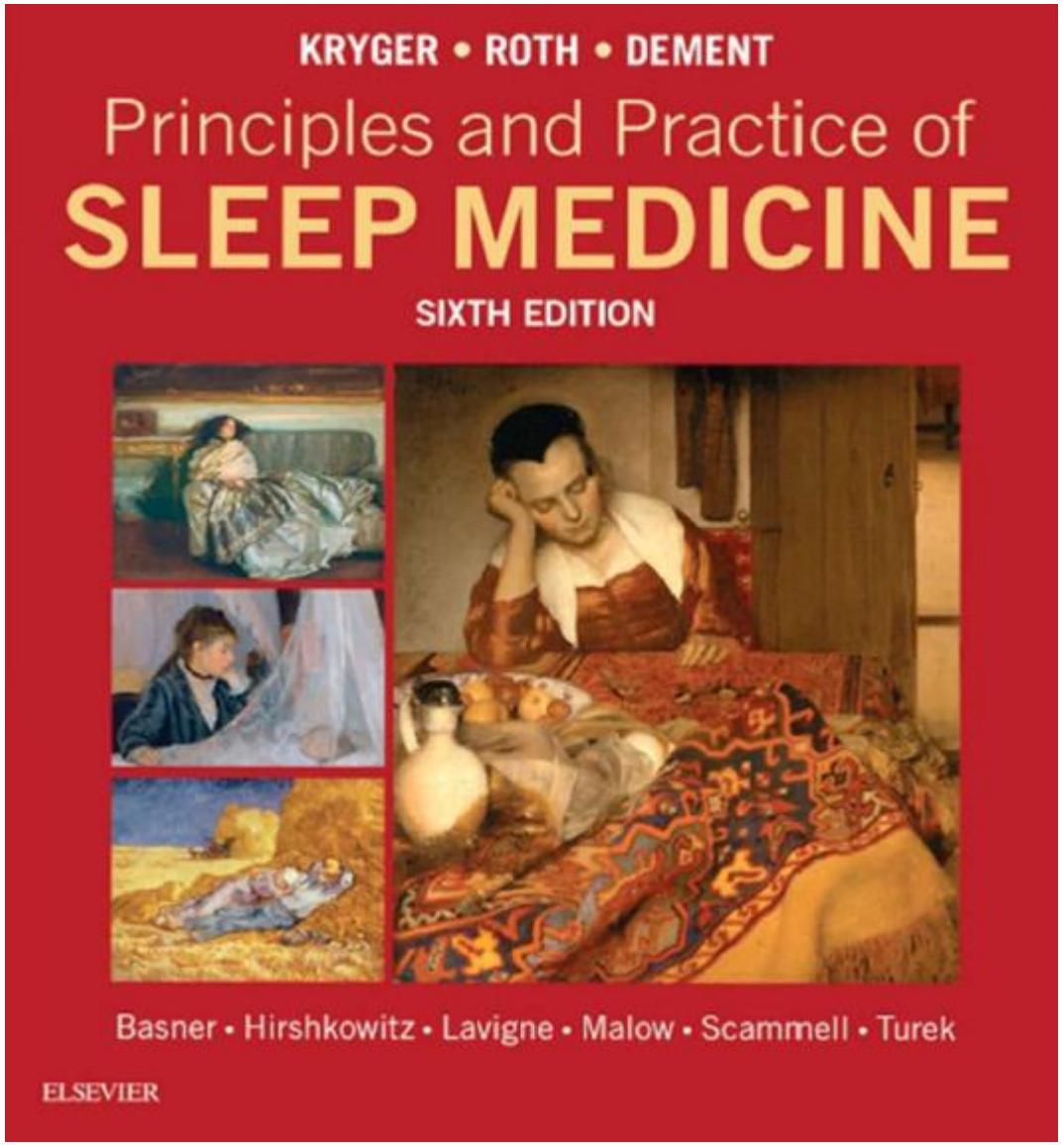
Pharmacology of Sleep



M.S. Badr (ed.), *Essentials of Sleep Medicine,* Springer 2012



Chapter 41

Hypnotic Medications: Mechanisms of Action and Pharmacologic Effects

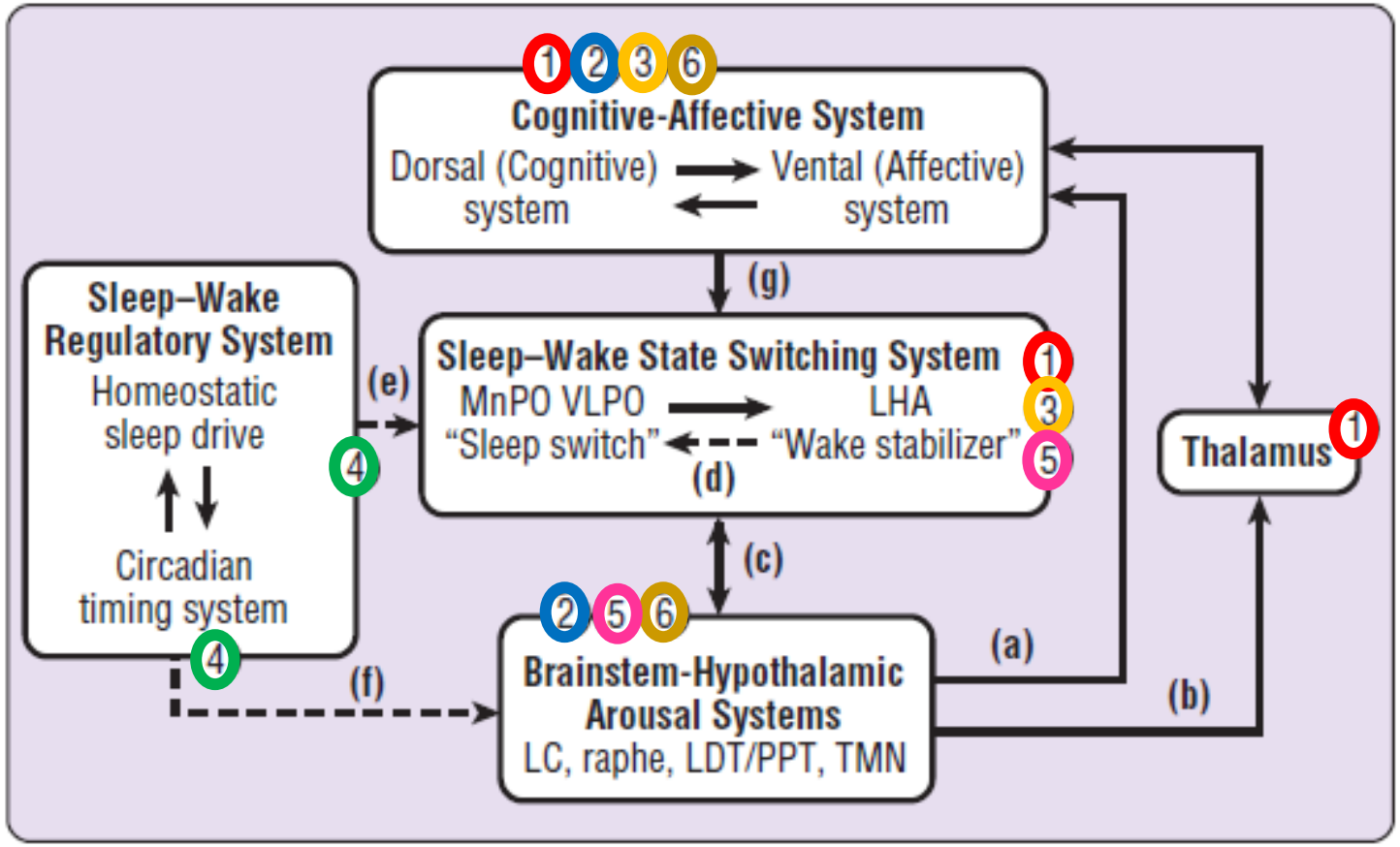
Thomas S. Kilduff; Wallace B. Mendelson

Chapter 42

Clinical Pharmacology of Other Drugs Used as Hypnotics

Daniel J. Buysse; Shachi Tyagi

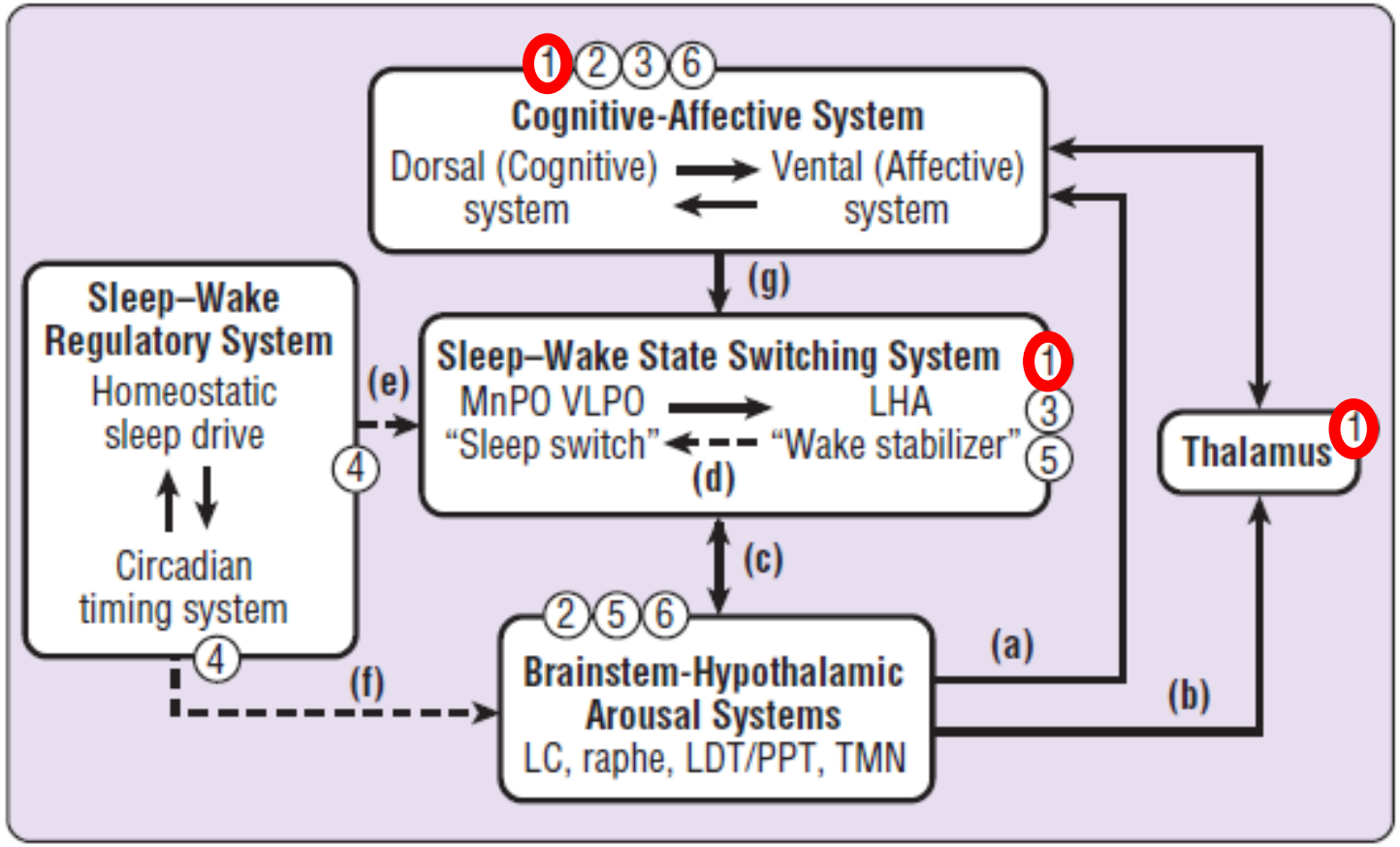
SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Benzodiazepine receptor agonists (1) may directly affect the sleep-wake state-switching system but also have direct cortical, thalamic, and brainstem effect due to the widespread distribution of GABA-A receptors. **Sedating antidepressant and antipsychotic medications (2),** through their activity on monoaminergic systems, affect corticolimbic systems and brainstem-hypothalamic arousal systems. **Antihistamines (3)** antagonize histamine-1 (H1) receptors in the hypothalamus and cortex that receive projections from the tuberomamillary nucleus. **Melatonin and melatonin receptor agonists (4),** through their effects on melatonin-1 (MT1) and MT2 receptors, influence the "wake signal" from the suprachiasmatic nucleus and circadian timing system. **Orexin antagonists(5)** inhibit the effect of orexin-hypocretin on brainstem and hypothalamic arousal centers, and **5-HT2 antagonists (6)** are most likely to have corticolimbic and brainstem sites of action. Thus different types of sleep-promoting drugs achieve their effects through very different actions on very different components of the sleep-wake regulatory system.

SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



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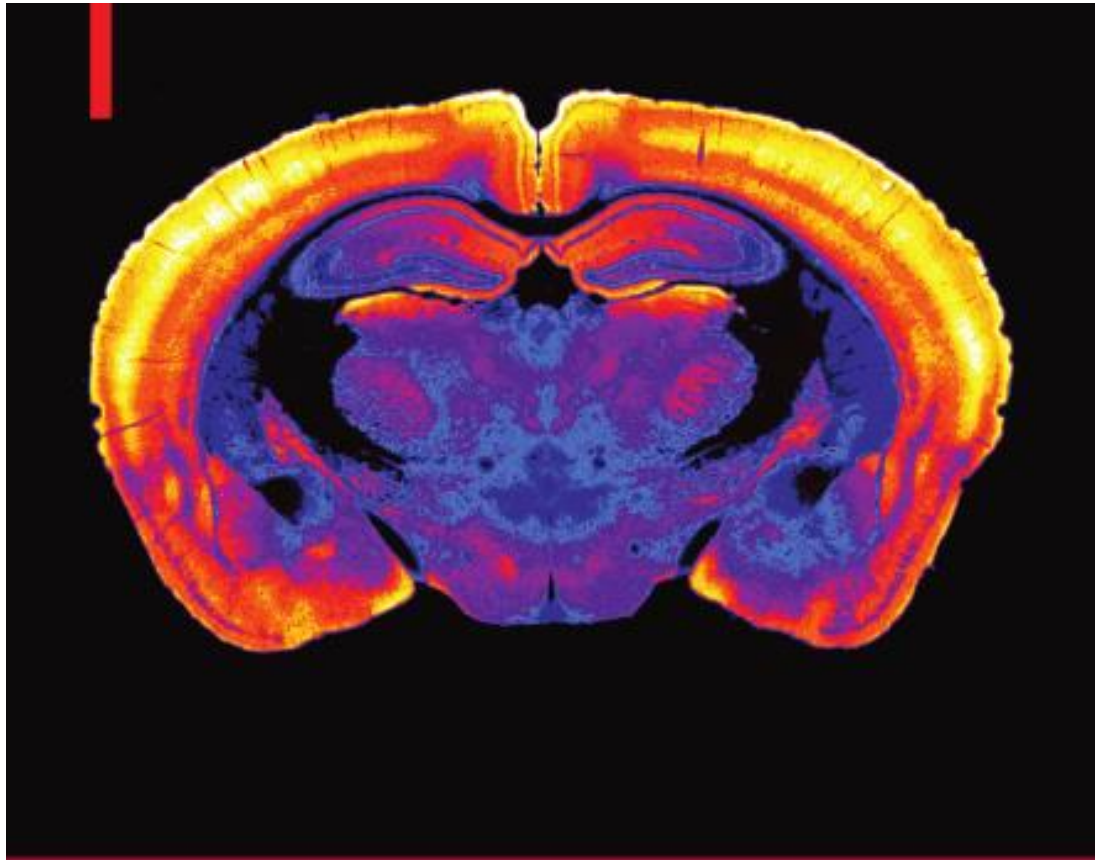


GABA and Sleep

Molecular, Functional and Clinical Aspects

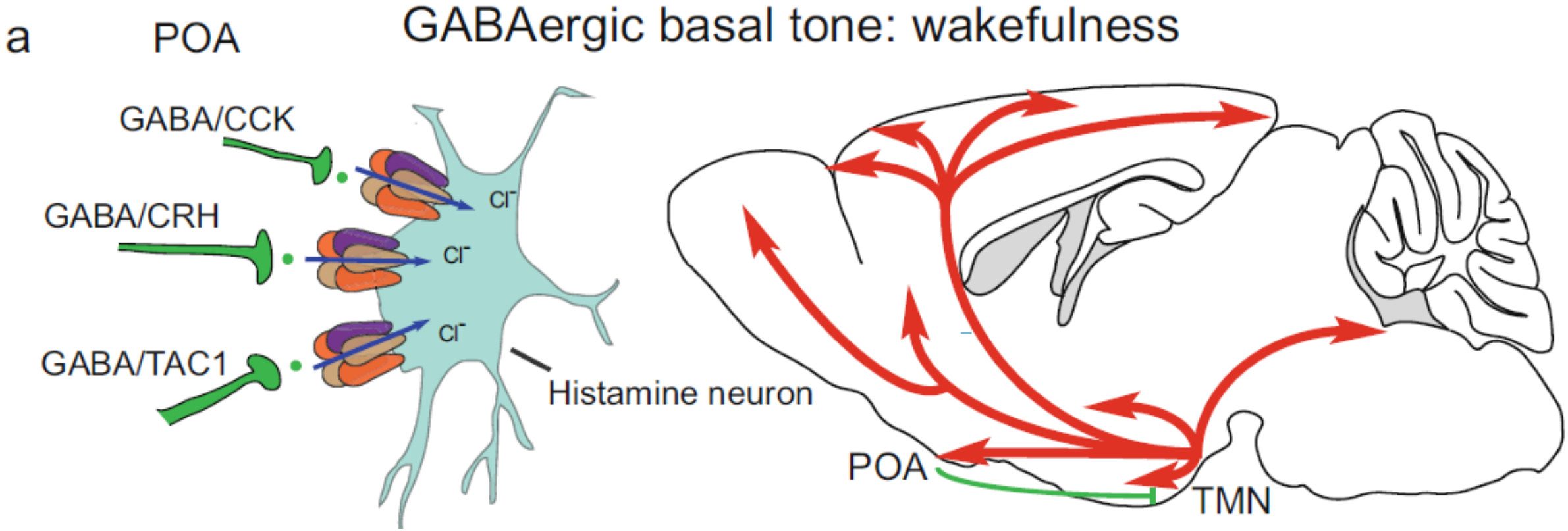
Jaime M. Monti
S. R. Pandi-Perumal
Hanns Möhler
(Editors)

2010
Springer

Activating GABAergic Neurons Generally Promotes Sleep: GABA A Receptor Positive Allosteric Modulators (PAMs) and GABA Agonists Induce Sleep

- The natural sleep-promoting circuitry in the brain uses sleep-active GABAergic neurons to inhibit wake-active neurons in wake-promoting circuitry.
- Enhancing GABAergic transmission throughout the brain with PAMs of GABA A receptors, and thus enhancing network inhibition, will induce sedation.
- Most effective hypnotics/sedatives and anaesthetics developed to date enhance GABA's action at GABA A receptors, working as PAMs at the receptor.

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier



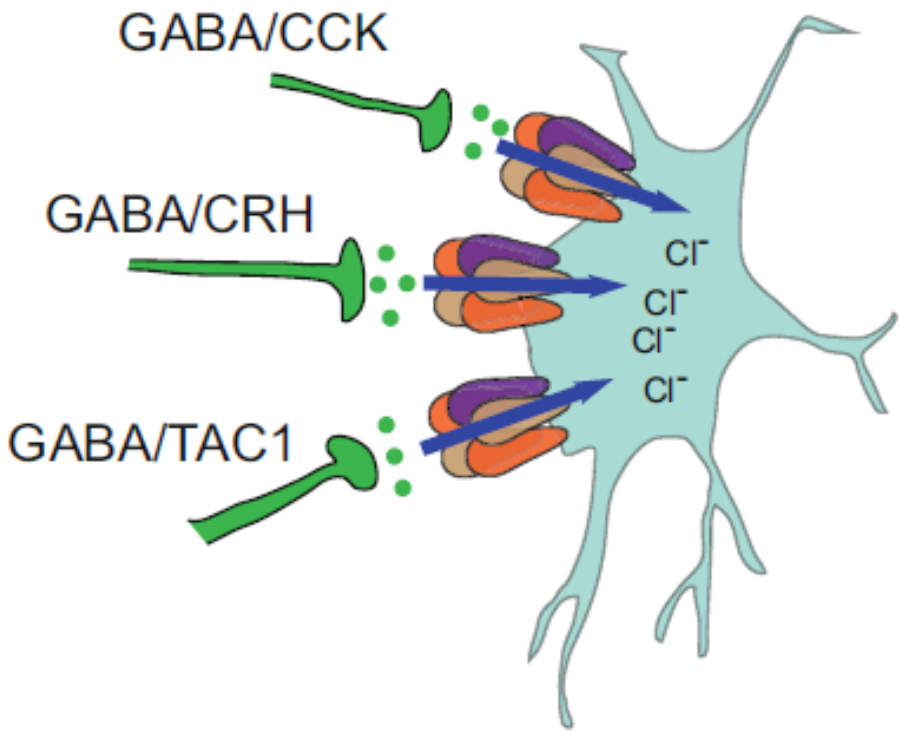
GABAergic afferents from the preoptic area

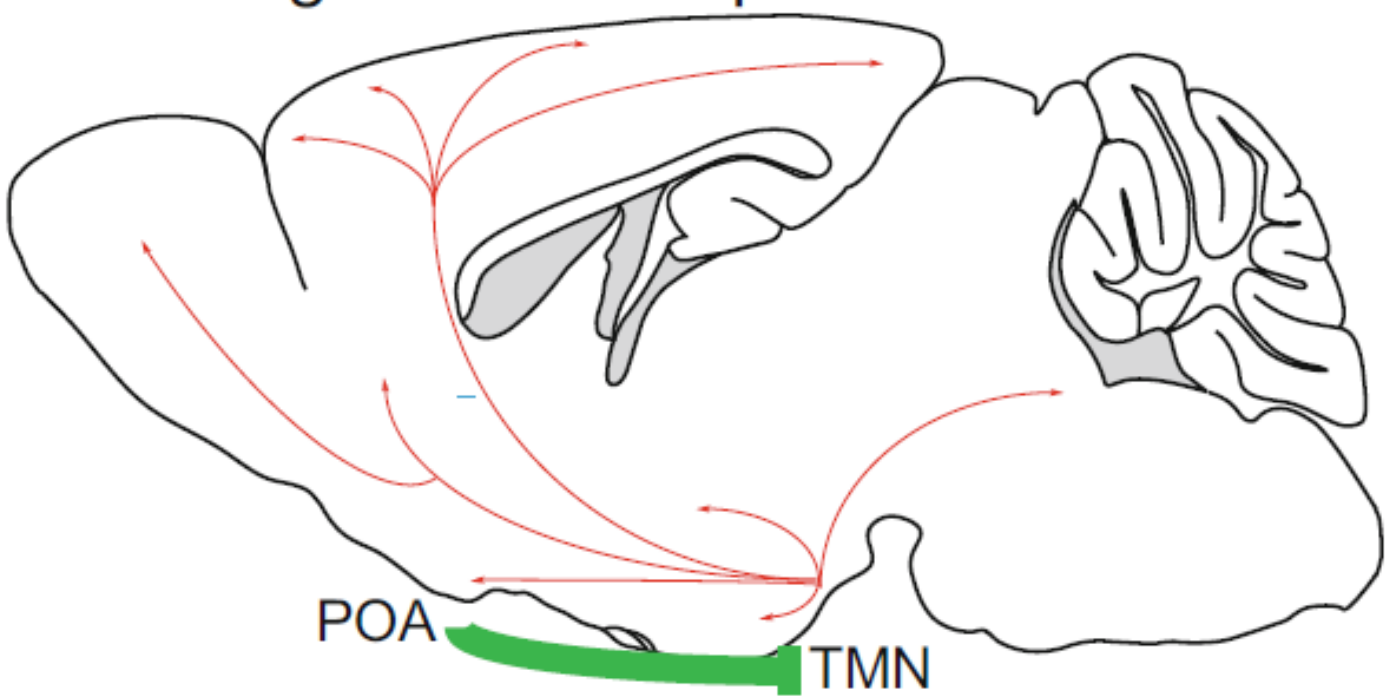
tuberomammillary area

Handbook of Experimental Pharmacology
Springer 2017

b

Increased GABAergic tone: sleep





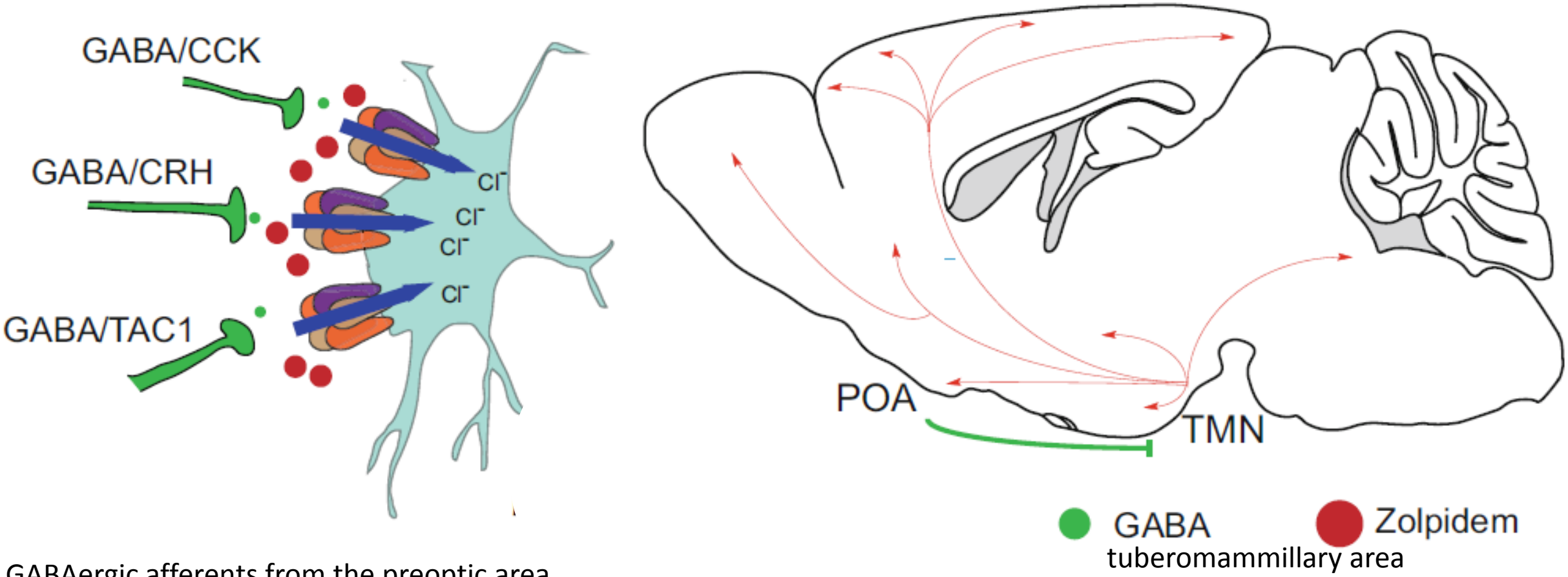
GABAergic afferents from the preoptic area

tuberomammillary area

Handbook of Experimental Pharmacology
Springer 2017

c

Basal tone + Zolpidem: sleep



GABAergic afferents from the preoptic area

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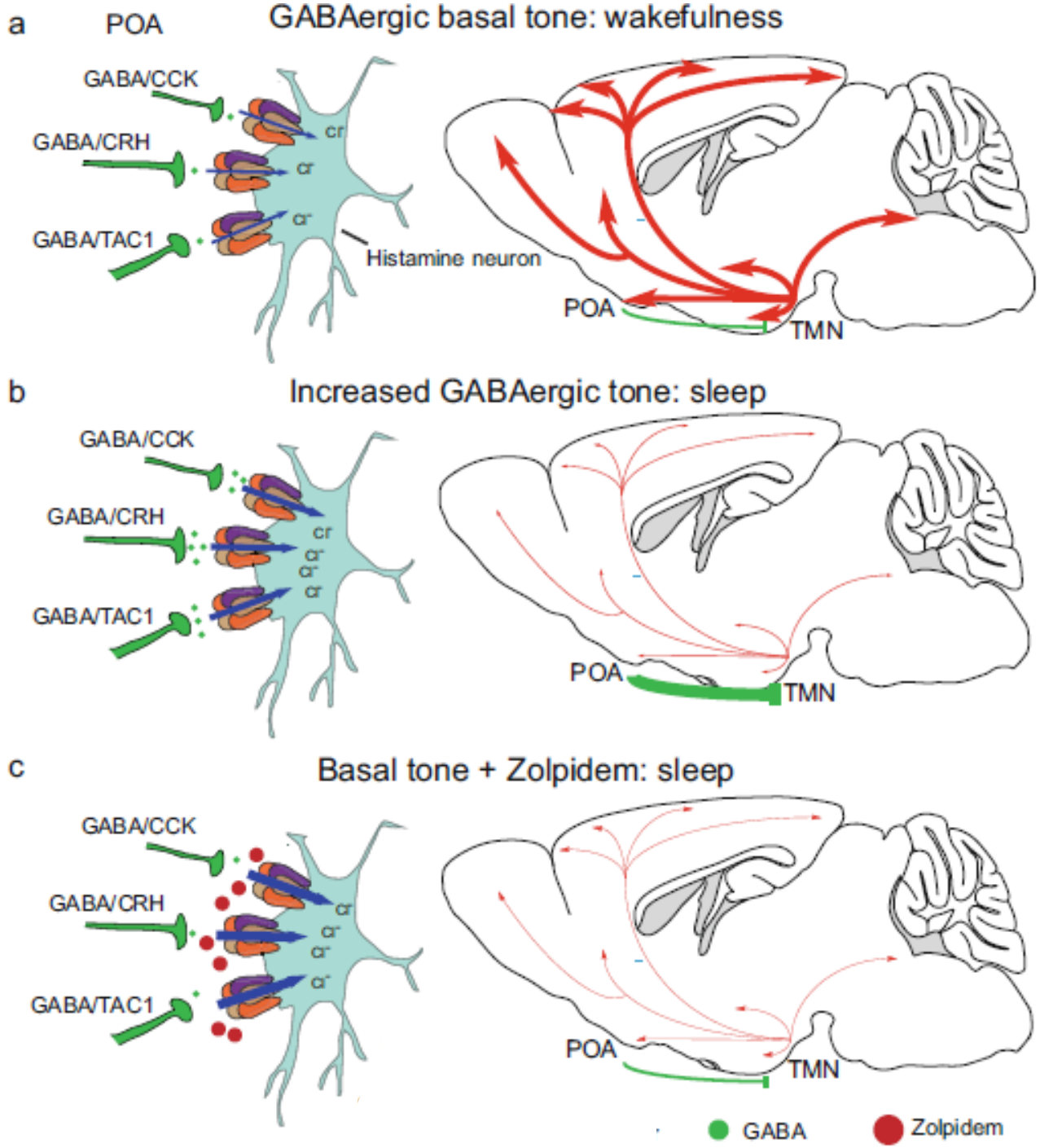
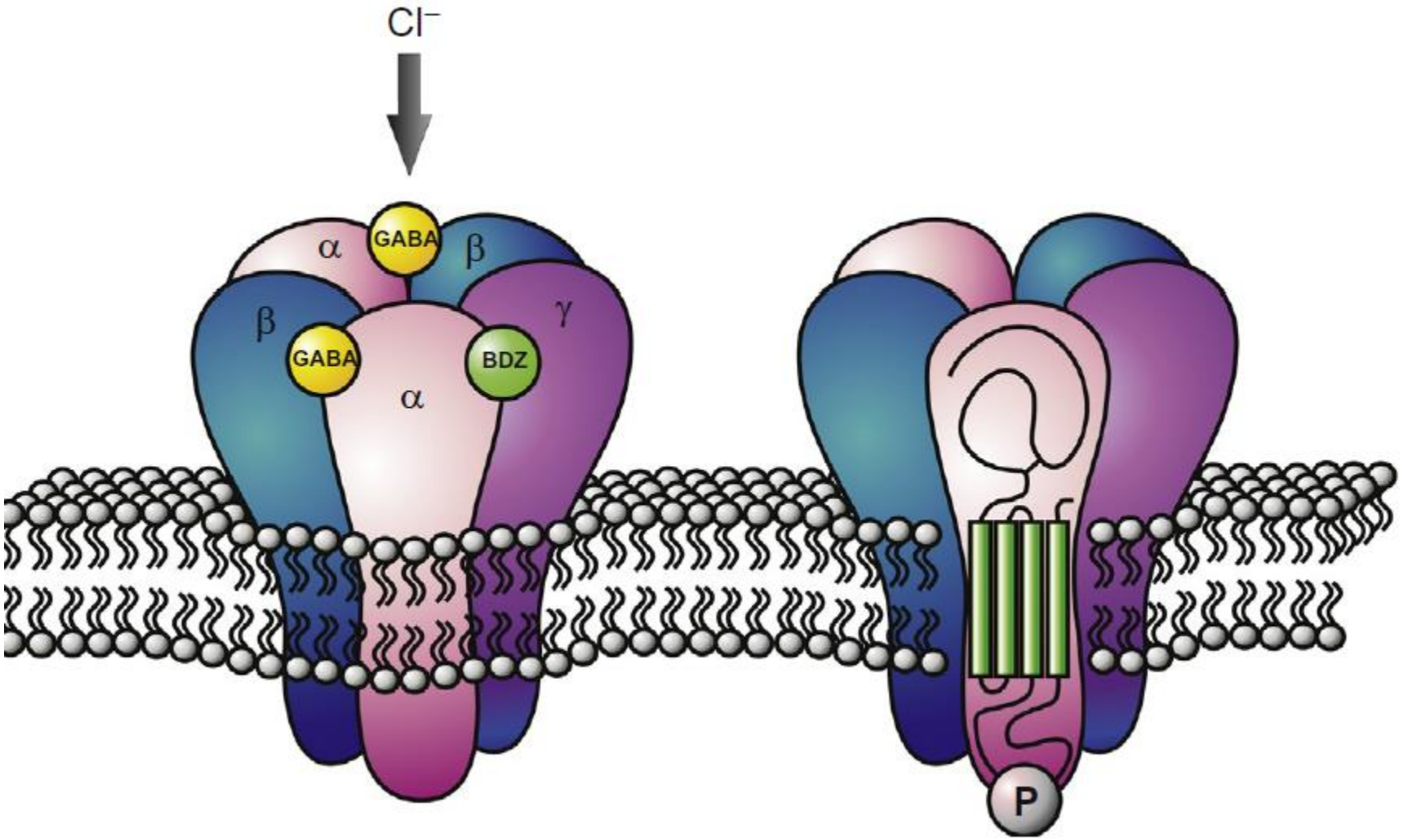

a
POA
GABAergic basal tone: wakefulness
GABA/CCK
GABA/CRH
GABA/TAC1
cr
α
α
Histamine neuron
POA
TMN
b
Increased GABAergic tone: sleep
GABA/CCK
GABA/CRH
GABA/TAC1
cr
α
α
α
POA
TMN
c
Basal tone + Zolpidem: sleep
GABA/CCK
GABA/CRH
GABA/TAC1
α
α
α
α
POA
TMN
GABA
Zolpidem

GABA A Receptors

- They are GABA-gated chloride channels, in the same gene superfamily as glycine receptors, nicotinic acetylcholine receptors and serotonin 5-HT3 receptors.
- There are six alpha (α1–α6) subunit genes, three beta (β1–β3) subunit genes, three gamma (γ1–γ3) subunit genes and one delta (δ) subunit gene; additionally, there are also epsilon (ε), theta (θ) and pi (π) subunit genes and three rho (ρ) subunit genes.
- The subunit genes are differentially expressed throughout the brain and enteric nervous system.

Handbook of Experimental Pharmacology
Springer 2017

The pentameric GABA A R



GABA A Rs are composed of a large extracellular N-terminal domain, four-transmembrane domains (TM1–4), and a major intracellular loop between TM3 and TM4 where phosphorylation (℗) primarily occurs.

Advances in Pharmacology, Volume 72. 2015 Elsevier

GABA A RECEPTORS

- GABA A receptors are heteropentamers, assembling from 19 known protein subunits (α1–6, β1–3, γ1–3, δ, ε, π, ρ1–3).
- Approximately **60% of all GABA A receptors are built from α1, β2, and γ2 subunits**, 15–20% show an α2, β3, γ2 combination, and 10–15% have an α3, βn, γ2 combination.
- There are two binding sites for the agonist on each receptor formed by parts of an α- and a β-subunit.
- GABA A receptors can be located at synapses or **extrasynaptically**, mediating phasic or tonic inhibition.
- Agonist-induced activation of GABA A receptors causes these ion channels to open, allowing anions to flow into cells, thereby reducing the excitability of the respective neuron.

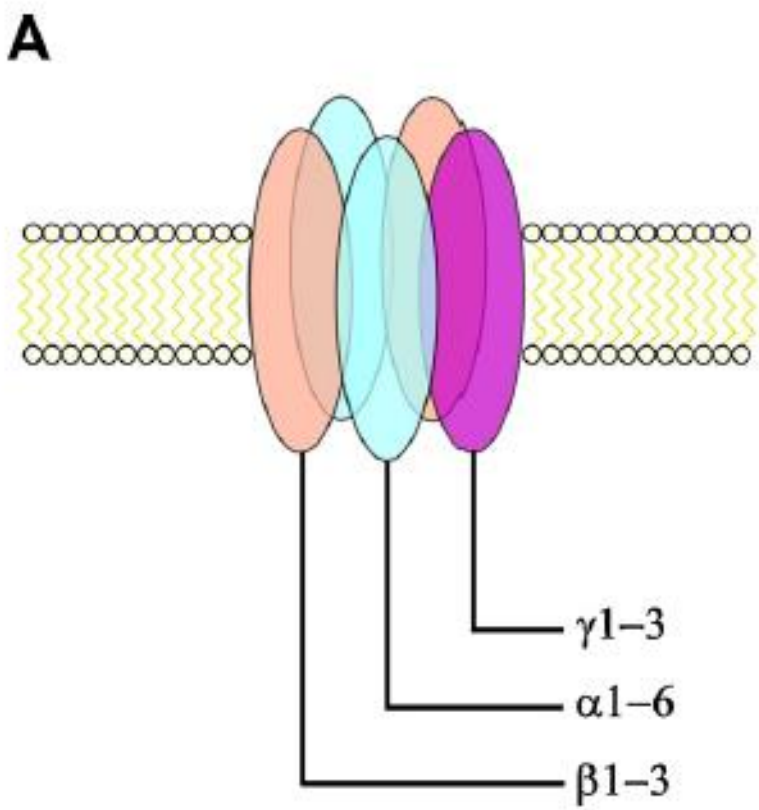
Advances in Pharmacology, Volume 72 2015 Elsevier

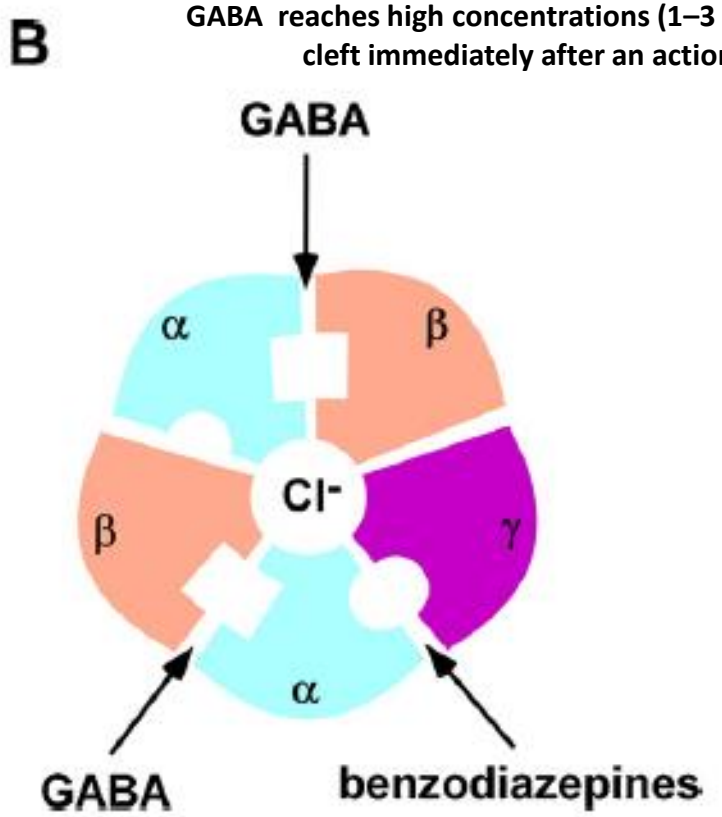
GABA A Receptors

- For current drugs the important target combinations of receptor subunits are α1βγ2, α2βγ2, α3βγ2, and α5β1/2/3γ2 receptors.
- Benzodiazepines and the "z-drugs" (e.g. **zolpidem**, s-zopiclone) require an α and γ2 subunit in the receptor complex.
- Receptors that contain the γ2 subunit are enriched in the postsynaptic area but are also present extrasynaptically

Handbook of Experimental Pharmacology
Springer 2017

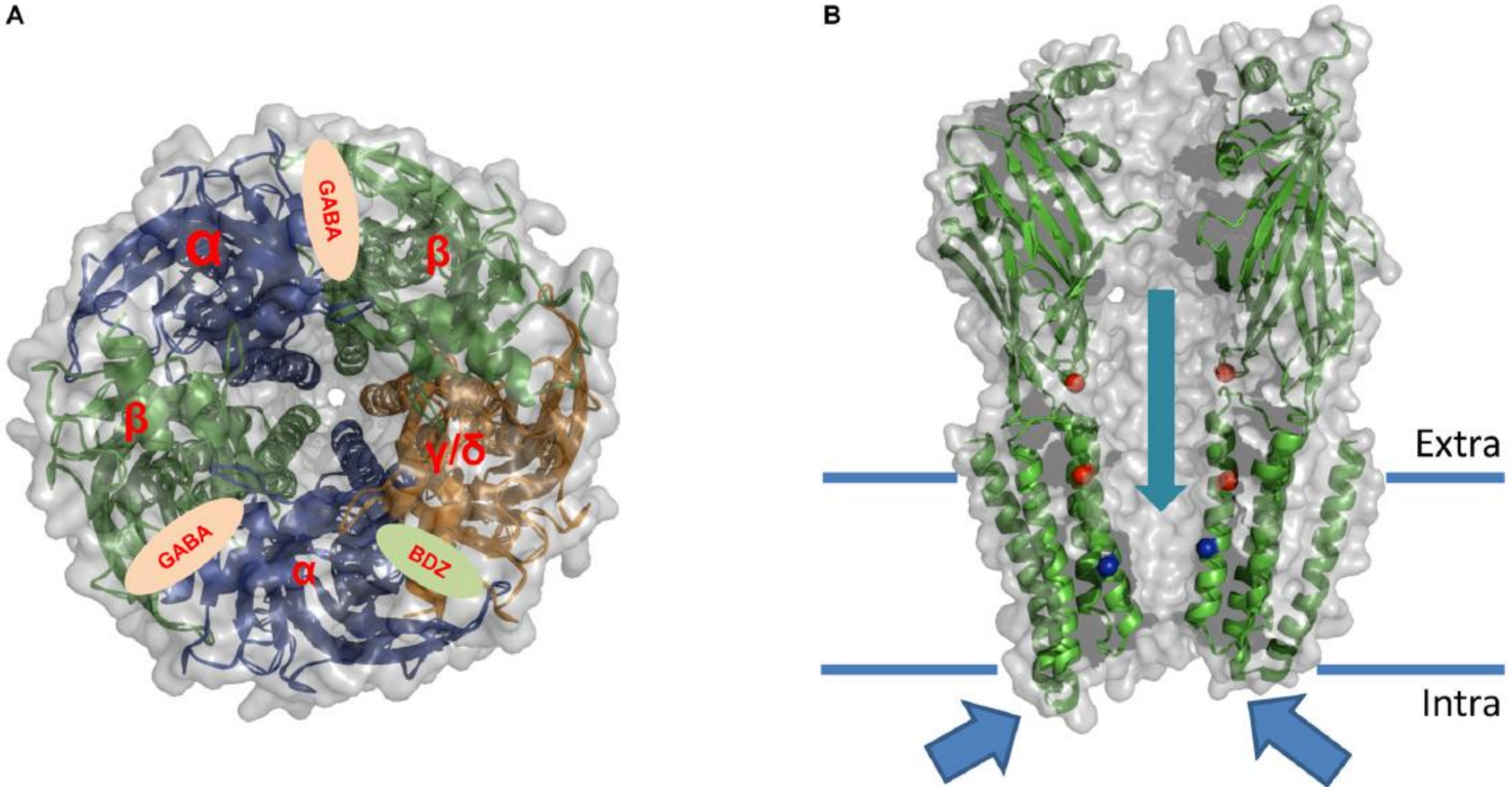
GABA A receptor structure





Gravielle MC. Pharmacol Res. 2016 ;109:92-100

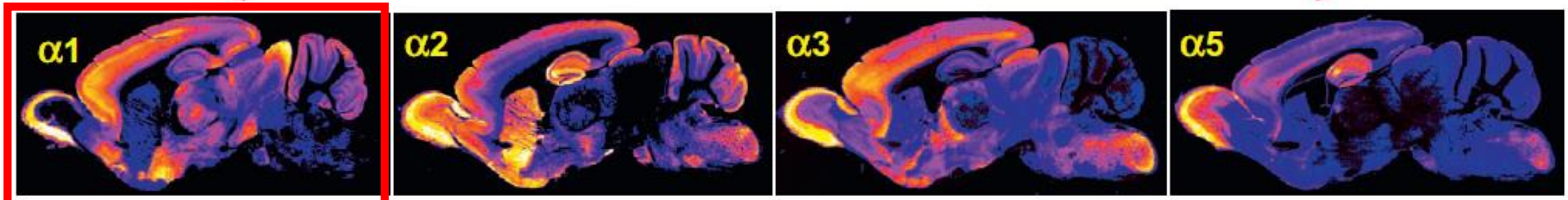
Sites of action for allosteric modulation of GABA A R



Frontiers in Cellular Neuroscience, **7** May 2016, Vol10:114

$GABA_A$ receptor subtypes and their distinct pharmacology.

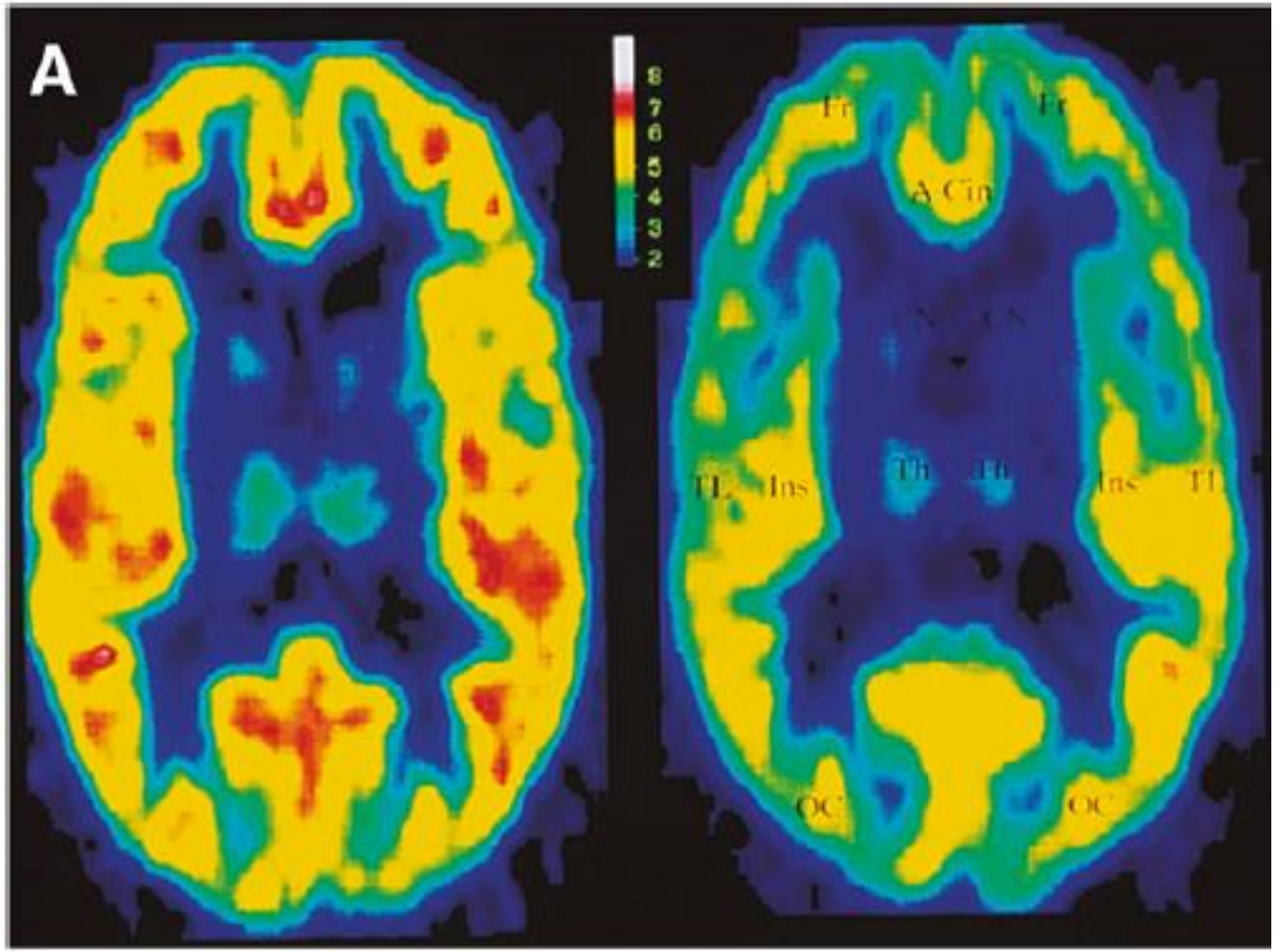
$GABA_A$ receptors: $\alpha_x\beta_2/_3\gamma_2$



α1	α2	α3	α5
Sedative action Anticonvulsant action Anterograde amnesia Dependence liability	Anxiolytic action Anti-depression Anti-autism-like behavior (α_2 plus α_3, α_5) Pain suppression (via spinal α_2 receptors)	Anxiolytic action at high receptor occupancy Anti-schizophrenia-like behavior (α_3 and α_2, α_5)	Cognition enhancement Learning and memory

Advances in Pharmacology, Volume 72 2015 Elsevier

Results of PET studies using radiolabeled [11C]flumazenil to study BZDR kinetics in vivo.



controls **panic disorder**

Pharmacol Rev 66:1002–1032, 2014

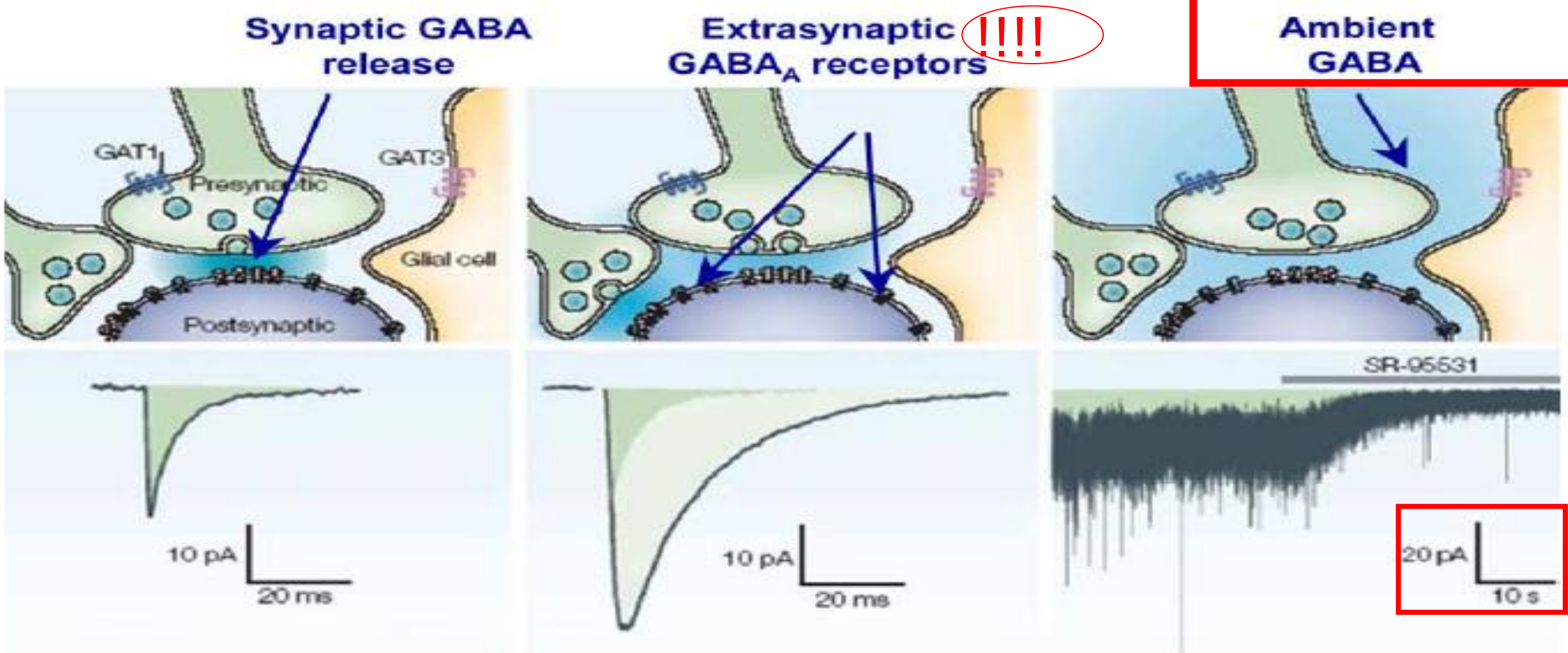
Extrasynaptic GABA A Receptors, δ Subunits and Sleep

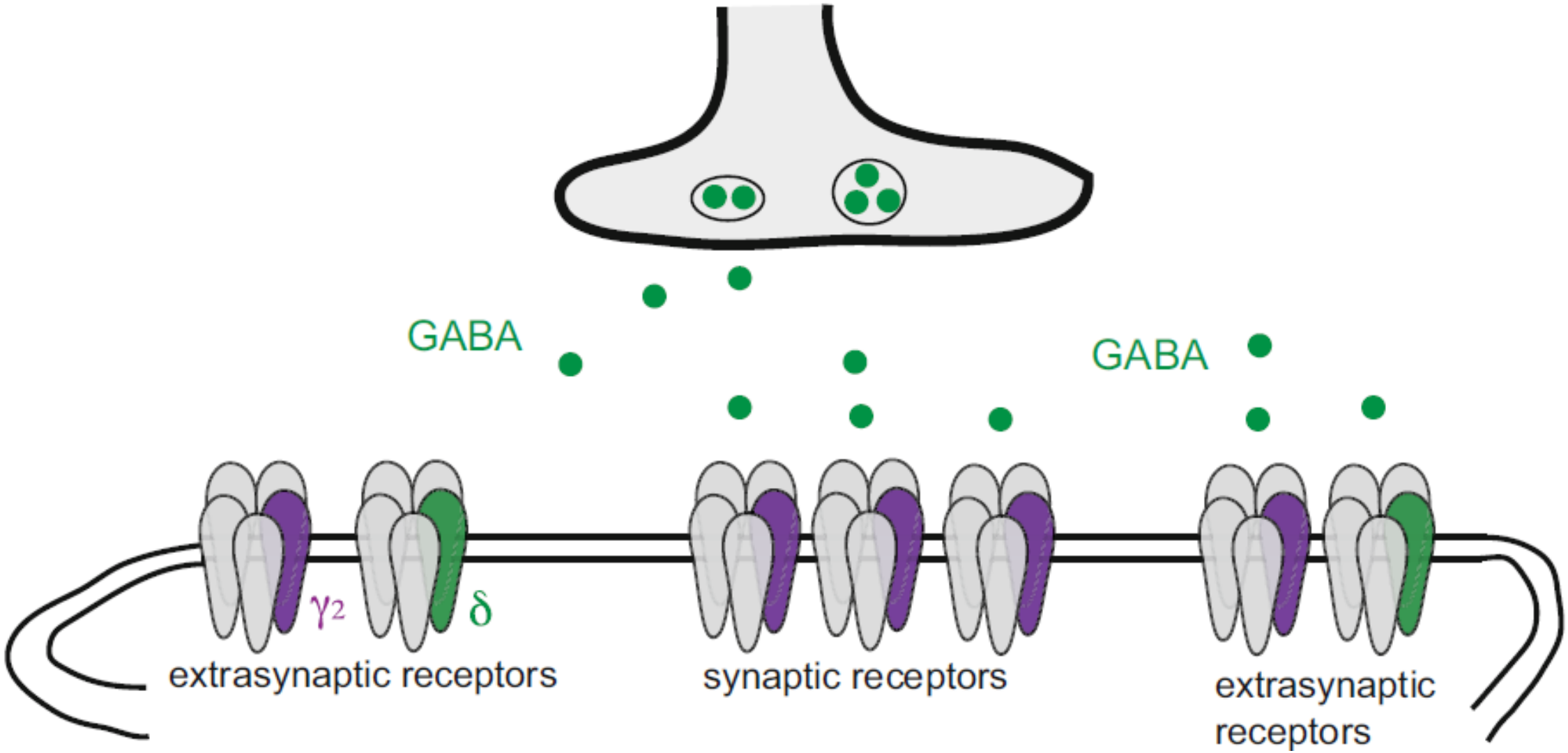
- An important class of GABA A receptors exists exclusively outside the synapse and contains δ subunits.
- Delta-containing receptors are involved in tonic inhibition, sensing extrasynaptic GABA.
- In the forebrain, the δ subunit is paired primarily with the α4 and **α1** subunits.
- It was suggested that GABA acting at δ-containing GABA A receptors at thalamic extrasynaptic GABA A receptors on thalamic relay cells might induce slow wave activity – the delta oscillations of NREM sleep.
- However, global δ knockout mice have normal sleep-wake cycles and vigilance states.

Handbook of Experimental Pharmacology
Springer 2017

A.N. Bateson / Sleep Medicine 7S1 (2006) S3–S9

ACCION METABOLICA DEL GABA EN EL INICIO DEL sNREM





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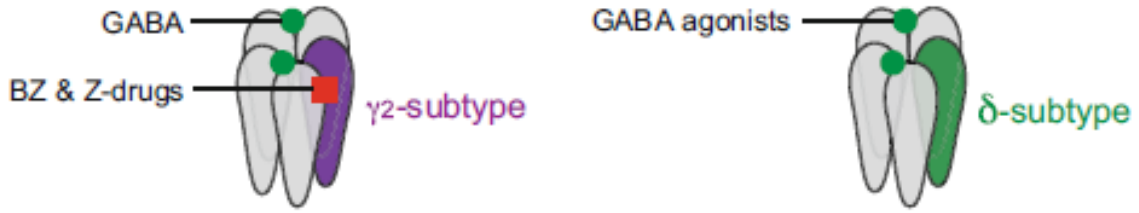
Summary of how sleep-promoting drugs work on synaptic (αβγ2 type) and extrasynaptic (αβγ2 and αβδ) GABA A receptors.

Effects of drugs on sleep and other parameters:	$GABA_A$ sub-type modulated by sedative-hypnotics: 
Sleep onset latency:	↓
Sleep continuity:	↑
Total sleep time:	↑
REM sleep:	↓
REM sleep latency:	↑
EEG power:	↓ in frequency< 10 Hz ↑ in spindle frequency
Residual effects:	sedation
Effects on cognitive performance:	cognitive impairment & amnesic effects
Development of tolerance and/or dependance:	YES
Rebound insomnia:	YES

—	
↑	
↑	
—	
—	
↑ in frequency< 10 Hz ↓ in spindle frequency	
none reported	
not altered & sustain attention during sleep restriction	
NO	
NO	

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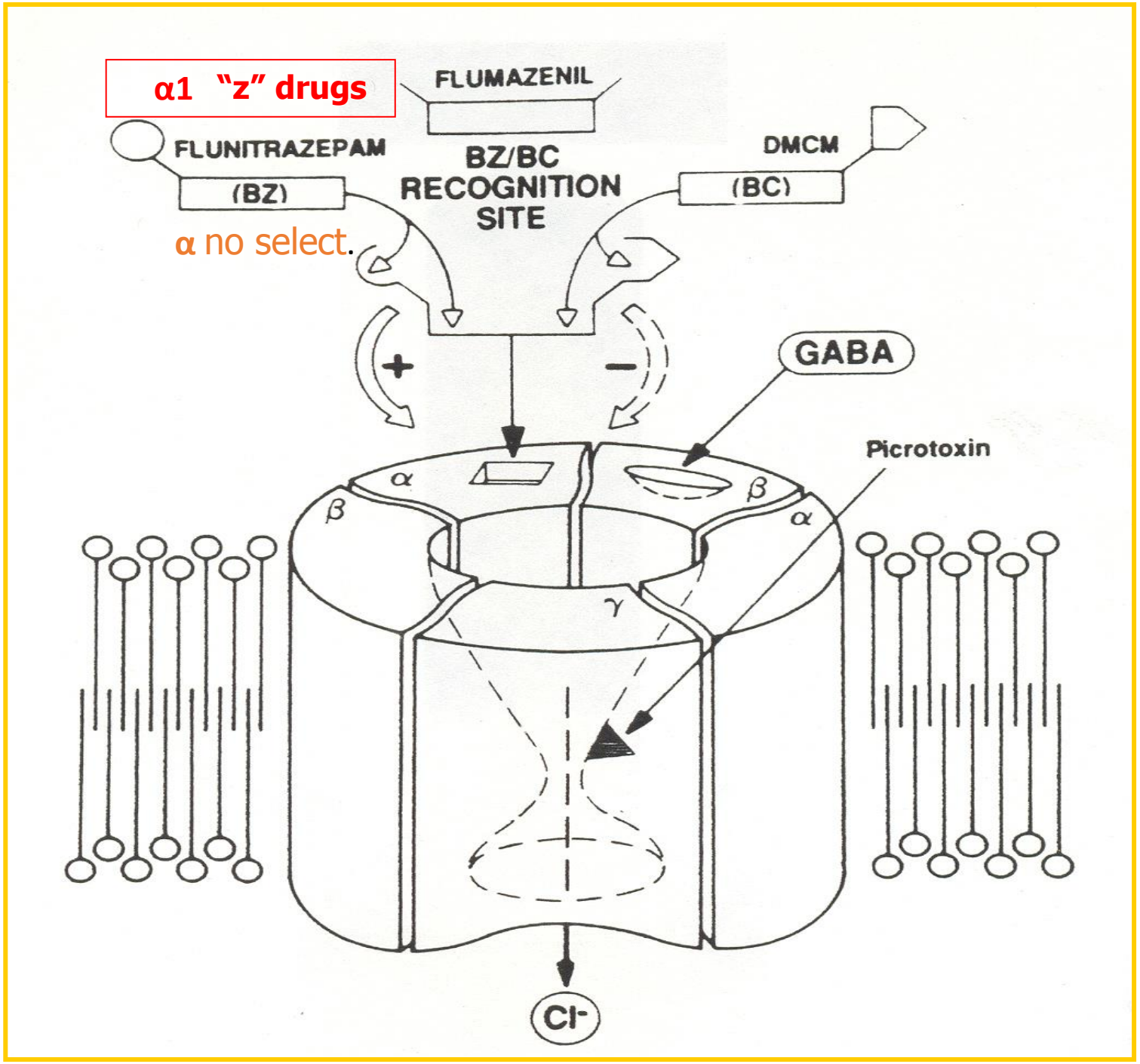
Conceptos previos importantes

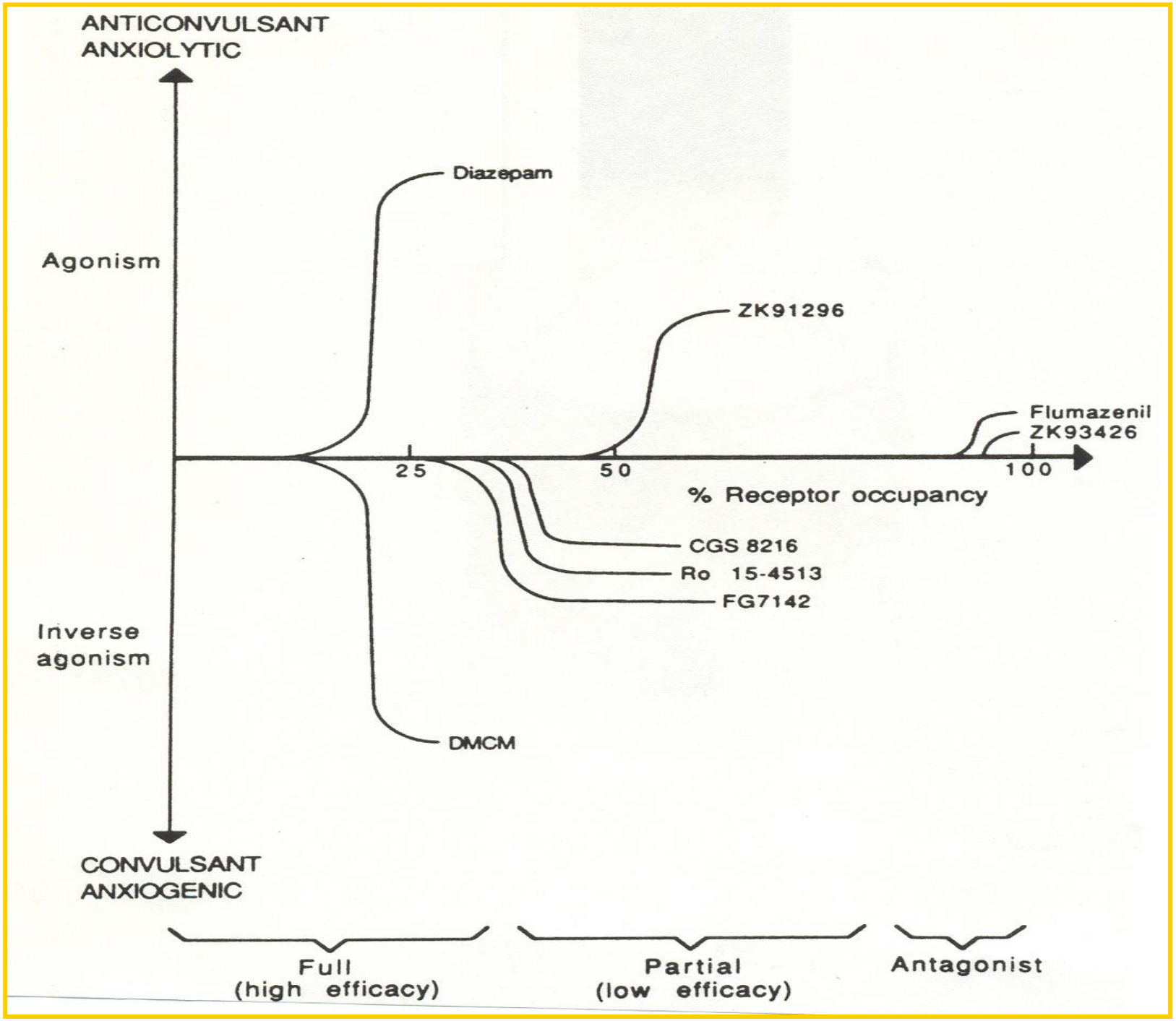
- Afinidad
- Actividad intrínseca (AI)
- Espectro de AI
  - Antagonista
  - Agonistas parciales
  - Agonistas totales
  - Agonistas inversos
- Reserva Receptorial
- Constante de disociación
- Transmisión por volumen
- Transmisión punto a punto (wired trans)

allosteric ligands

Erminio Costa

(1924-2009)




ANTICONVULSANT
ANXIOLYTIC
Agonism
Diazepam
ZK91296
Flumazenil
ZK93426
25
50
100
% Receptor occupancy
CGS 8216
Ro 15-4513
FG7142
Inverse
agonism
DMCM
CONVULSANT
ANXIOGENIC
Full
(high efficacy)
Partial
(low efficacy)
Antagonist

$GABA_A$ Receptor Alpha Subunits and Associated Actions

	ACTION	PROPORTION OF GABA RECEPTORS	LOCATION
α_1	Sedative, amnestic, anticonvulsant	60%	All brain regions Cortex, hippocampus
α_2	Anxiolytic, myorelaxant	15–20%	Cortex, hippocampus, amygdala, forebrain, hypothalamus
α_3	Anxiolytic, myorelaxant	10–15%	Cerebral cortex, thalamus (reticular nucleus)
α_4, α_6	Insensitive to BZ		Dentate gyrus
α_5	High affinity for BZ Low affinity for zolpidem BZ tolerance		Cerebral cortex, hippocampus

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonhypnotics Sometimes Used to Aid Sleep‖				
Clonazepam (Klonopin)	20–40	1–2.5	4-Amino derivative	0.5–1**
Diazepam (Valium)	30–100		*N*-desmethyl	2–10**
Chlordiazepoxide (Librium)	24–28		*N*-desmethyl (chlordiazepoxide, demoxepam, oxazepam)	10–25**
Alprazolam	6–20	0.6–1.4		0.5–1**
Lorazepam	10–20	0.7–1		0.5–1**
Quetiapine (Seroquel)	6	1–2	Quetiapine sulfoxide	25–50**
Trazodone (Desyrel)	9 (7–15)	1–2	*m*-CPP	25–50**

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

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Diazepam (Valium)	30–100		*N*-desmethyl	2–10**
Chlordiazepoxide (Librium)	24–28		*N*-desmethyl (chlordiazepoxide, demoxepam, oxazepam)	10–25**
Alprazolam	6–20	0.6–1.4		0.5–1**
Lorazepam	10–20	0.7–1		0.5–1**
Quetiapine (Seroquel)	6	1–2	Quetiapine sulfoxide	25–50**
Trazodone (Desyrel)	9 (7–15)	1–2	*m*-CPP	25–50**

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Benzodiazepine Hypnotics†				
Quazepam (Doral)	48–120	2–3	*N*-desalkyl (flurazepam)	7.5–15
Flurazepam (Dalmane)	48–120	1.5–4.5	*N*-desalkyl (flurazepam)	15–30
Triazolam (Halcion)	2–6	1–2	None	0.125–0.25
Estazolam (ProSom)	8–24	1.5–2	None	1–2
Temazepam‡ (Restoril)	8–20	1–2	None	15–30
Loprazolam§ (Dormonoct)	4.6–11.4		None	1–2
Flunitrazepam§ (Rohypnol)	10.7–20.3		*N*-desmethyl (flunitrazepam)	0.5–1
Lormetazepam§ (Loramet)	7.9–11.4		None	1–2 (Elderly: 0.5–1)
Nitrazepam§ (Alodorm)	25–35		None	5–10

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonbenzodiazepine Hypnotics				
Zolpidem: Oral tablet	2.5 (1.4–4.5)	1.6 (0.5–1.5)	None	5 (age >65 yrs) 5–10 (age <65 yr)
Zolpidem: Extended release (Ambien CR)	2.8 (1.6–4.5)	1.5 (1.5–2.0)	None	6.25–12.5
Zolpidem: Sublingual (Intermezzo)	2.5 (1.4–3.6)	0.6 (0.6–1.3)		women: 1.75; men: 3.5
Zolpidem: Sublingual (Edluar)	2.7 (1.5–6.7)	1.4 (0.5–3.0)		5–10
Zolpidem: Oral spray (Zolpimist)	2.8 (1.7–8.4)	0.9		10
Zopiclone[§] (Imovane)	5–6		None	3.75 (age >65 yr) 7.5 (age <65 yrs)
Zaleplon (Sonata)	1 (0.8–1.3)	1 (0.5–2)	None	5–10
Eszopiclone (Lunesta) **(the first hypnotic by the FDA without a limit on duration of administration).**	6 (5–8)	1.5 (0.5–2)	None	2–3 (age <65 yr); 1–2 (age >65 yr)
Ramelteon, tasimelteon	1–2.6[¶]	0.75 (0.5–1.5)	M-II	8
Doxepin	15 (10–30)	3.5 (1.5–4)		3–6 (Silenor) 10–50[**] (generic)
Suvorexant **(dual orexin receptor antagonist)**	12	0.5–6.0	None	10–20

Benzodiazepines and “Z-Drug”-Induced Sleep/Sedation: Mechanisms and Circuitry

- Benzodiazepines such as diazepam and the z-drugs (e.g. zolpidem) reduce the time to sleep (decrease sleep latency), increase sleep continuity and total sleep time, decrease REM sleep and increase REM sleep latency.
- Lower power in the NREM range induced by these drugs might mean a less deep sleep or a less restorative sleep.
- Zolpidem-induced sleep has decreased EEG power in the 5–16 HZ range, relative to that in natural sleep, and benzodiazepines depress the EEG power even further.

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Benzodiazepines and “Z-Drug”-Induced Sleep/Sedation: Mechanisms and Circuitry

- Diazepam and the other benzodiazepines work as PAMs on α1βγ2, α2βγ2, α3βγ2 and α5βγ2 receptors and do not differentiate between them, whereas zolpidem enhances GABA’s action mainly on three GABA A receptor subtypes: α1βγ2, α2βγ2 and α3βγ2.
- Zolpidem has the highest binding affinity at α1βγ2-containing receptors but only by 20-fold, meaning that in practice at normal doses in vivo zolpidem also acts as a PAM at α2βγ2 and α3βγ2 receptors , and zolpidem cannot really be called an “α1-selective compound”.

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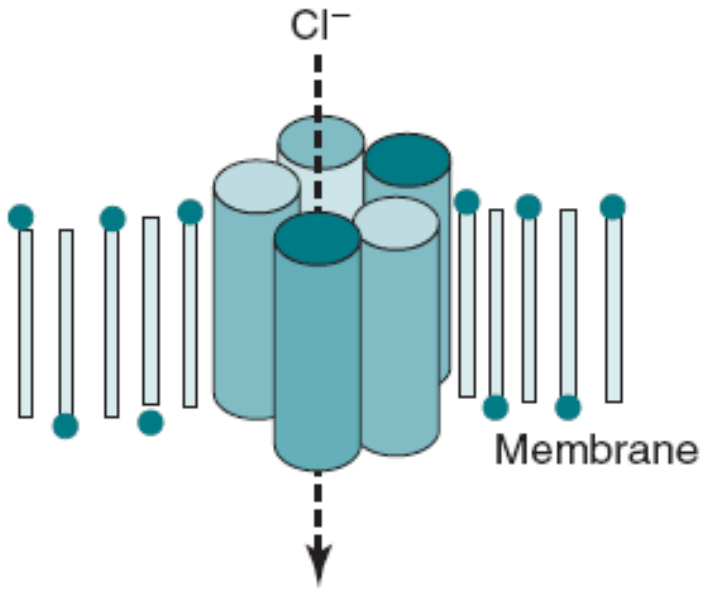
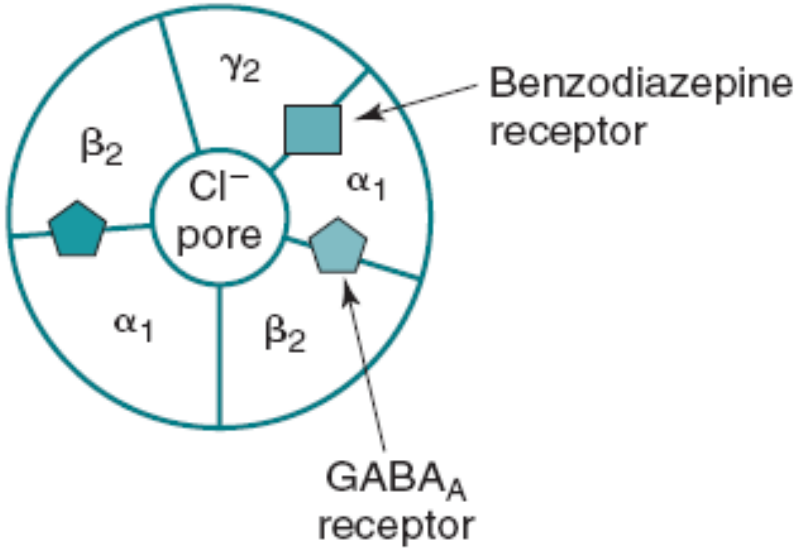
ZOLPIDEM

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonbenzodiazepine Hypnotics				
Zolpidem: Oral tablet	2.5 (1.4–4.5)	1.6 (0.5–1.5)	None	5 (age >65 yrs) 5–10 (age <65 yr)
Zolpidem: Extended release (Ambien CR)	2.8 (1.6–4.5)	1.5 (1.5–2.0)	None	6.25–12.5
Zolpidem: Sublingual (Intermezzo)	2.5 (1.4–3.6)	0.6 (0.6–1.3)		women: 1.75; men: 3.5
Zolpidem: Sublingual (Edluar)	2.7 (1.5–6.7)	1.4 (0.5–3.0)		5–10
Zolpidem: Oral spray (Zolpimist)	2.8 (1.7–8.4)	0.9		10
Zopiclone[§] (Imovane)	5–6		None	3.75 (age >65 yr) 7.5 (age <65 yrs)
Zaleplon (Sonata)	1 (0.8–1.3)	1 (0.5–2)	None	5–10
Eszopiclone (Lunesta)	6 (5–8)	1.5 (0.5–2)	None	2–3 (age <65 yr); 1–2 (age >65 yr)
Ramelteon, tasimelteon	1–2.6[¶]	0.75 (0.5–1.5)	M-II	8
Doxepin	15 (10–30)	3.5 (1.5–4)		3–6 (Silenor) 10–50[**] (generic)
Suvorexant (dual orexin receptor antagonist)	12	0.5–6.0	None	10–20

(the first hypnotic by the FDA without a limit on duration of administration).





SUBUNITS

- Alpha (α_1, α_2, α_3, α_4, α_5, α_6)
- Beta (β_1, β_2, β_3, β_4)
- Gamma (γ_1, γ_2, γ_3)
- Delta (δ)
- Epislon (ε)
- Pi (π)
- Rho (ρ_1, ρ_2, ρ_3)
- Most common $GABA_A$ receptor is (α_1, β_2, γ_2) (understood to mean 2 α_1, 2 β_2, 1 γ_2)

Relative Binding of Benzodiazepine Receptor Subtypes

	ALPHA 1	ALPHA 2	ALPHA 3	ALPHA 5
Zaleplon	17×	2×	2×	1×
Zolpidem	21×	1×	1×	Negligible
Eszopiclone	8×	5×	1×	8×

1× = the lowest affinity of a given drug for any receptor.

- Zolpidem tartrate is a non-benzodiazepine sedative-hypnotic for the short-term treatment of insomnia.
- Unlike the benzodiazepines, zolpidem produces muscle relaxation and anticonvulsant effects only at doses much higher than the hypnotic dose.
- Zolpidem has a rapid onset of action and should be taken immediately before retiring or for middle-of-the night awakening.
- Zolpidem has a short half-life and no active metabolites, which reduces the possibility of residual next-day effects from prolonged or excessive sedation.
- Rebound insomnia or signs of withdrawal have not been significantly greater than placebo.

(Drug Information Provided By Gold Standard, november 10, 2017)

- **Mechanism of Action:** Subunit modulation of the GABA-A receptor chloride channel macromolecular complex is responsible for sedative drug properties. The main site of modulatory drug action is located within the GABA-A receptor complex on the alpha-subunit, which is known as the benzodiazepine (BZ) or omega receptor.
- In contrast to the benzodiazepines, which non-selectively interact with all three known omega-receptor subtypes; zolpidem preferentially binds to the omega-1 receptor.

(Drug Information Provided By Gold Standard, november 10, 2017)

Abstract: The effect of ω (benzodiazepine)-receptor agonists, antagonists, and inverse agonists on the electrically evoked release of 5-[^{3}H]hydroxytryptamine ([^{3}H]5-HT) was studied in superfused slices of the rat frontal cerebral cortex.

Alvaro Lista, Sonia Arbilla, and Salomon Z. Langer

Department of Biology, Laboratoires d'Etudes et de Recherches Synthélabo (L.E.R.S.), Paris, France

J. Neurochem. **51, 1414-1421 (1988)**

Langer S. Z. and Arbilla S. (1988*a*) Imidazopyridines as a tool for the characterization of benzodiazepine receptors: a proposal for a pharmacological classification as omega receptor subtypes. *Pharmacol. Biochem. Behav.* **29,** 763–766.

Langer S. Z. and Arbilla S. (1988*b*) Limitations of the benzodiazepine receptor nomenclature: a proposal for a pharmacological classification as omega receptor subtypes. *Fund. Clin. Pharmacol.* **2,** 159–170.

(CINP CONGRESS, MUNICH, 1988. OLEN RAFAELSEN AWARD CEREMONY)

- **Pharmacokinetics:** Zolpidem is administered orally as an immediate-release tablet, controlled-release tablet, lingual spray, and sublingual tablet.
- It is about 92% bound to plasma protein.
- Hepatic metabolism through CYP isoenzymes produces inactive metabolites that are primarily excreted in the urine. Approximately 61% of zolpidem is metabolized by CYP3A4, with minor metabolism pathways by CYP2C9 (22%), CYP1A2 (14%), CYP2D6 (less than 3%), and CYP2C19 (less than 3%)
- Immediate-release zolpidem has not been shown to accumulate in studies ranging up to 2 weeks.
- The **mean elimination half-life** of the immediate-release tablets is **2.6 hours** in patients with normal hepatic and renal function.
- In single-dose studies in subjects administered 5 mg and 10 mg zolpidem, the mean peak concentrations (Cmax) were 59 (range: 29—113) and 121 (range: 58—272) ng/ml, respectively, occurring at a mean time **(Tmax) of 1.6** hours for both

(Drug Information Provided By Gold Standard, november 10, 2017)

- Most of the adverse effects associated with zolpidem therapy are dose-dependent and CNS-related.
- Drowsiness (> 1—8%), lethargy (3%), fatigue (3%) and confusion (> 1%).
- Tolerance has been reported in less than 1/1000 patients across the entire pre-approval database of zolpidem.

(Drug Information Provided By Gold Standard, november 10, 2017)

ESZOPICLONA

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
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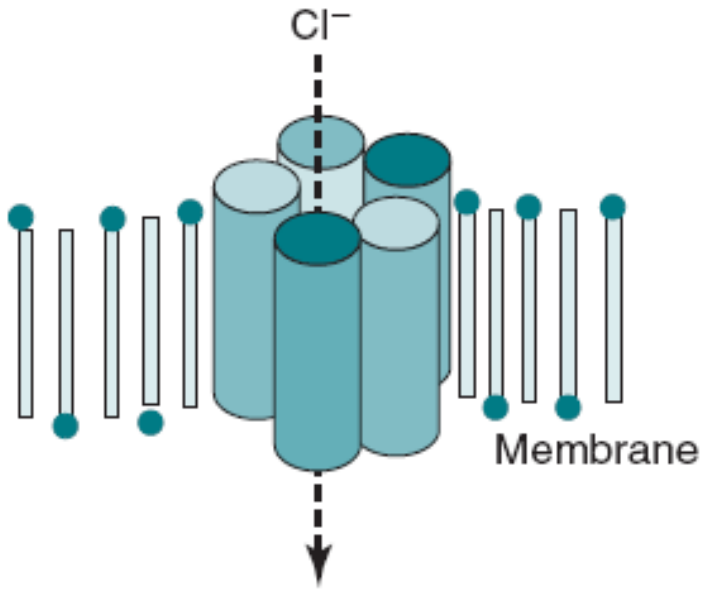
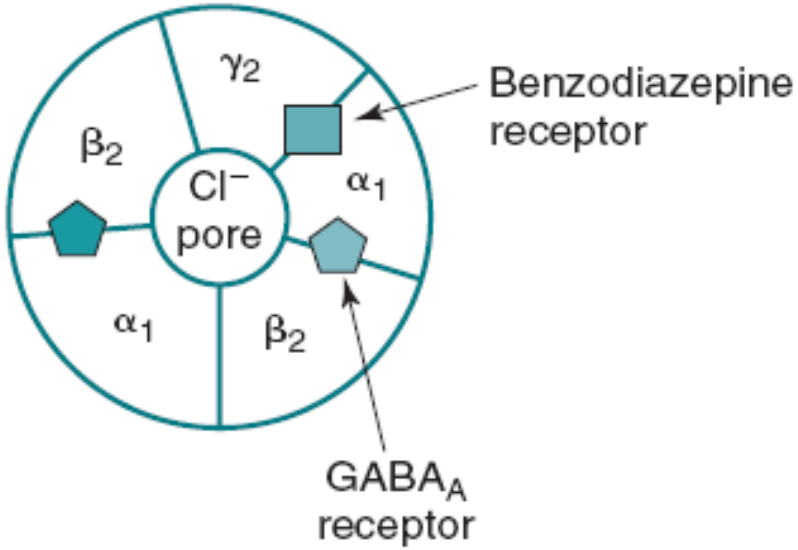
Zolpidem: Extended release (Ambien CR)	2.8 (1.6–4.5)	1.5 (1.5–2.0)	None	6.25–12.5
Zolpidem: Sublingual (Intermezzo)	2.5 (1.4–3.6)	0.6 (0.6–1.3)		women: 1.75; men: 3.5
Zolpidem: Sublingual (Edluar)	2.7 (1.5–6.7)	1.4 (0.5–3.0)		5–10
Zolpidem: Oral spray (Zolpimist)	2.8 (1.7–8.4)	0.9		10
Zopiclone[§] (Imovane)	5–6		None	3.75 (age >65 yr) 7.5 (age <65 yrs)
Zaleplon (Sonata)	1 (0.8–1.3)	1 (0.5–2)	None	5–10
Eszopiclone (Lunesta)	6 (5–8)	1.5 (0.5–2)	None	2–3 (age <65 yr); 1–2 (age >65 yr)
Ramelteon, tasimelteon	1–2.6[¶]	0.75 (0.5–1.5)	M-II	8
Doxepin	15 (10–30)	3.5 (1.5–4)		3–6 (Silenor) 10–50[**] (generic)
Suvorexant (dual orexin receptor antagonist)	12	0.5–6.0	None	10–20

(the first hypnotic by the FDA without a limit on duration of administration).





SUBUNITS

- Alpha (α_1, α_2, α_3, α_4, α_5, α_6)
- Beta (β_1, β_2, β_3, β_4)
- Gamma (γ_1, γ_2, γ_3)
- Delta (δ)
- Epislon (ε)
- Pi (π)
- Rho (ρ_1, ρ_2, ρ_3)
- Most common $GABA_A$ receptor is (α_1, β_2, γ_2) (understood to mean 2 α_1, 2 β_2, 1 γ_2)

Relative Binding of Benzodiazepine Receptor Subtypes

	ALPHA 1	ALPHA 2	ALPHA 3	ALPHA 5
Zaleplon	17×	2×	2×	1×
Zolpidem	21×	1×	1×	Negligible
Eszopiclone	8×	5×	1×	8×

1× = the lowest affinity of a given drug for any receptor.

- Eszopiclone is the S-isomer of racemic zopiclone, a cyclopyrrolone with sedative-hypnotic activity.
- Bind at all $GABA_A$subtypes.
- **The pharmacokinetics of eszopiclone**: is rapidly absorbed and extensively distributed to body tissues including the brain. It is weakly bound to plasma protein (52%–59%).
- Peak plasma concentrations (t_{max}) are attained 1.0–1.6 hours after a single therapeutic dose of 3 mg, and the terminal-phase elimination half-life ($t_{½}$) amounts to approximately 6.0 hours.
- Eszopiclone is metabolized in the liver, CYP3A4 and CYP2E1 are the major enzymes involved in metabolism.

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

- The recommended starting dose of eszopiclone for non-elderly insomniac patients is 2 mg. If necessary the amount of drug can be increased to 3 mg. Elderly patients should receive initially 1 mg eszopiclone immediately before bedtime.
- The most commonly reported side-effect was unpleasant or bitter taste followed by headache, dyspepsia, pain, diarrhea, dry mouth, dizziness, and accidental injury.
- Rebound insomnia: discontinuation of the active treatment was followed by a significant increase of WASO and a reduction of sleep efficiency on the first night of withdrawal compared with baseline.

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Chapter 41 Hypnotic Medications: Mechanisms of Action and Pharmacologic Effects

- The benzodiazepines are potent suppressors of slow wave sleep.
- The non benzodiazepine **zolpidem** shares with the benzodiazepines the very mild effects on REM sleep but, in contrast, **does not alter slow wave sleep**, which may even increase toward more expected values in patients with insomnia and low baseline levels.
- Potential for dependence. A review of this topic by a panel from academia, industry, and the government concluded that the dependence potential of currently available hypnotics in patients without a history of substance abuse is minimal.

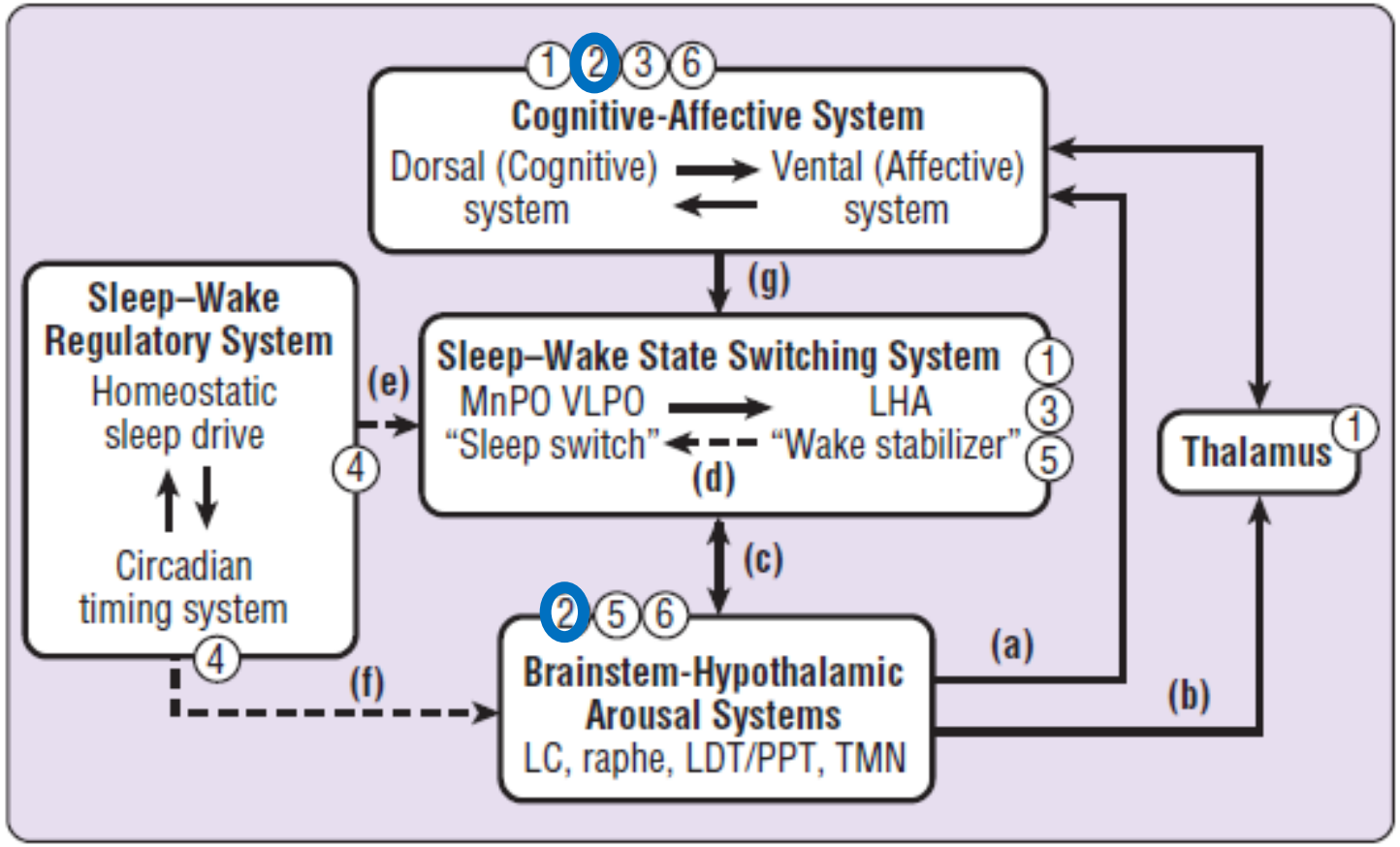
Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

GABA in Neurogenesis

- GABA contributes to the stimulation of proliferation, migration, and neurite outgrowth.
- GABA is essential for the maturation of neurons and formation of functional synapses.
- GABA's role is not simply the creation of new neurons, but also the formation of functional synapses that ultimately lead to repair or improved neurological function.

T. Ikezu, H.E. Gendelman (eds.), *Neuroimmune Pharmacology,* Springer 2017

SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Benzodiazepine receptor agonists (1) may directly affect the sleep-wake state-switching system but also have direct cortical, thalamic, and brainstem effect due to the widespread distribution of GABA-A receptors. **Sedating antidepressant and antipsychotic medications (2), through their activity on monoaminergic systems, affect corticolimbic systems and brainstem-hypothalamic arousal systems.** Antihistamines (3) antagonize histamine-1 (H1) receptors in the hypothalamus and cortex that receive projections from the tuberomamillary nucleus. Melatonin and melatonin receptor agonists (4), through their effects on melatonin-1 (MT1) and MT2 receptors, influence the "wake signal" from the suprachiasmatic nucleus and circadian timing system. Orexin antagonists (5) inhibit the effect of orexin-hypocretin on brainstem and hypothalamic arousal centers, and 5-HT2 antagonists (6) are most likely to have corticolimbic and brainstem sites of action. Thus different types of sleep-promoting drugs achieve their effects through very different actions on very different components of the sleep-wake regulatory system.

Table 42-3 Polysomnographic Effects of Sedating Antidepressant Drugs on Sleep*

Drug	Sleep Latency	Sleep Continuity†	Stage 3/4 NREM Sleep Amount (%)	REM Sleep	Other
Doxepin	↓	↑	↔	↓ amount, % of REM ↑ phasic eye movements (REM density)	↓ sleep apnea (minor effect); ↔ or ↑ periodic limb movements; ↑ restless legs symptoms; may induce eye movements during NREM sleep
Amitriptyline	↓	↑	↔	↓ amount, % of REM ↑ phasic eye movements (REM density)	
Trimipramine	↓	↑	↔	↔ amount, %	
Trazodone	↓	↔ to ↑	↑	↔ amount, % (↓ to ↑ in individual studies)	
Nefazodone	↔	↑	↔	↔	
Mirtazapine	↓	↑	↔	↔	

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

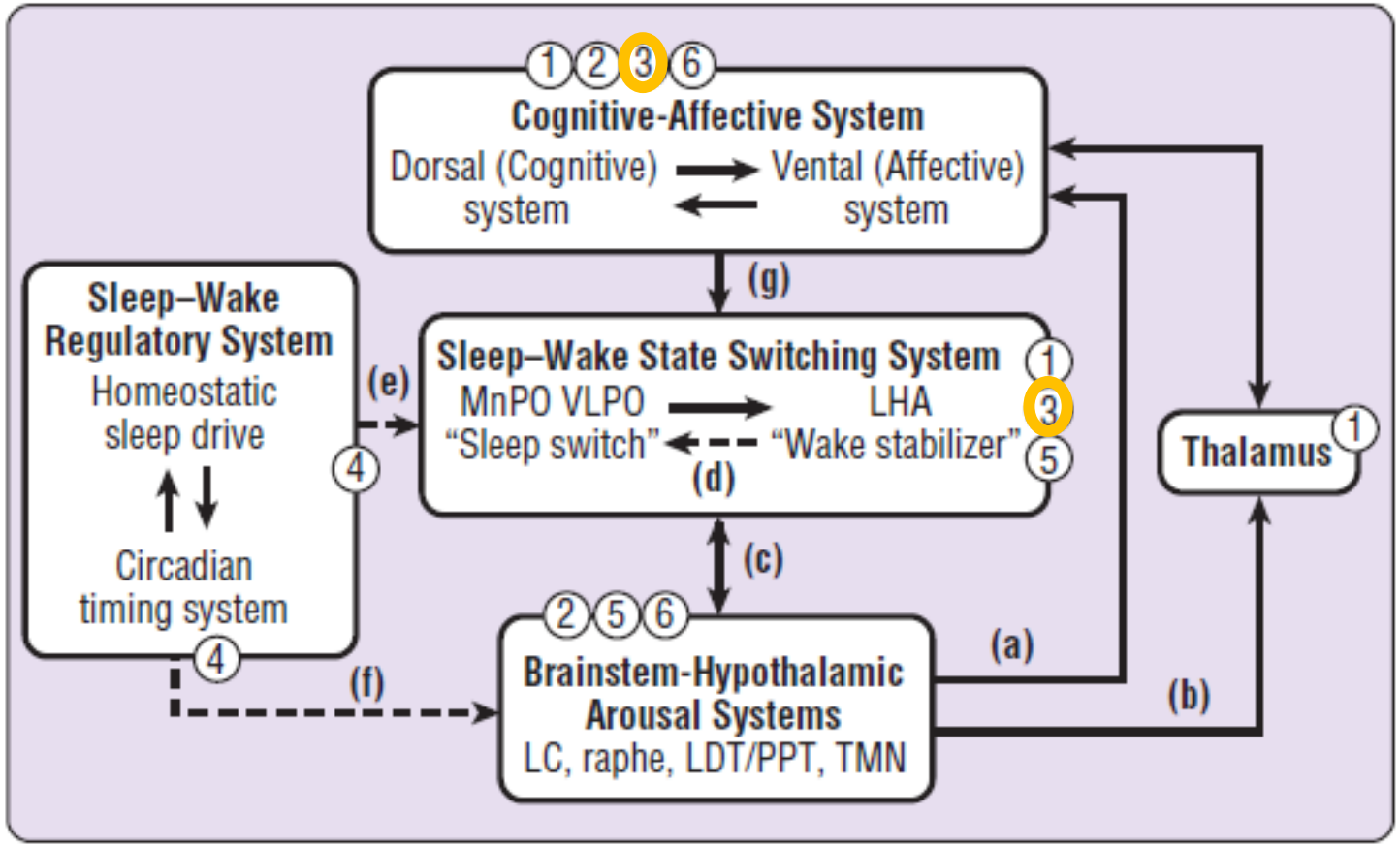
Classes of antidepressant drugs

Class	Generic name of antidepressants	Mode of action
Tricyclic antidepressants (TCAs)	Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine, Desipramine, Nortriptyline, Protriptyline, Amoxapine, Maprotiline	Inhibition of both serotonin and noradrenaline reuptake
Monoamine oxidase inhibitors (MAOIs)		
Irreversible	Iproniazid, Isocarboxazid, Phenelzine, Tranylcypromine	Inhibition of MAO-A and MAO-B
Reversible (Type A)	Moclobemide, Brofaromine	Inhibition of MAO-A (the only MAO implicated in antidepressant effects)
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, Paroxetine, Citalopram, Escitalopram, Fluvoxamine, Sertraline	Selective inhibition of serotonin reuptake
Noradrenaline reuptake inhibitors (NRIs)	Atomoxetine, Reboxetine	Selective inhibition of noradrenaline reuptake
Mixed reuptake inhibitors		
Serotonin–noradrenaline reuptake inhibitiors (SNRIs)	Venlafaxine, Duloxetine	Inhibition of both serotonin and noradrenaline reuptake
Noradrenaline-dopamine reuptake inhibitor (NDRI)	Bupropion	Inhibition of both noradrenaline and dopamine reuptake
Serotonin-2 antagonist and reuptake inhibitors (SARIs)	Nefazodone, Trazodone	Blockade of 5-HT2 receptors and inhibition of serotonin reuptake
Noradrenaline and specific serotonergic antidepressant (NaSSA)	Mirtazapine	Blockade of 5-HT2 receptors and potent antagonist for 5-HT3 and noradrenergic $\alpha 2$ receptors
Modern antidepressant	Agomelatine	Agonist of melatonergic (MT(1) and MT(2)) receptors and antagonist for 5-HT_{2C} receptors

Current Opinion in Neurobiology 2011, 21:858–865

VEMOS LA FARMACOLOGÍA DE TRAZODONA, MIRTAZAPINA Y OTROS EN EL PUNTO 6. (ANTAGONISTAS 5HT2)

SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Benzodiazepine receptor agonists (1) may directly affect the sleep-wake state-switching system but also have direct cortical, thalamic, and brainstem effect due to the widespread distribution of GABA-A receptors. Sedating antidepressant and antipsychotic medications (2), through their activity on monoaminergic systems, affect corticolimbic systems and brainstem-hypothalamic arousal systems. Antihistamines (3) **antagonize histamine-1 (H1) receptors in the hypothalamus and cortex that receive projections from the tuberomamillary nucleus.** Melatonin and melatonin receptor agonists (4), through their effects on melatonin-1 (MT1) and MT2 receptors, influence the "wake signal" from the suprachiasmatic nucleus and circadian timing system. Orexin antagonists (5) inhibit the effect of orexin-hypocretin on brainstem and hypothalamic arousal centers, and 5-HT2 antagonists (6) are most likely to have corticolimbic and brainstem sites of action. Thus different types of sleep-promoting drugs achieve their effects through very different actions on very different components of the sleep-wake regulatory system.

Table 42-4 Summary of Other Drugs Used to Treat Insomnia*

Drug	Drug Type	Time to Maximal Concentration	Metabolism	Elimination Half-Life	Mechanism of Action
Diphenhydramine	Ethanolamine antihistamine	2–2.5 h	Hepatic demethylation, oxidation	4–8 h	Antagonize H_1 receptors
Doxylamine	Ethanolamine antihistamine	2–3 h	Most excreted unchanged in urine; some hepatic metabolism	10	Antagonize H_1 receptors

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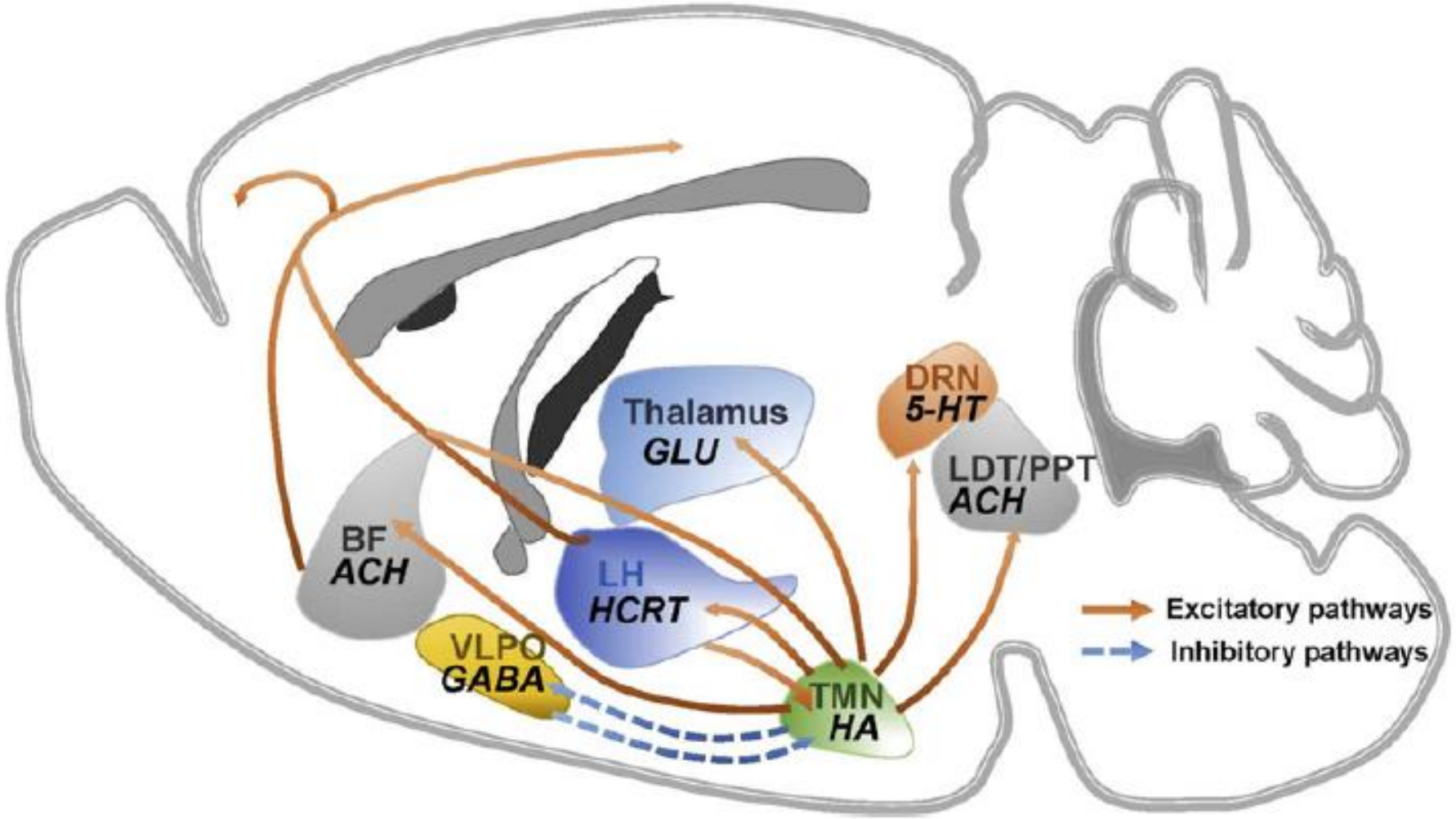
Histamine and Sleep disorders

- Histamine system is known to play a significant role in the modulation of sleep and wakefulness.
- During the transition from wakefulness to sleep, histaminergic neurons stop firing and then remain silent during slow-wave and rapid eye movement (REM) sleep.
- In contrast, they begin firing after the transition from sleep to wakefulness.
- **Histaminergic neuron activity** is lowest during quiet waking, moderate during active waking and **maximal during high vigilance.**
- Central administration of H1R agonists increases wakefulness, whereas administration of H1R antagonists promotes sleep.
- The ventrolateral preoptic nucleus (VLPO) has been implicated in promoting sleep.
- Histamine indirectly inhibits VLPO neurons through the activation of the GABAergic interneuron, which also reciprocally disinhibits histaminergic neurons to favor the wake state.
- In addition, histaminergic axons in the neocortex co-release paracrine GABA to prevent over-activation from histamine, regulating the wakefulness levels. histamine induces cortical activation.
- Histamine can also directly modulate glutamatergic neurons of the thalamus, causing a general excitation effect in multiple brain regions, the cholinergic neurons in the basal forebrain or in the mesopontine tegmentum and activating the serotonergic neurons in the dorsal raphe nucleus, but also by direct projections to the cortex.

W. Hu, Z. Chen / Pharmacology & Therapeutics 175 (2017) 116–132

The action of the histaminergic system in wakefulness through interaction with other neurons in different brain regions



ACH, cholinergic neurons; BF, basal ganglia; DRN, dorsal raphe nucleus; GABA, GABAergic neurons; GLU, glutaminergic neurons; HA, histaminergic neurons; HCRT, hypocretin neurons; 5-HT, 5-hydroxytryptamine expressing (serotonergic) neurons; LDT/PPT: laterodorsal/pedunculopontine tegmental nuclei; LH, lateral hypothalamic; TMN, tuberomammillary nucleus; and VLPO, ventrolateral preoptic nucleus.

W. Hu, Z. Chen / Pharmacology & Therapeutics 175 (2017) 116–132

ANTIHISTAMINES

- Antihistamine drugs used in the treatment of insomnia are reversible antagonists of H1 receptors. Antihistamines are a diverse group of drugs broadly divided clinically into two groups based on their sedative potential.
- First-generation agents include doxepin, diphenhydramine, doxylamine, chlorpheniramine, hydroxyzine, meclizine, promethazine, and cyproheptadine.
- Essentially all of the over-the-counter antihistamine drugs marketed for insomnia treatment include diphenhydramine, the prototype of this class, or doxylamine.
- Second-generation non sedating antihistamine drugs are used primarily for treatment of seasonal, environmental, and other allergic reactions and are not used for the treatment of insomnia.

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

ANTIHISTAMINES
Pharmacokinetics

- Antihistamines are well absorbed from the gastrointestinal tract and widely distributed throughout the body, including the CNS.
- Most first-generation antihistamines, including diphenhydramine, achieve peak plasma concentrations in 2 to 3 hours, and effects usually last 4 to 6 hours; however, specific agents such as chlorpheniramine, hydroxyzine, and meclizine may last up to 24 hours.
- Diphenhydramine is extensively metabolized by CYP enzymes and has an elimination half-life of 4 to 8 hours.

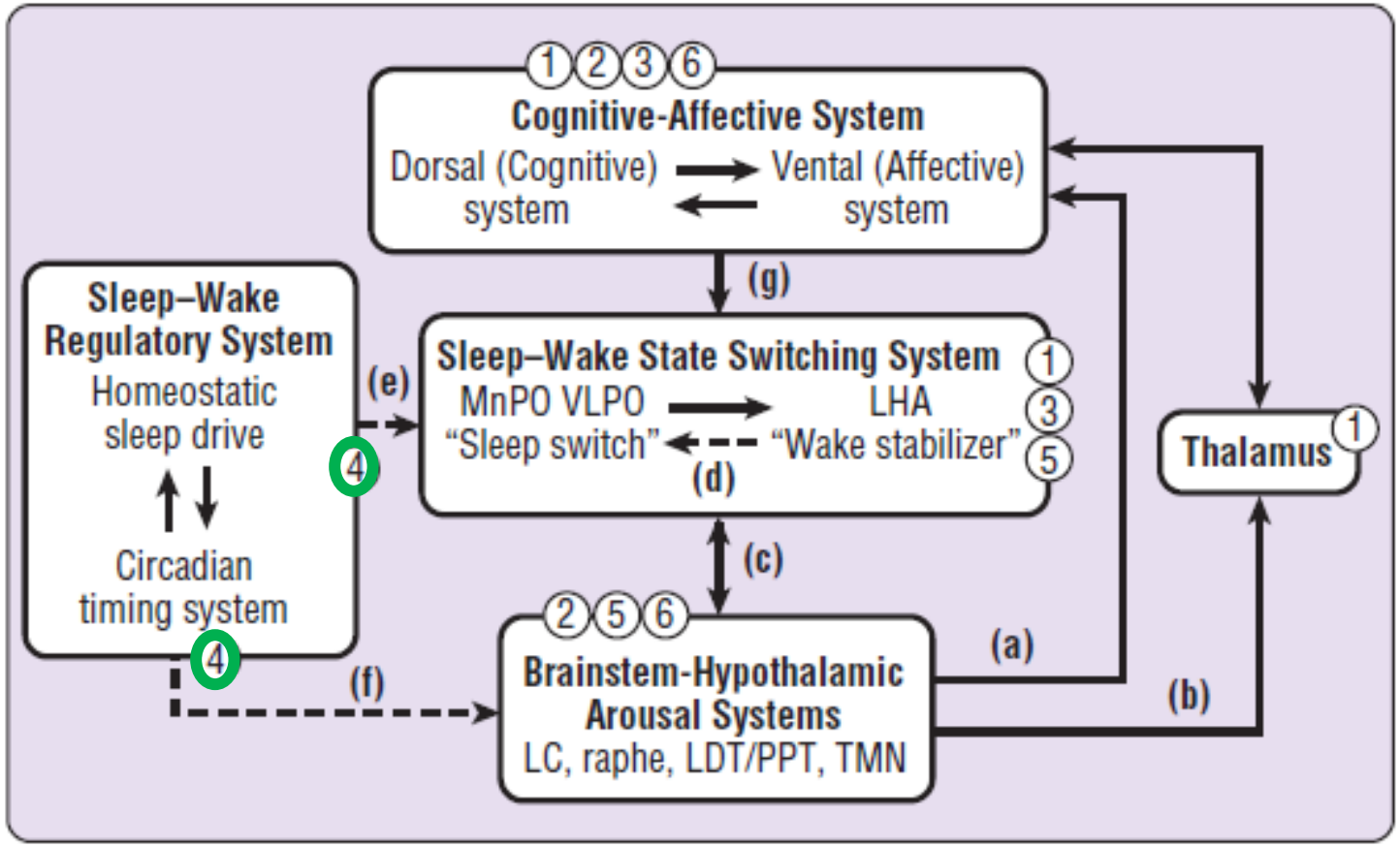
Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

ANTIHISTAMINES
Side Effects

- Impairment of psychomotor performance with diphenhydramine has been well documented.
- Epidemiologic studies have also suggested cognitive impairment associated with diphenhydramine use in the older adults.
- Other side effects related to CNS activity include dizziness, fatigue, and tinnitus.
- Peripheral side effects can include decreased appetite, nausea, vomiting, diarrhea, and constipation as well as **weight gain.**

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Benzodiazepine receptor agonists (1) may directly affect the sleep-wake state-switching system but also have direct cortical, thalamic, and brainstem effect due to the widespread distribution of GABA-A receptors. Sedating antidepressant and antipsychotic medications (2), through their activity on monoaminergic systems, affect corticolimbic systems and brainstem-hypothalamic arousal systems. Antihistamines (3) antagonize histamine-1 (H1) receptors in the hypothalamus and cortex that receive projections from the tuberomamillary nucleus. **Melatonin and melatonin receptor agonists (4), through their effects on melatonin-1 (MT1) and MT2 receptors, influence the "wake signal" from the suprachiasmatic nucleus and circadian timing system**. Orexin antagonists (5) inhibit the effect of orexin-hypocretin on brainstem and hypothalamic arousal centers, and 5-HT2 antagonists (6) are most likely to have corticolimbic and brainstem sites of action. Thus different types of sleep-promoting drugs achieve their effects through very different actions on very different components of the sleep-wake regulatory system.

Table 42-4 Summary of Other Drugs Used to Treat Insomnia*

Drug	Drug Type	Time to Maximal Concentration	Metabolism	Elimination Half-Life	Mechanism of Action
Melatonin	Hormone	20–60 min	Conjugation; oxidation by CYP enzymes	40–60 min	Agonist at melatonin type 1 and type 2 receptors
Diphenhydramine	Ethanolamine antihistamine	2–2.5 h	Hepatic demethylation, oxidation	4–8 h	Antagonize H_1 receptors
Doxylamine	Ethanolamine antihistamine	2–3 h	Most excreted unchanged in urine; some hepatic metabolism	10	Antagonize H_1 receptors
Valerian	Plant extract	Uncertain because of multiple constituents	Uncertain because of multiple constituents	Uncertain because of multiple constituents	Uncertain; may increase GABA formation, interact with L-amino acid transporter receptor, or act as adenosine receptor agonist

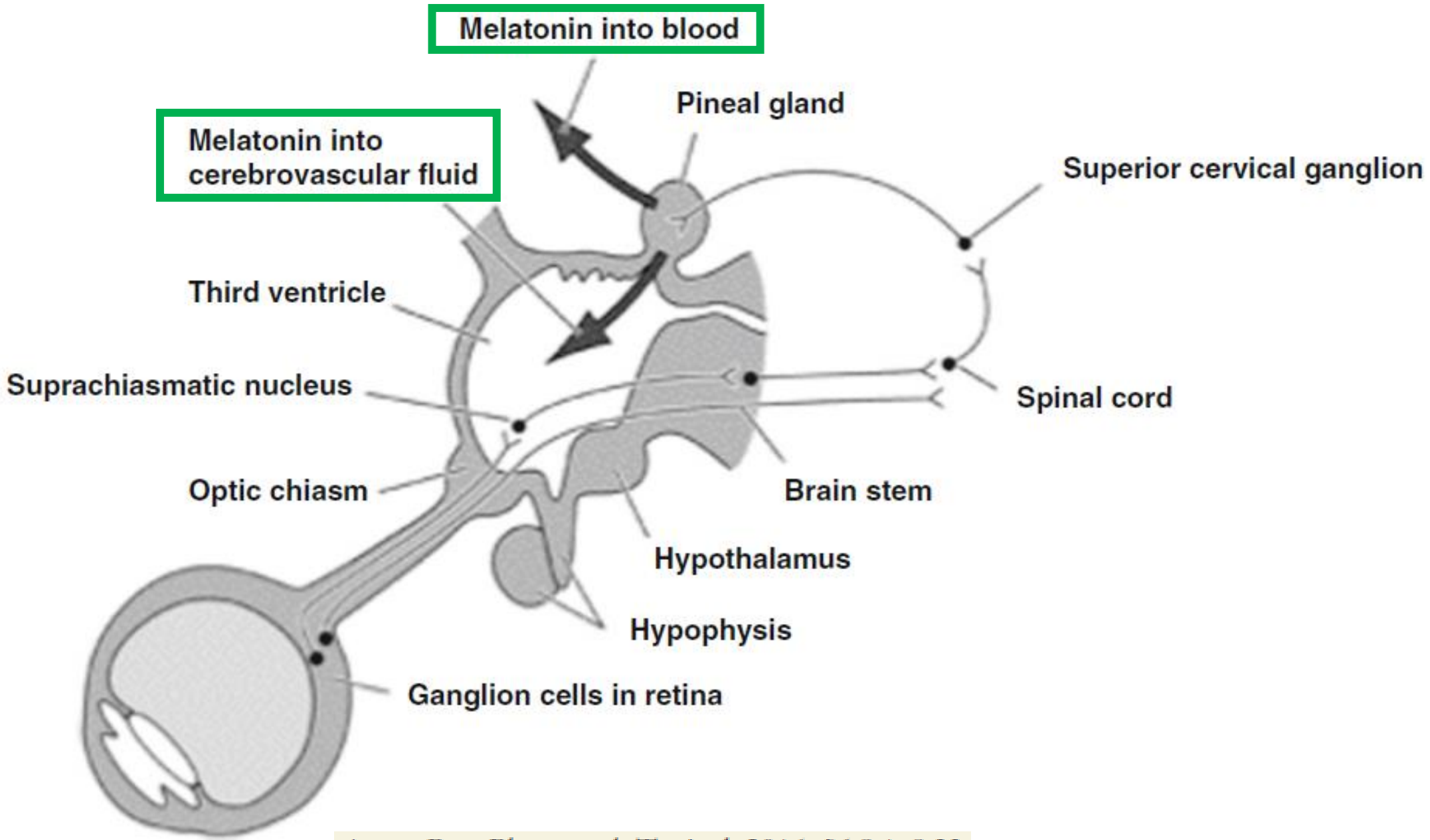
Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Melatonin is a hormone secreted from the pineal gland at night.

- Its peak levels in the dark are associated with age as well as various illnesses.
- **Melatonin plays roles in regulating sleep-wake cycle**, pubertal development and seasonal adaptation.
- Melatonin regulates memory formation by directly affecting hippocampal neurons.
- Melatonin has antinociceptive, antidepressant, anxiolytic, antineophobic and locomotor activity-regulating effects.
- **Melatonin is neuroprotective, anti-inflammatory, pain-modulating, blood pressure-reducing, participates in retinal, vascular, seasonal reproductive, ovarian physiology, osteoblast differentiation, and has anti-tumor and antioxidant effects.**

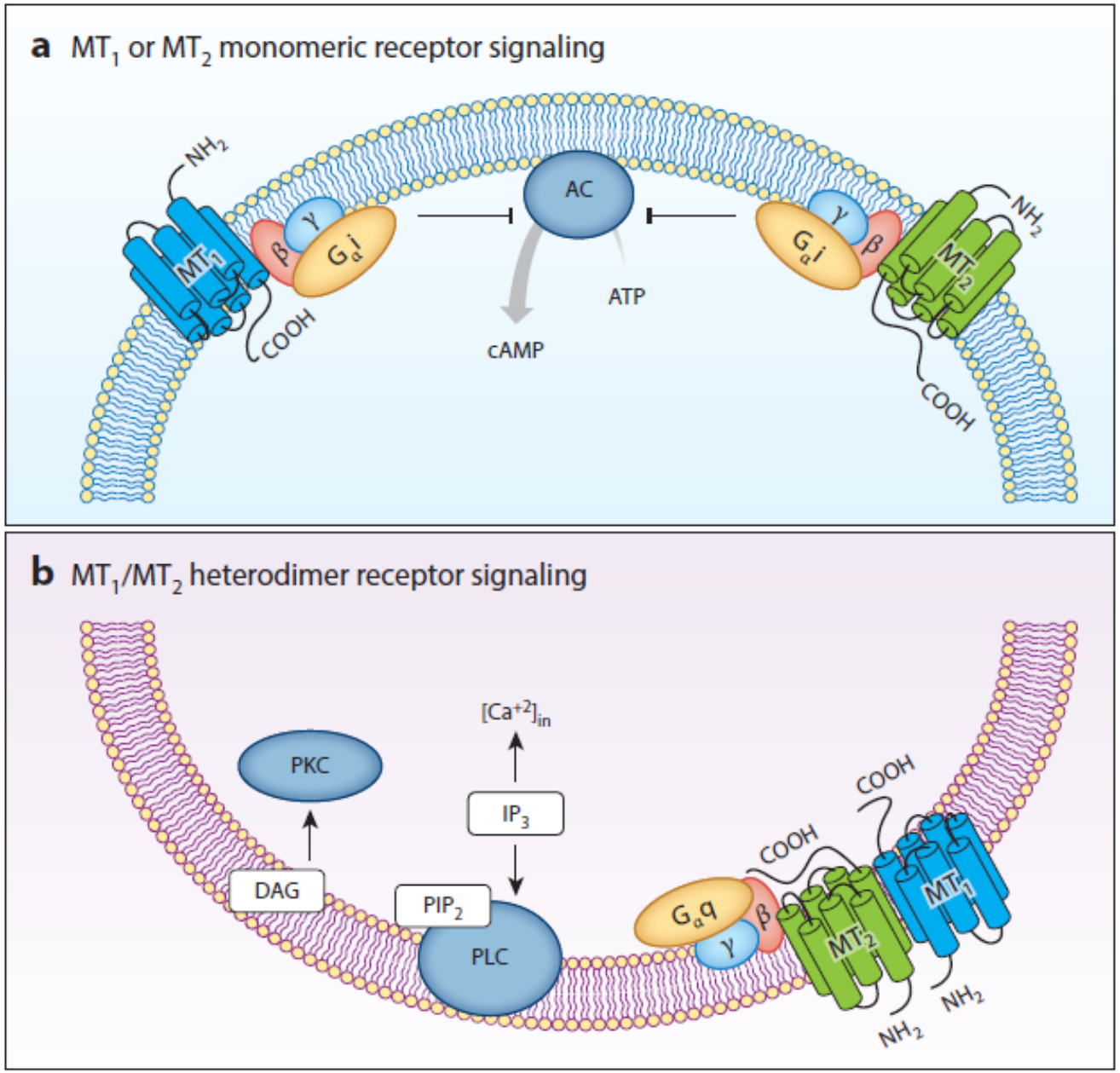
Eurasian J Med. 2016 Jun; 48(2): 135–141.

Retina-pineal gland neuronal circuit, with corresponding hubs



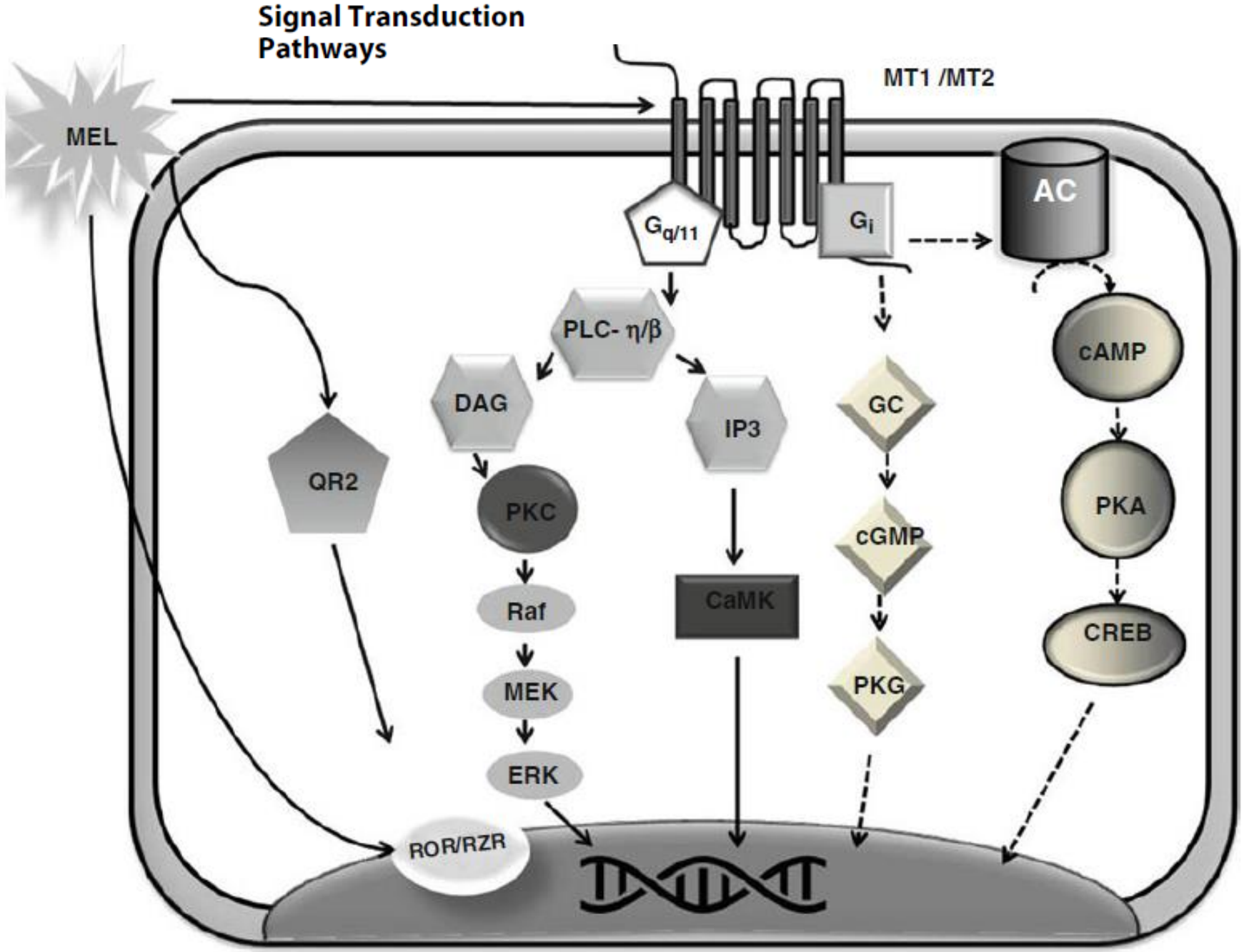
Annu. Rev. Pharmacol. Toxicol. 2016. 56:8.1–8.23

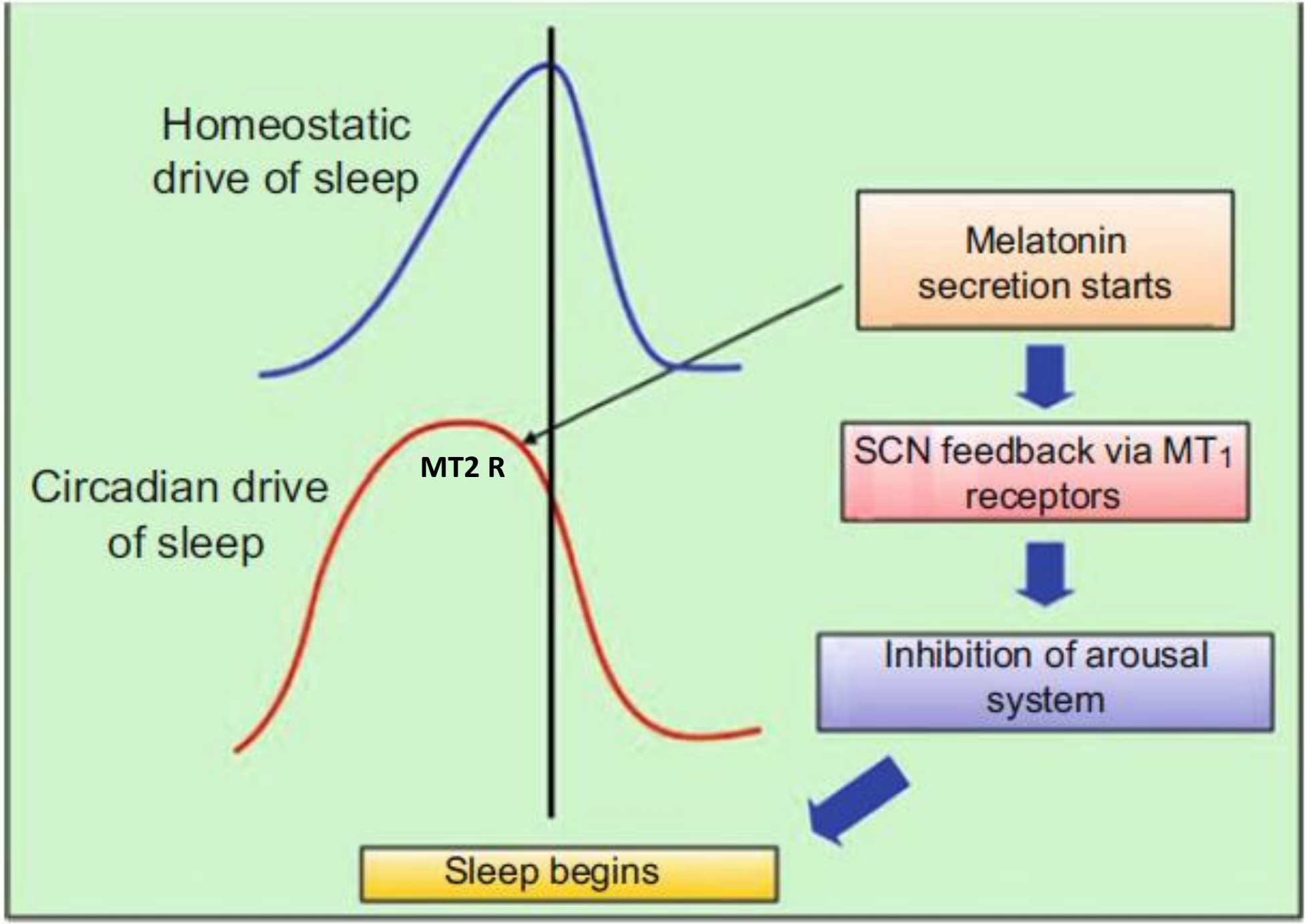
Melatonin receptor signaling.



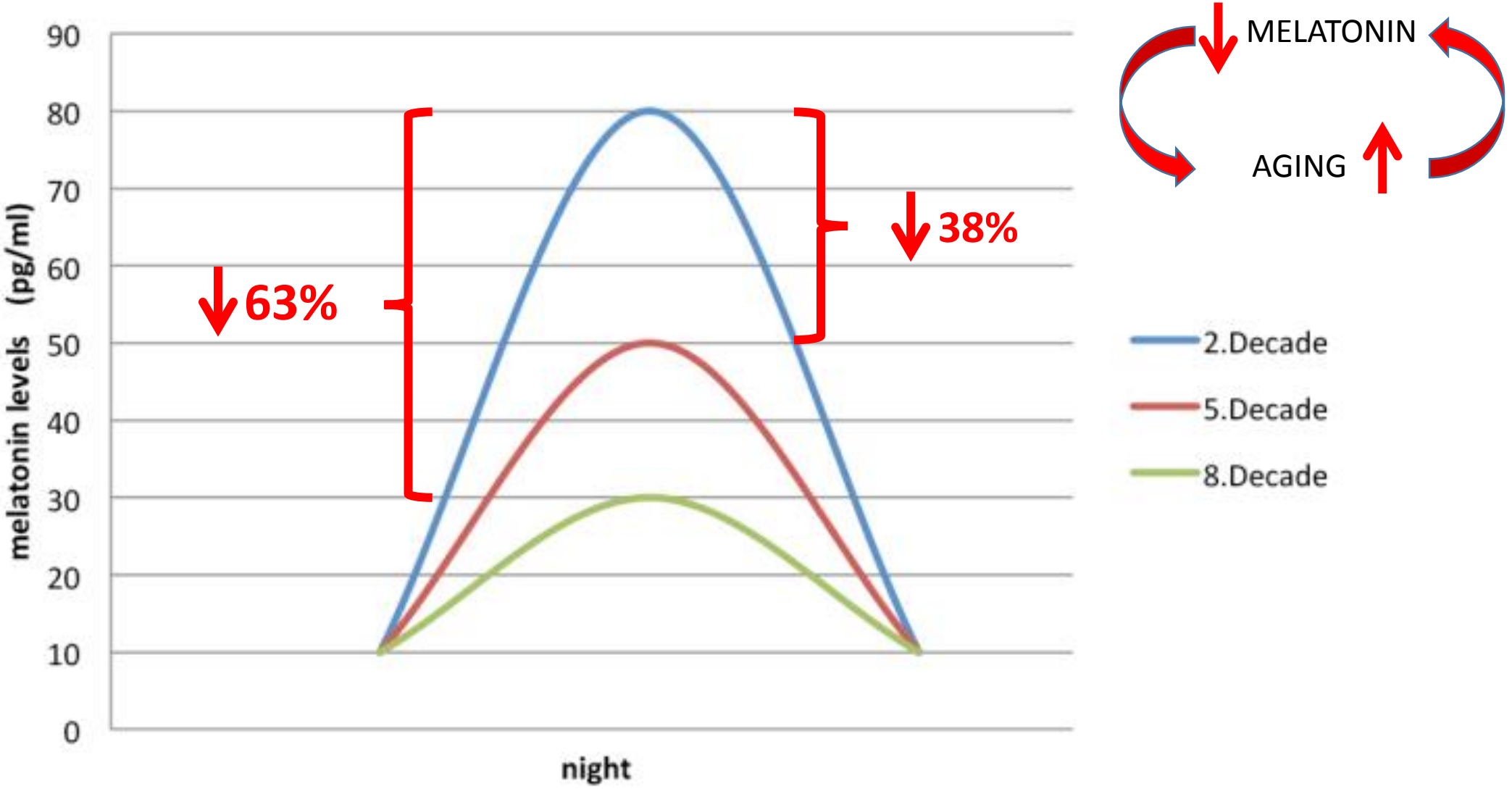
GPCRs

Annu. Rev. Pharmacol. Toxicol. 2016. 56:8.1–8.23

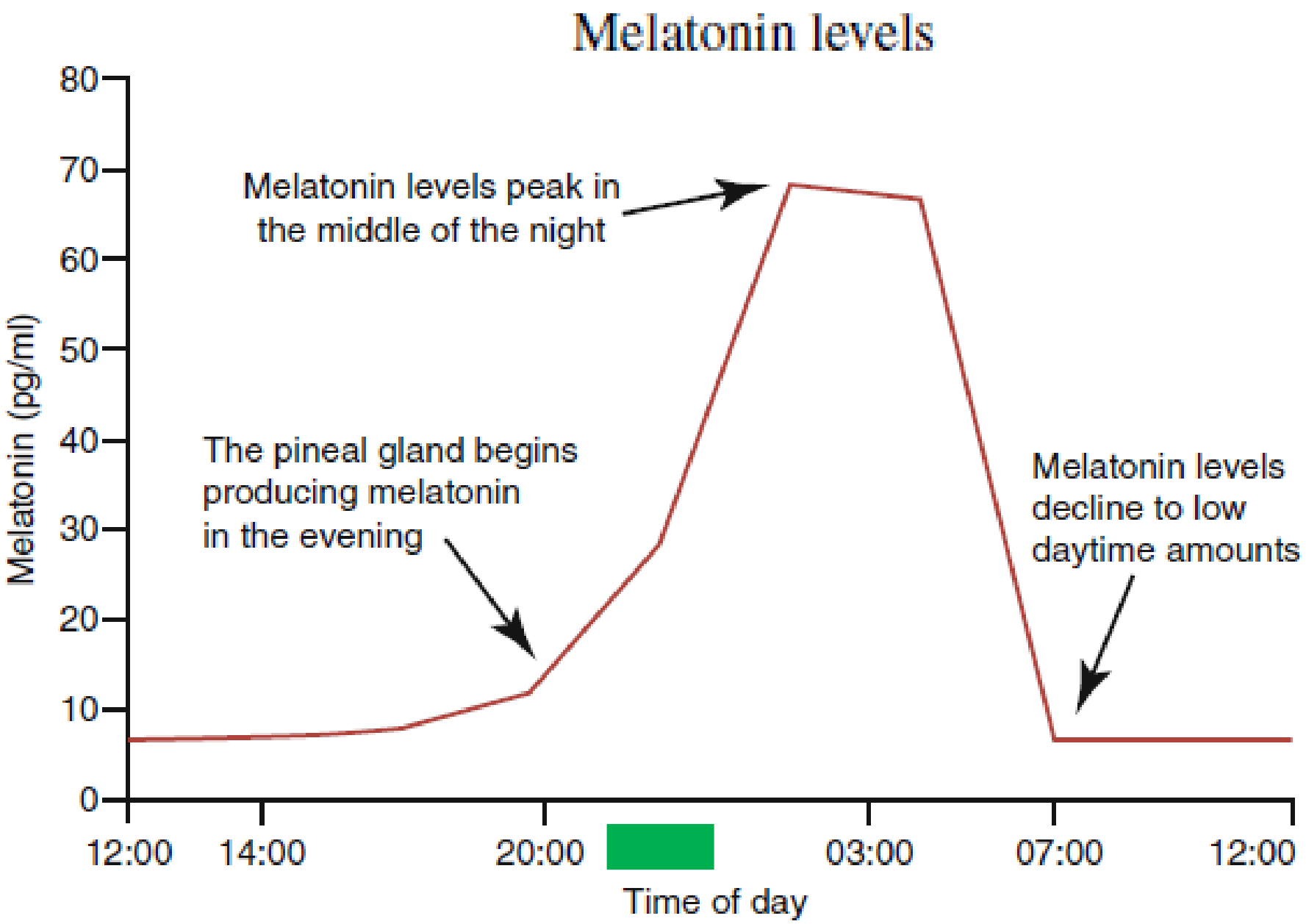

Signal Transduction Pathways
MEL
MT1 /MT2
$G_{q/11}$
G_i
AC
PLC- η/β
DAG
IP3
GC
cAMP
QR2
PKC
cGMP
PKA
Raf
CaMK
CREB
MEK
PKG
ERK
ROR/RZR


Homeostatic drive of sleep
Circadian drive of sleep
MT2 R
Melatonin secretion starts
SCN feedback via MT1 receptors
Inhibition of arousal system
Sleep begins

Peak melatonin levels at night tend to decrease with advanced age in human.

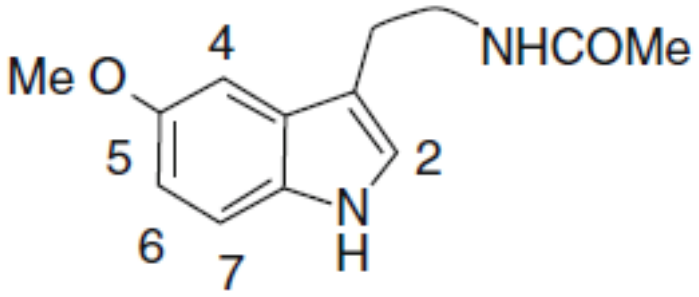


Eurasian J Med. 2016 Jun; 48(2): 135–141.

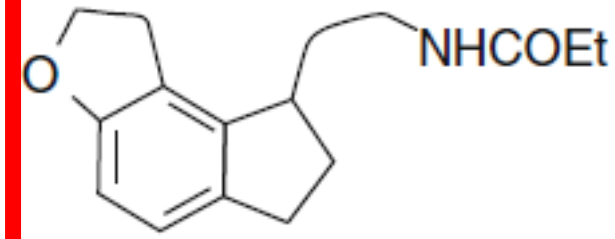


ADMINISTRACIÓN EXÓGENA ENTRE LAS 21 Y 24 HS

Melatonin and melatonergic agonists

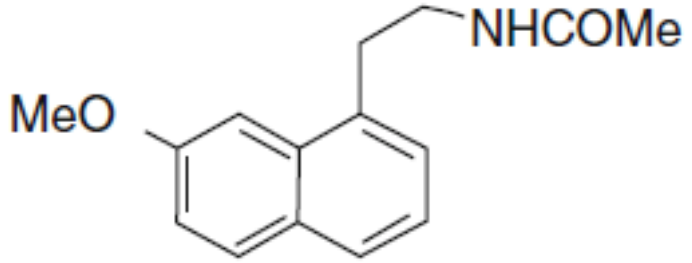


Melatonin



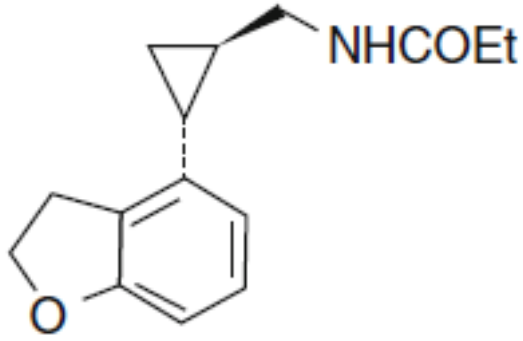
Ramelteon

ROZEREM Takeda



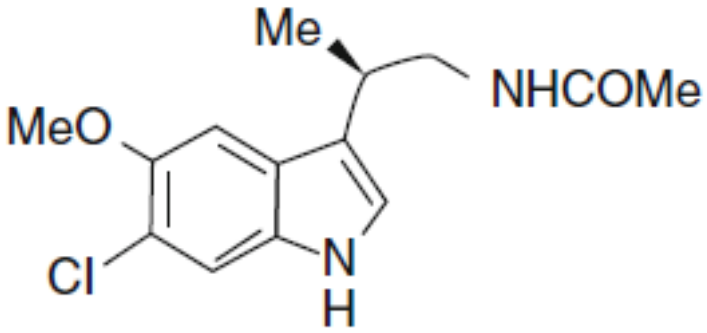
Agomelatine

Valdoxan SERVIER



Tasimelteon (VEC - 162)

HETLIOZ VANDA



TIK-301 (PD-6735, LY15673)

V. Srinivasan et al. (eds.), *Melatonin and Melatonergic Drugs in Clinical Practice*, Springer India 2014

MT_1 receptor

Ligand	Action	Affinity	Units
[^{3}H]melatonin	Full agonist	9.4 – 9.9	pK_d
ramelteon	Full agonist	10.9	pK_i
tasimelteon	Full agonist	9.5	pK_i
agomelatine	Full agonist	10.0 – 10.4	pK_i

MT_2 receptor

[^{3}H]melatonin	Full agonist	9.0 – 9.6	pK_d
ramelteon	Full agonist	10.0	pK_i
tasimelteon	Full agonist	10.2	pK_i
agomelatine	Full agonist	9.9 – 10.5	pK_i

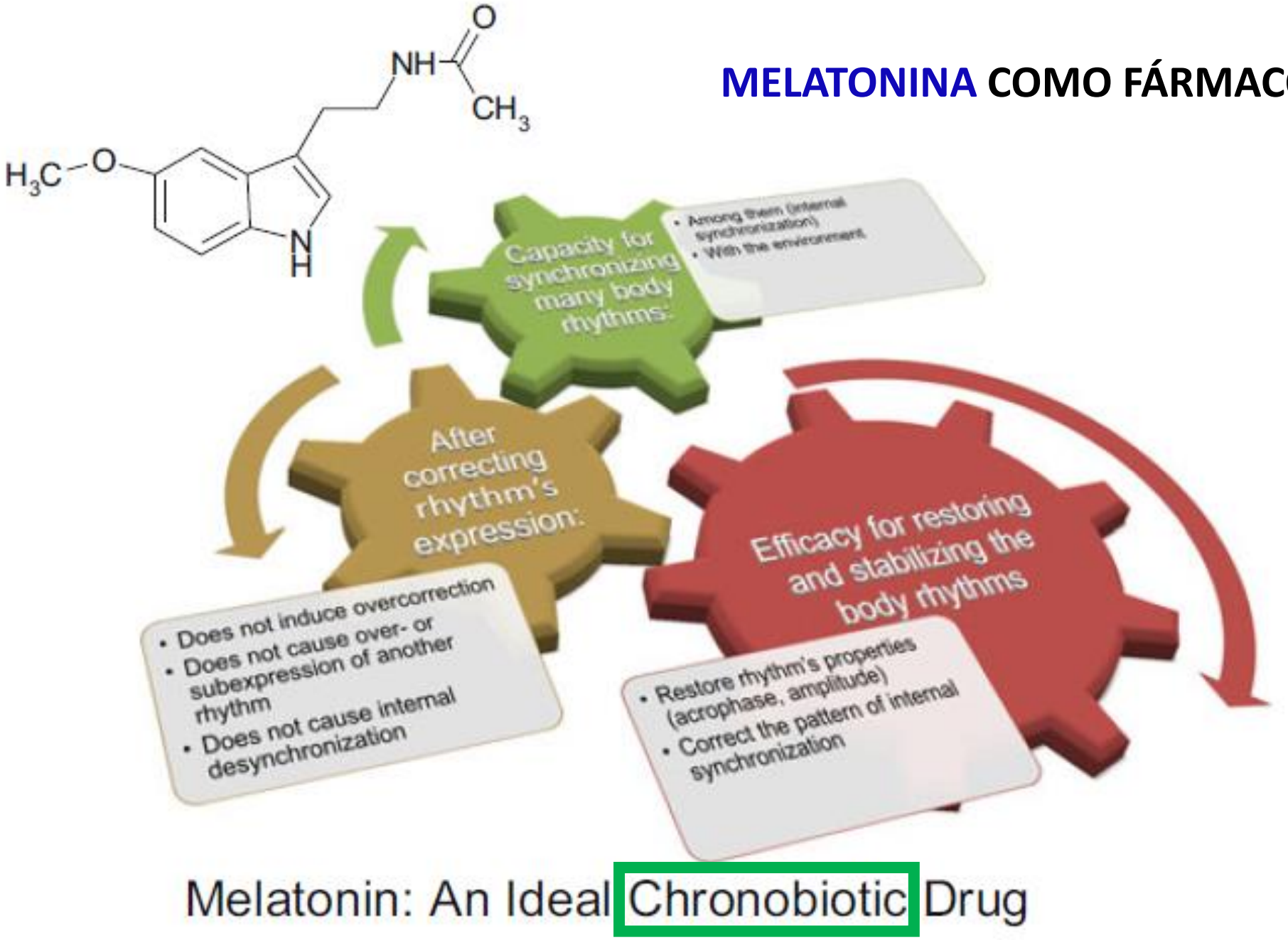
FARMACOLOGÍA

- **Farmacocinética:** La concentración plasmática máxima de la melatonina endógena en adultos llega a 60-70 pg/ml entre las 2 a 4 am. La suplementación exógena de melatonina tiene una baja biodisponibilidad, entre 15 a 20 % en dosis de 3 a 5 mg vía oral. Melatonina tiene una rápida absorción, con una **Tmax** de 23 minutos. La **vida media** de la melatonina es de 36 a 45 minutos.
- **Dosificación:** Para el uso más extendido, mejorar la calidad del sueño, la dosis de 3 mg 30 a 40 minutos antes de ir dormir es la más usada. Las indicaciones cada vez más extendidas de melatonina en diferentes situaciones clínicas ha llevado al uso de dosis variables.

FARMACOLOGÍA

- **Interacciones farmacológicas:**
- Melatonina tiene un perfil de seguridad único. En experimentos animales no se pudo determinar toxicidad en dosis 10.000 veces superiores a las usadas en humanos. Además, la melatonina fue usada en estudios clínicos en pacientes con cáncer diseminado en dosis entre 2.000 y 4.000 mg día, siendo excelentemente tolerada.
- Sin embargo, sí se han descrito interacciones farmacológicas, especialmente con zolpidem y fluvoxamina.

MELATONINA COMO FÁRMACO!!!!!!



Melatonin: An Ideal Chronobiotic Drug

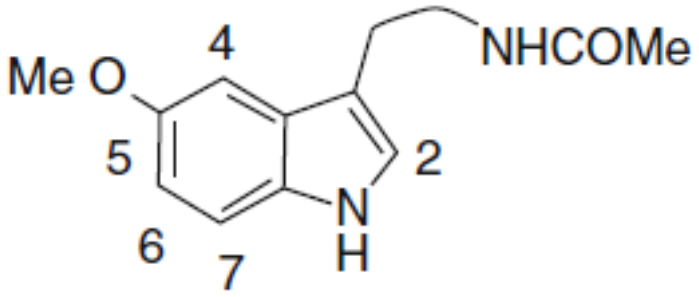
D.P. Cardinali, *Ma Vie en Noir*, Springer Biographies, Springer International Publishing Switzerland 2016

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

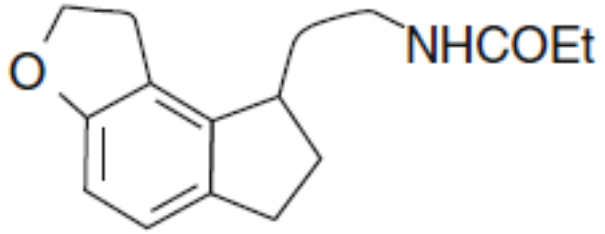
	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonbenzodiazepine Hypnotics				
Zolpidem: Oral tablet	2.5 (1.4–4.5)	1.6 (0.5–1.5)	None	5 (age >65 yrs) 5–10 (age <65 yr)
Zolpidem: Extended release (Ambien CR)	2.8 (1.6–4.5)	1.5 (1.5–2.0)	None	6.25–12.5
Zolpidem: Sublingual (Intermezzo)	2.5 (1.4–3.6)	0.6 (0.6–1.3)		women: 1.75; men: 3.5
Zolpidem: Sublingual (Edluar)	2.7 (1.5–6.7)	1.4 (0.5–3.0)		5–10
Zolpidem: Oral spray (Zolpimist)	2.8 (1.7–8.4)	0.9		10
Zopiclone[§] (Imovane)	5–6		None	3.75 (age >65 yr) 7.5 (age <65 yrs)
Zaleplon (Sonata)	1 (0.8–1.3)	1 (0.5–2)	None	5–10
Eszopiclone (Lunesta)	6 (5–8)	1.5 (0.5–2)	None	2–3 (age <65 yr); 1–2 (age >65 yr)
Ramelteon, tasimelteon	1–2.6[¶]	0.75 (0.5–1.5)	M-II	8
Doxepin	15 (10–30)	3.5 (1.5–4)		3–6 (Silenor) 10–50[**] (generic)
Suvorexant (dual orexin receptor antagonist)	12	0.5–6.0	None	10–20

(the first hypnotic by the FDA without a limit on duration of administration).

Melatonin and melatonergic agonists

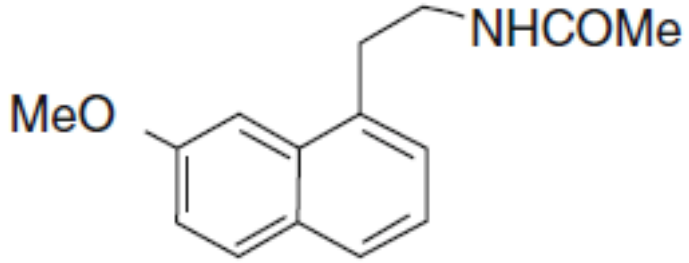


Melatonin



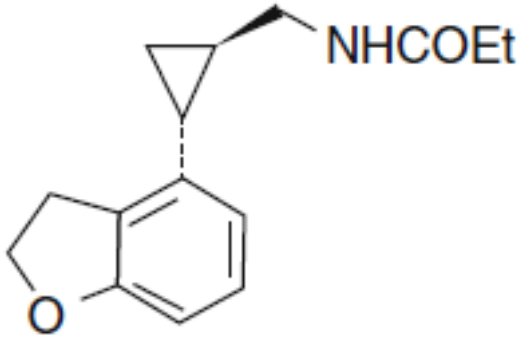
Ramelteon

ROZEREM Takeda



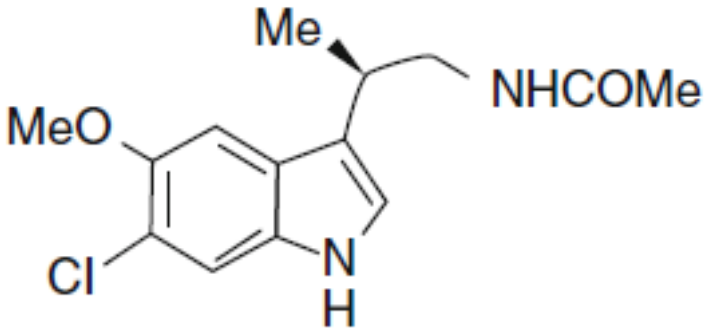
Agomelatine

Valdoxan SERVIER



Tasimelteon (VEC - 162)

HETLIOZ VANDA



TIK-301 (PD-6735, LY15673)

V. Srinivasan et al. (eds.), *Melatonin and Melatonergic Drugs in Clinical Practice*, Springer India 2014

RAMELTON, A MELATONERGIC AGONIST WITH SLEEP PROMOTING PROPERTIES

- Ramelteon {(S)-*N*-[2-(1,6,7,8-tetrahydro-2Hindeno[5,4-b]furan-8-yl)ethyl] propionamide; TAK-375} is a novel melatonin receptor agonist that has been shown to be selective for MT1 and MT2 receptors, but without affinity for the melatonin-binding quinone reductase 2.
- Ramelteon has no affinity for GABA-ergic, dopaminergic, opioidergic, noradrenergic or any other major CNS receptors, binding sites of neurotransmitters or neuropeptides, regulatory enzymes, or ion channels.

Adv Ther (2009) 26(6):613-626.

RAMELTON, A MELATONERGIC AGONIST WITH SLEEP PROMOTING PROPERTIES

- In-vitro binding studies have shown that ramelteon's affinity for MT1 and MT2 receptors is 3-16 times higher than that of melatonin itself.
- Although ramelteon has a relatively short half-life (1.2 hours), it is, however, substantially longer than that of melatonin.
- When administered orally, ramelteon is absorbed rapidly in fasting conditions and reaches its peak concentration in plasma in 45 minutes, which ranges from 30 minutes to 1.5 hours.
- The total absorption of this drug is 84%, but its total bioavailability is only 1.8%.
- After administration of the therapeutic dose (8 mg), the peak plasma concentration of ramelteon increases up to 57,000 pg/mL.

Adv Ther (2009) 26(6):613-626.

RAMELTON, A MELATONERGIC AGONIST WITH SLEEP PROMOTING PROPERTIES

- Ramelteon, like melatonin, exerts its direct sleep-inducing effects via MT1 receptors located in the SCN, while inducing phase shifting, mainly via MT2 receptors.
- Because ramelteon's direct soporific effect is indistinguishable at 4 mg and 8 mg, ramelteon seems to promote sleep by regulating the sleep-wake cycle rather than having a more generalized CNS depressant effect.
- This is supported by observations that ramelteon does not worsen sleep apnea in insomniacs.

Adv Ther (2009) 26(6):613-626.

Ramelteon's Effects on Sleep: Clinical Studies

- All doses of ramelteon resulted in statistically significant reductions in latency to persistent sleep (LPS) and increased sleep duration, as measured by PSG.
- Ramelteon did not produce any residual sedation, nor psychomotor nor memory impairment.
- All doses of ramelteon (4, 8, 16, and 32 mg) resulted in statistically significant reductions in LPS ($P<0.001$) and increases in TST ($P<0.05$).
- Sleep promotion by ramelteon was dose-independent as in a previous study.
- Ramelteon is a chronohypnotic agent with a specific action on MT1 and MT2 receptors in the SCN that are involved in the normal regulation of a sleep wake cycle.

Adv Ther (2009) 26(6):613-626.

Ramelteon's Effects on Sleep: Clinical Studies

- In a 6-month randomized, double-blind, placebo-controlled study carried out in 46 centers 451 adults (age ≥18 years) with chronic primary insomnia received ramelteon 8 mg or placebo 30 minutes before bedtime.
- Over the 6 months of treatment, ramelteon consistently reduced LPS compared with baseline and with placebo with no significant next morning residual effects, withdrawal symptoms, or rebound insomnia.

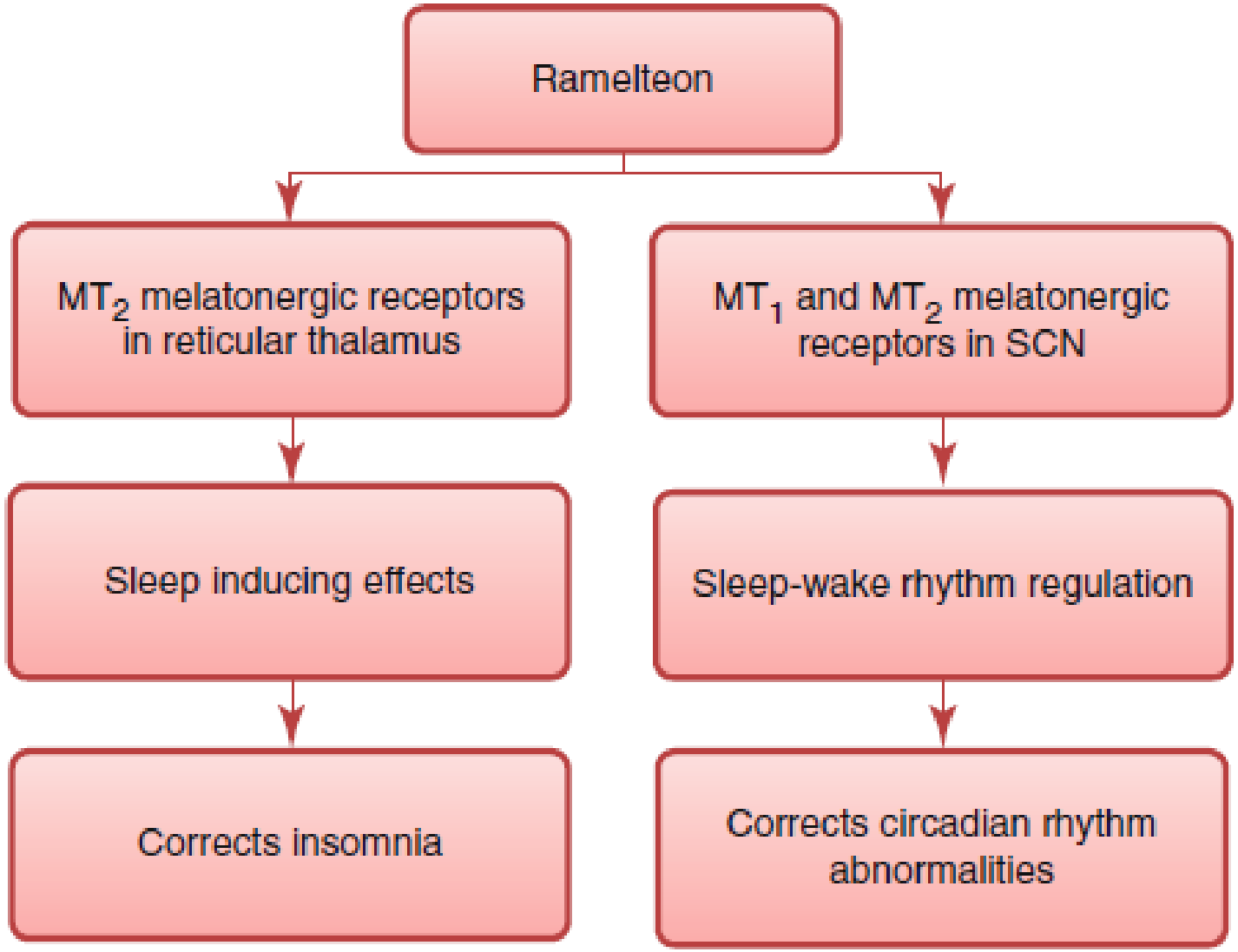
Adv Ther (2009) 26(6):613-626.

ADVERSE EFFECTS OF RAMELTEON AND SAFETY

- The incidence of adverse effects of ramelteon, as inferred from subjects' complaints and neurologic parameters, has been reported to be similar to that of placebo.
- The incidence of treatment-emergent adverse events ranged from 8.4% to 10.7% among the ramelteon groups and was 8.7% in the placebo group.
- The most commonly reported adverse events were headache, somnolence, dizziness, and sore throat.
- Ramelteon was found to be well tolerated and showed no significant next-day morning psychomotor, memory, or cognitive effects.

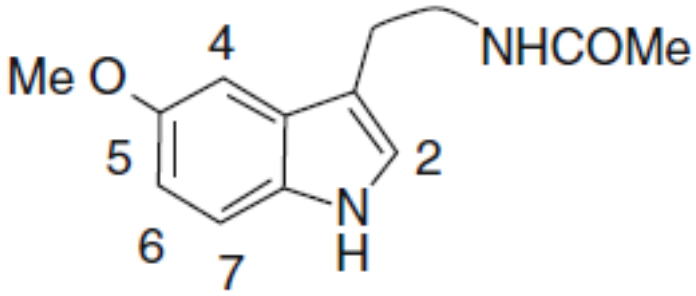
Adv Ther (2009) 26(6):613-626.

Mechanism of ramelteon's sleep-promoting and chronobiotic action

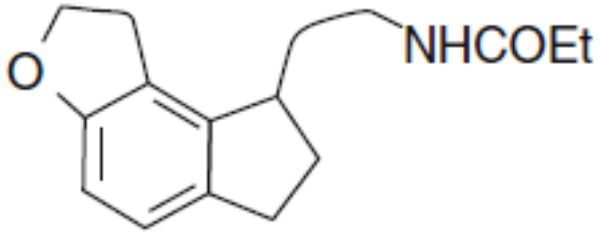


F. López-Muñoz et al. (eds.), *Melatonin, Neuroprotective Agents and Antidepressant Therapy*, Springer 2016

Melatonin and melatonergic agonists

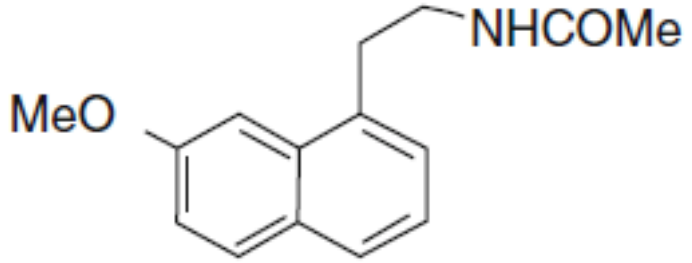


Melatonin



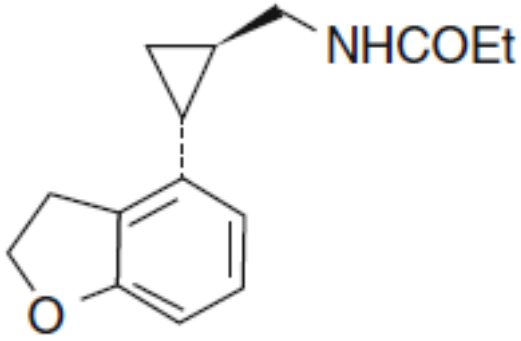
Ramelteon

ROZEREM Takeda



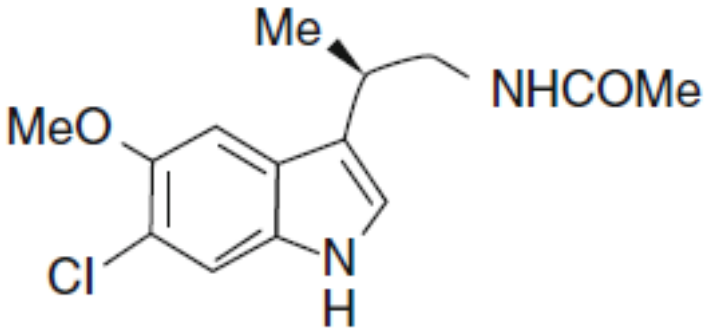
Agomelatine

Valdoxan SERVIER



Tasimelteon (VEC - 162)

HETLIOZ VANDA



TIK-301 (PD-6735, LY15673)

V. Srinivasan et al. (eds.), *Melatonin and Melatonergic Drugs in Clinical Practice*, Springer India 2014

Effects of melatonin and melatonin analogues

	Trade names	Approval	Binding*	Sleep effects
Hormone				
Melatonin[37]	..	..	MT_1, MT_2, MT_3	Promotes sleep initiation, especially during biological day (ie, when endogenous concentrations are low)
Melatonin (Neurim Pharmaceuticals)[61]	Circadin	EMA 2007	MT_1, MT_2, MT_3	Mimics the endogenous melatonin profile by releasing melatonin gradually over 8–10 h
Analogues				
Agomelatine (Servier)[62,63]	Valdoxan, Melitor, Thymanax	EMA 2009	MT_1, MT_2, 5-HT_{2B} (antagonist), 5-HT_{2C} (antagonist)	Significant benefits in patients with depression
Ramelteon (Takeda Pharmaceutical Company)[64]	Rozerem	FDA 2005	MT_1, MT_2	Decreased sleep latency, increased total sleep time in patients with insomnia, reduction in slow-wave sleep
Tasimelteon (VEC-126; Vanda Pharmaceuticals)[65]	..	FDA phase 3 clinical trial completed 2010; orphan drug designation 2010	MT_1, MT_2	Promotes sleep initiation and sleep maintenance (tested during 5-h phase advance) and concurrent shift in endogenous circadian rhythms
TIK-301 (PD-6735, LY-156, 735; Tikvah Pharmaceuticals)[66]	..	FDA phase 2 clinical trial since 2002; orphan drug designation 2004	MT_1, MT_2	Decreased sleep latency in patients with insomnia

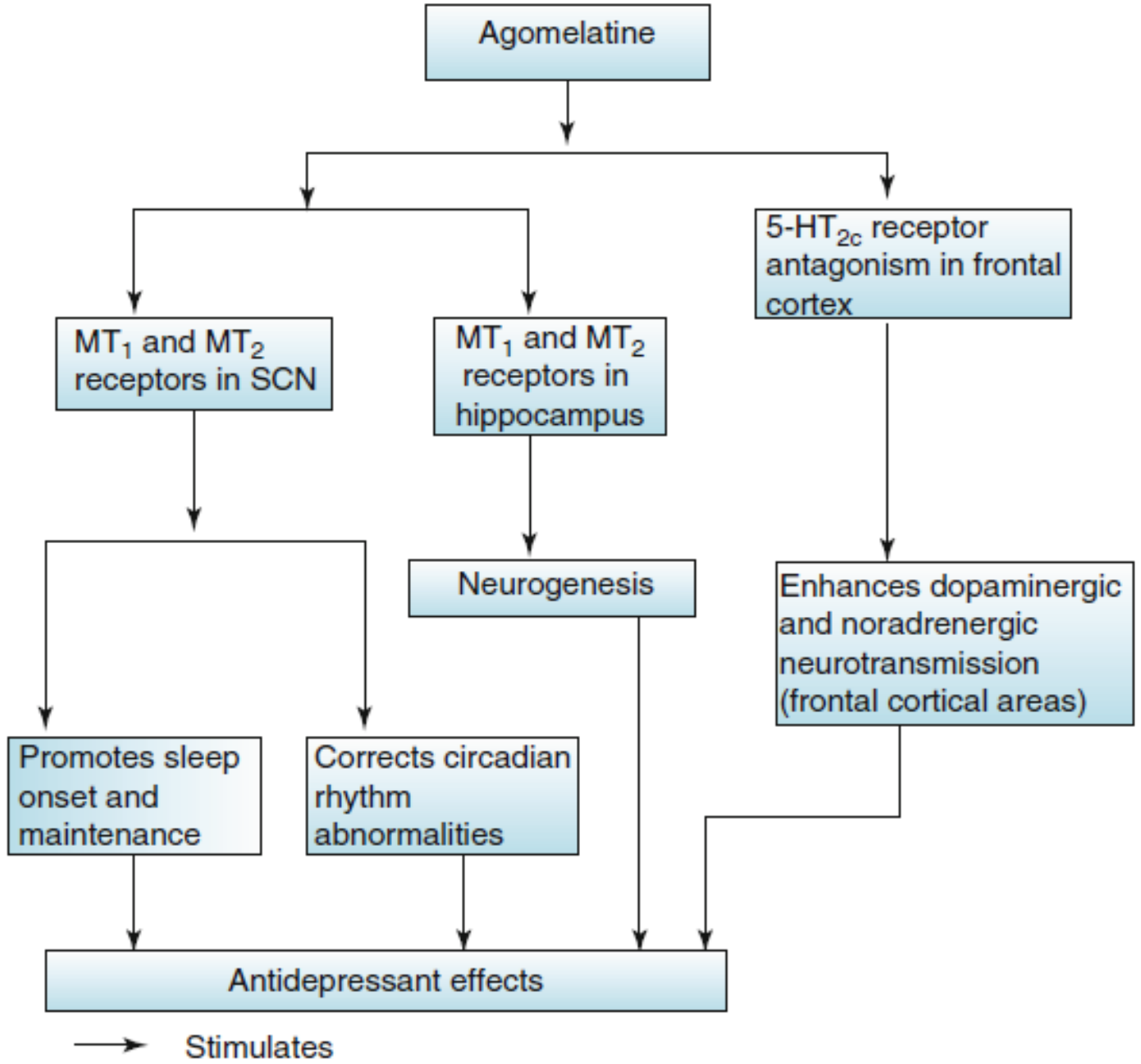
***Lancet* 2011; 378: 621–31**

Agomelatine

- Agomelatine is unique in that it is a selective agonist at MT1 and MT2 receptors and an antagonist at 5-HT2B and 5-HT2C.
- Agomelatine has a rapid absorption rate: the time at which maximum blood concentration was achieved was between 45 min and 90 min after a single oral dose of 25–50 mg.
- After oral ingestion, agomelatine undergoes high hepatic first-pass metabolism, which contributes to the wide degree of interindividual variability in bioavailability.
- Further factors affecting bioavailability include sex, use of oral contraceptives, and smoking.
- Circulating agomelatine is mainly bound to plasma proteins (>90%) and is almost completely metabolised (CYP1A2).
- The mean terminal half-life is 140 min. Significant improvements on a range of sleep variables, including improved sleep quality, reduced wake after sleep onset, and fewer insomnia reports were found with agomelatine than with venlafaxine.
- Nausea, dizziness, and headache are the symptoms most commonly reported by patients treated with agomelatine, these side effects were reported at similar rates by those receiving placebo.

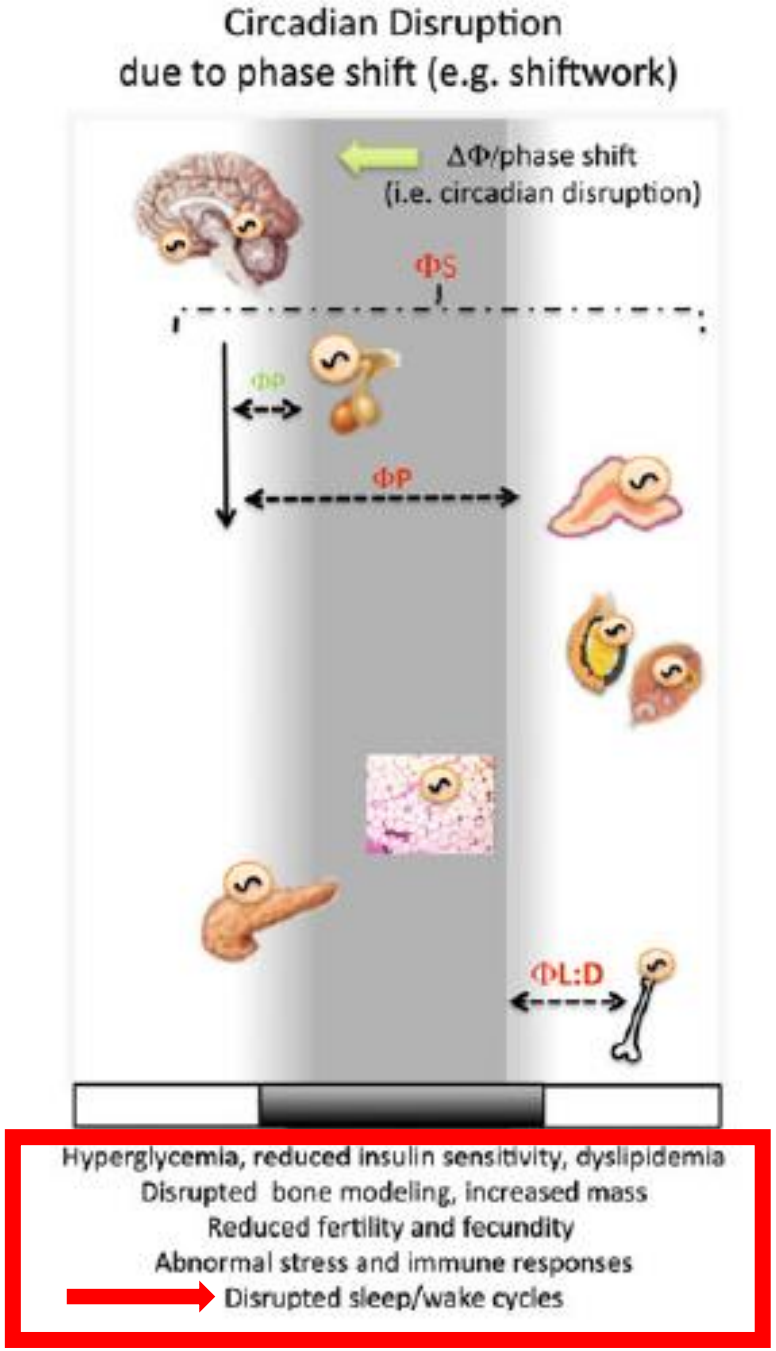
***Lancet* 2011; 378: 621–31**

Agomelatine



V. Srinivasan et al. (eds.), *Melatonin and Melatonergic Drugs in Clinical Practice*, Springer 2014

DESINCRONIZACIÓN



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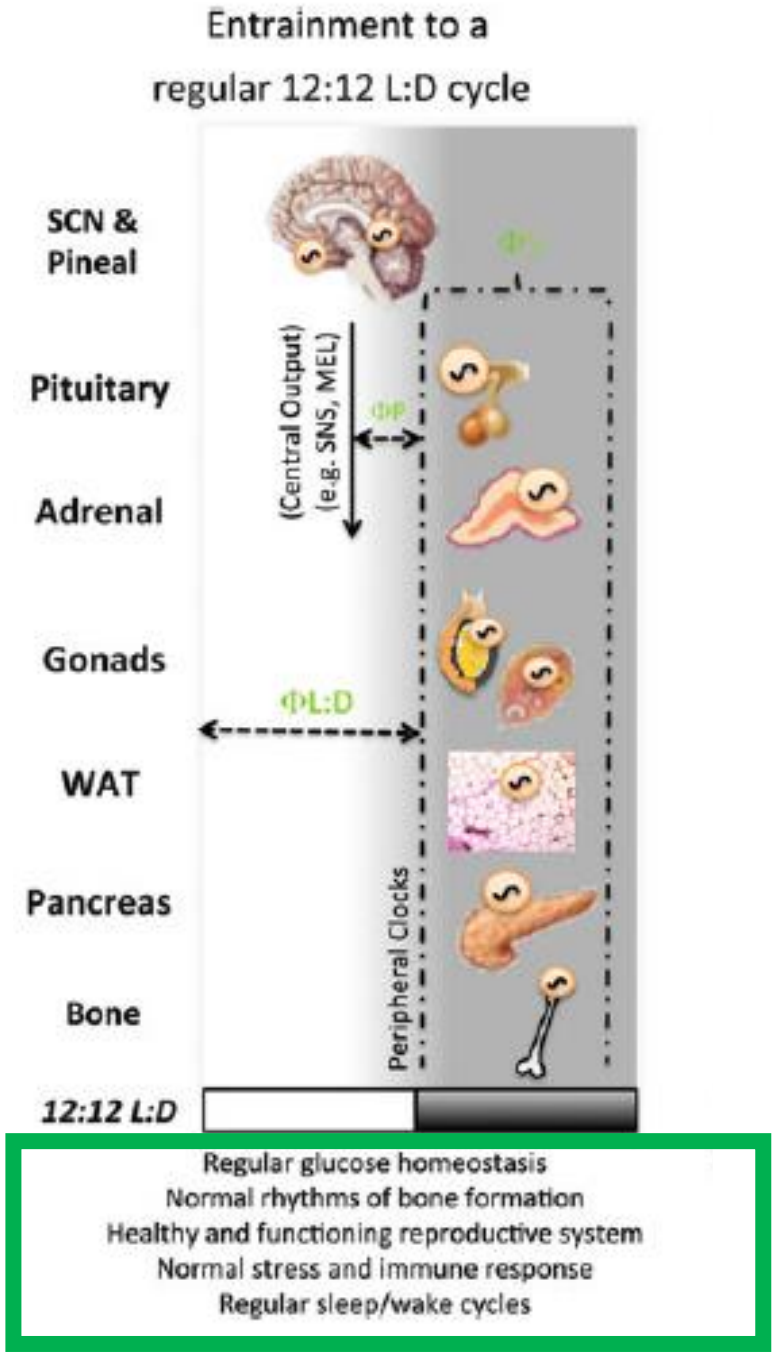
SINCRONIZACIÓN



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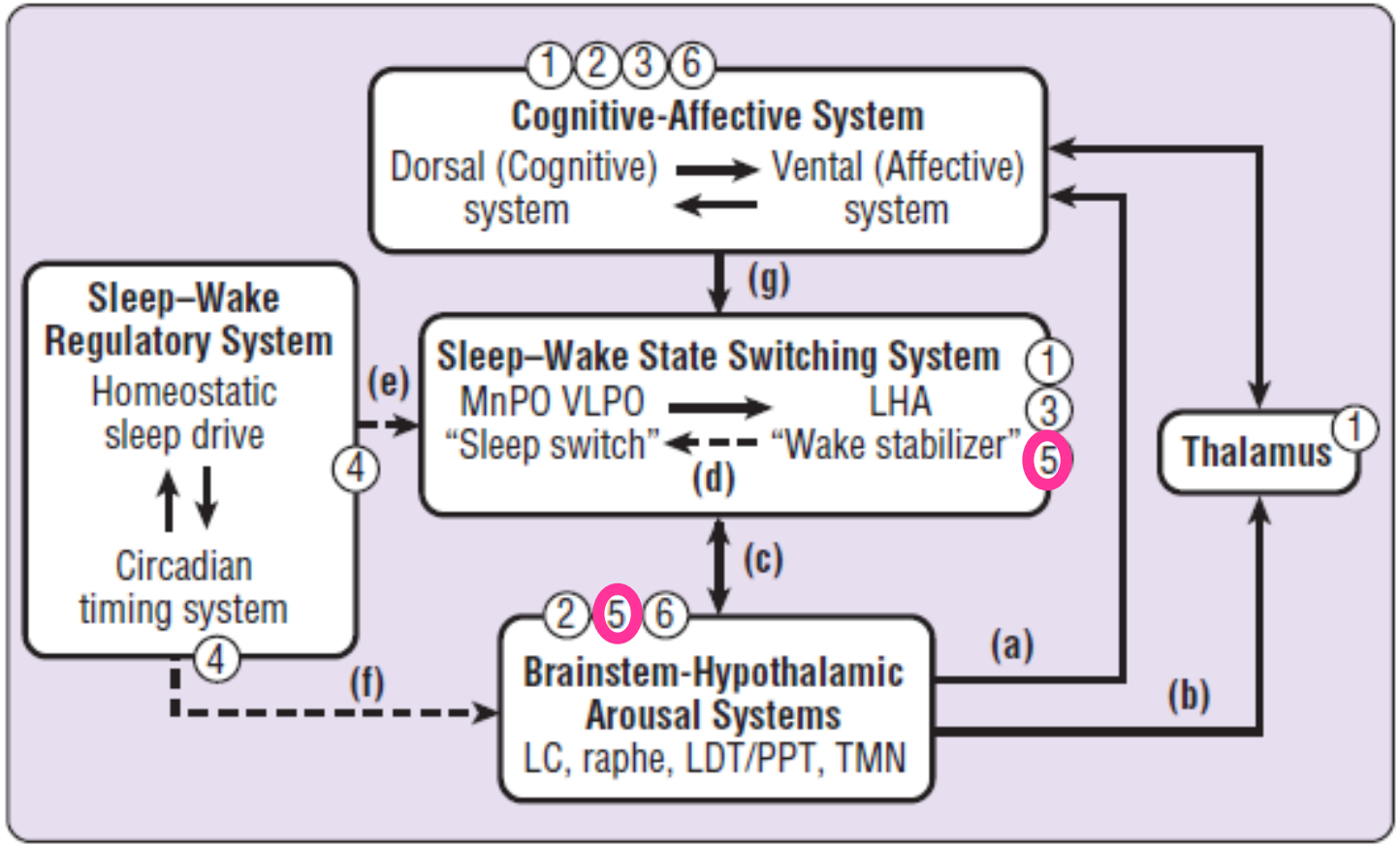
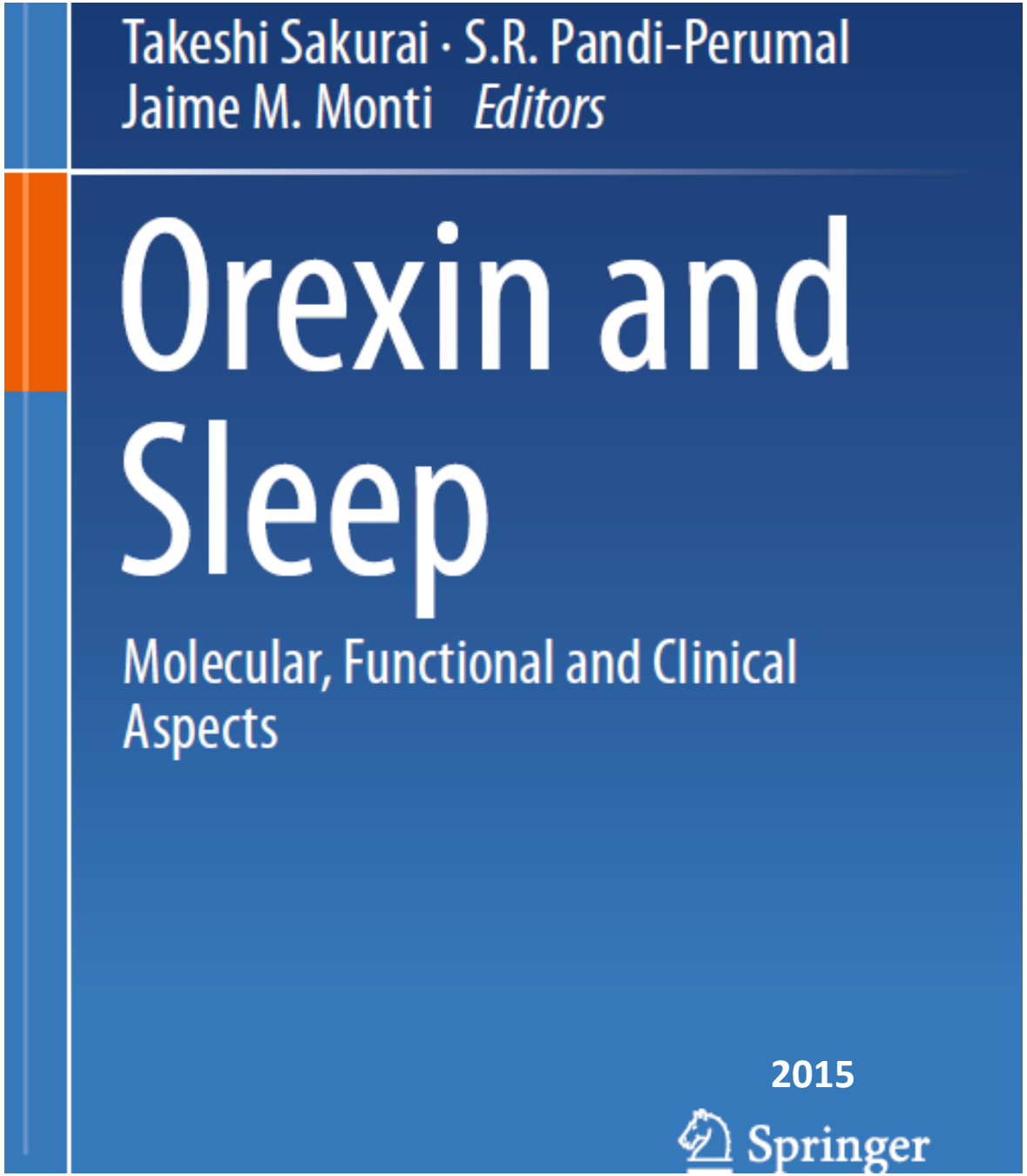
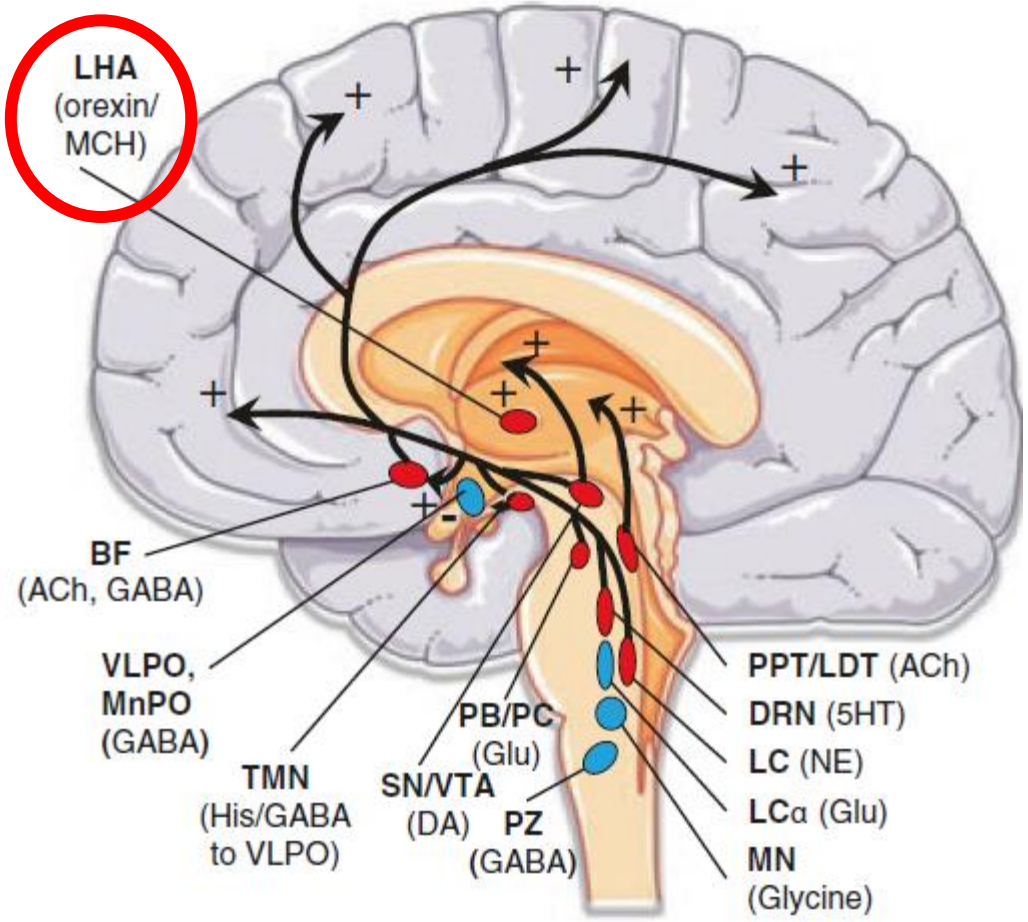
SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Benzodiazepine receptor agonists (1) may directly affect the sleep-wake state-switching system but also have direct cortical, thalamic, and brainstem effect due to the widespread distribution of GABA-A receptors. Sedating antidepressant and antipsychotic medications (2), through their activity on monoaminergic systems, affect corticolimbic systems and brainstem-hypothalamic arousal systems. Antihistamines (3) antagonize histamine-1 (H1) receptors in the hypothalamus and cortex that receive projections from the tuberomamillary nucleus. Melatonin and melatonin receptor agonists (4), through their effects on melatonin-1 (MT1) and MT2 receptors, influence the "wake signal" from the suprachiasmatic nucleus and circadian timing system. **Orexin antagonists (5) inhibit the effect of orexin-hypocretin on brainstem and hypothalamic arousal centers,** and 5-HT2 antagonists (6) are most likely to have corticolimbic and brainstem sites of action. Thus different types of sleep-promoting drugs achieve their effects through very different actions on very different components of the sleep-wake regulatory system.


Takeshi Sakurai · S.R. Pandi-Perumal
Jaime M. Monti Editors
Orexin and Sleep
Molecular, Functional and Clinical Aspects
2015
Springer



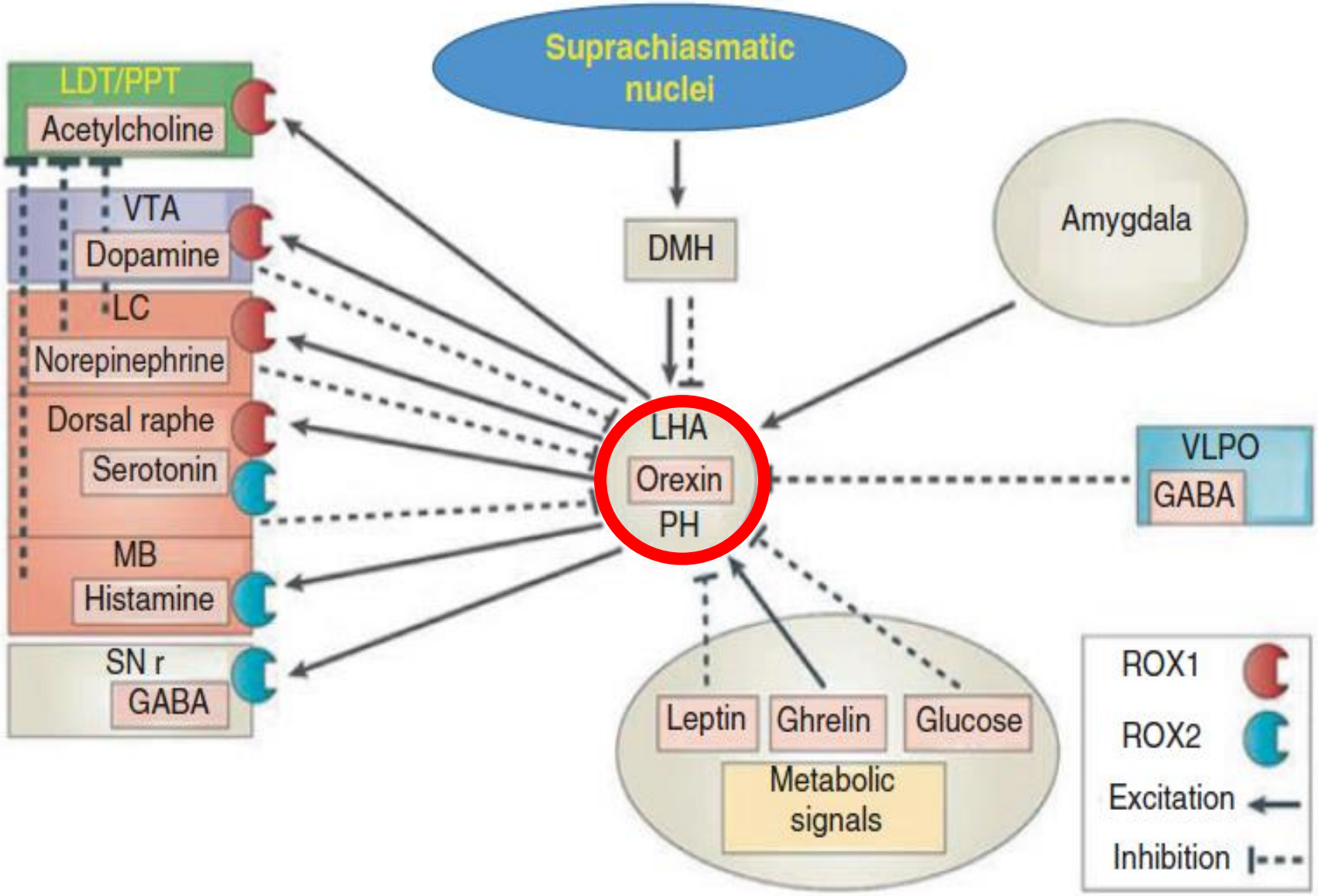
Representation of the neuronal pools promoting arousal to the forebrain.

During wakefulness, the histaminergic neurons in the ventral tuberomammillary nucleus (TMN) at the bottom of the posterior hypothalamus provide a strong inhibitory influence on the VLPO/MnPO (median preoptic area).

The components of the ascending reticular activating system further include the raphe nuclei (5HT neurons), the locus coeruleus (LC, noradrenergic neurons), the pedunculopontine and laterodorsal tegmenti (PPT/LDT) ACh-containing neurons, DA-containing neurons in the substantia nigra (SN) and the ventral tegmental area (VTA), Glu-containing neurons in the parabrachial/precoeruleus area (PB/PC) and the basal forebrain (BF), mainly cholinergic, but also containing a population of GABAergic neurons whose stimulation produces sustained wakefulness and EEG gamma activity.

Orexin-melanocyte concentrating hormone (MCH) neurons on the LHA provide stimulatory input to the wakefulness-promoting areas.

Interactions of neurons containing orexin with other regions of the brain involved in sleep and wakefulness regulation.



D.P. Cardinali, *Autonomic Nervous System*, Springer 2018

Orexinergic neurons in the lateral hypothalamic (LHA) and posterior hypothalamus (PH) are strategically located to serve as a link between the limbic system, the systems involved in energy and monoaminergic homeostasis, and cholinergic neurons in the brainstem.

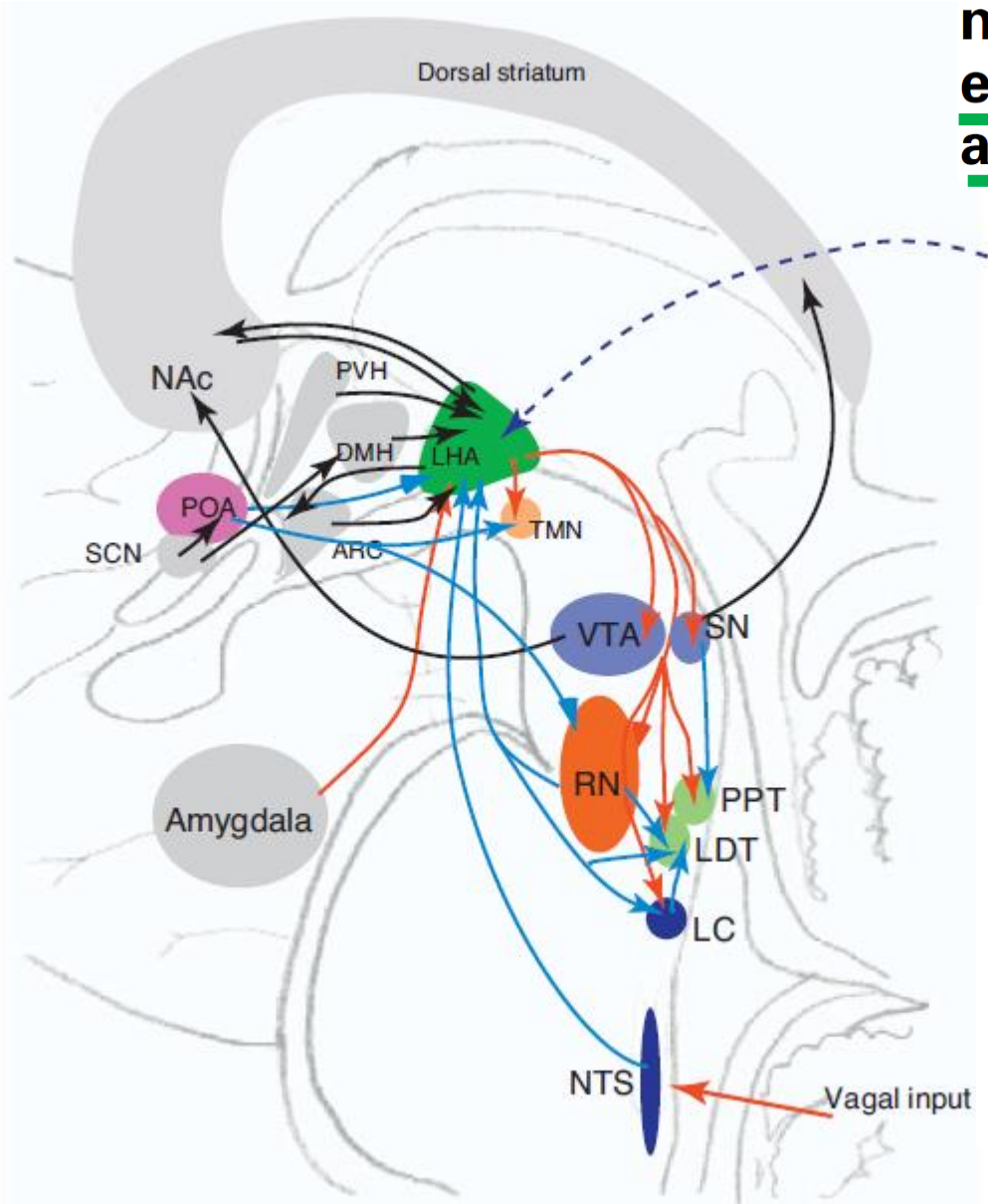
The SCN sends signals to orexin neurons through the dorsomedial hypothalamus (DMH). *VLPO* ventrolateral preoptic area, *NDR* dorsal raphe, *LC* locus coeruleus, *LDT* laterodorsal tegmental nucleus, *PPT* pedunculopontine tegmental nucleus, *SNR* substantia nigra pars reticulata, *TMN* tuberomammillary nucleus

Motivational activation: a unifying hypothesis of orexin/hypocretin function

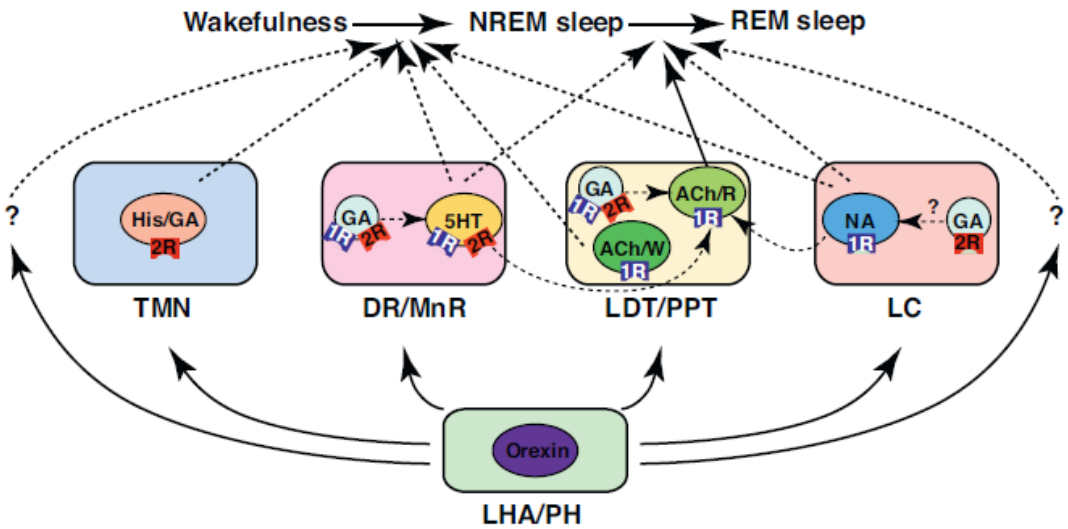
- Orexins have a fundamentally unified role that spans a variety of processes, including **arousal, reward seeking, homeostatic regulation and stress**, which we term **motivational activation**.
- This underlying function facilitates appetitive or aversive motivation and related **physiological responses in service of producing behaviors to address pressing threats or opportunities**.

Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal

Thus, the hypocretin peptides may be important molecules to change the set point that is associated with allostasis.

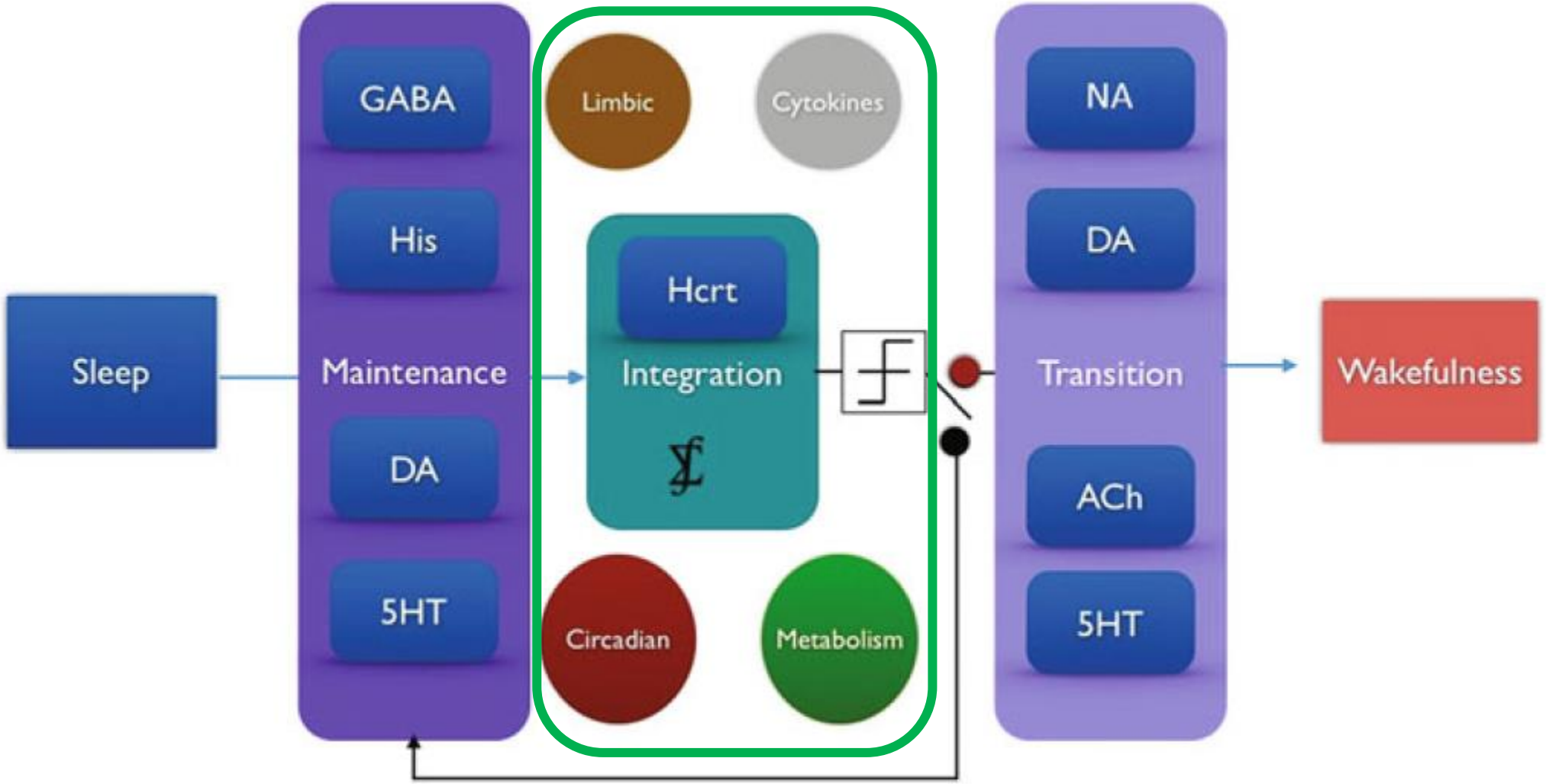


Key:
- Orexin
- Dopamine
- Serotonin
- Histamine
- Acetylcholine
- Noradrenaline



Trends in Pharmacological Sciences, August 2011, Vol. 32, No. 8

Arousal Circuits as Outputs of Hcrt Neurons



Hcrt neurons integrate the inputs from the circadian, metabolic, limbic, and cytokine systems. The integration of the activities of these systems either leads to maintenance of sleep, in which the GABAergic, histaminergic, dopaminergic, and serotonergic systems are involved, or triggers the transition to arousal, in which the noradrenergic, dopaminergic, cholinergic, and serotonergic systems are implicated. Depending on the integrated signals arriving in Hcrt neurons, sleep will either be maintained or will transition into wakefulness

(Curr Topics Behav Neurosci, Springer 2016)

OREXIN ANTAGONISTS

- The real attraction of the orexin system as a target in sleep disorders is that it acts essentially on an arousal triggering system, i.e. via a “wake on” modality, in contrast to the GABA A receptor which represents a “wake off” modality.
- Overall, activation of the GABA A receptor causes a general dampening of the CNS, which results in sleep, but also muscle relaxation and eventually motor impairment by muscle inactivation.
- When the GABA A receptor is profoundly activated, e.g. with high doses of alcohol or hypnotics, the state reached is akin to anaesthesia, which is challenging to reverse immediately.
- By contrast, it is expected that **an OXR antagonist simply blocks the wake state**, leaving the CNS in a more “normal” state of activity; thus, sleep could be reversed instantly in case of need. This has proven to be the case, as repeatedly shown in mice, rats, dogs and humans.
- A major drawback of GABA A receptor positive allosteric modulators is their negative impact on memory/cognition, due to the general dampening of the CNS.
- In contrast, due to their anti-“wake on” targeting, OXR antagonists are not expected to show such effects.

(**Curr Topics Behav Neurosci, Springer 2016**)

OREXIN ANTAGONISTS

- Orexinergic neurons have widespread excitatory projections to the brainstem and posterior hypothalamic arousal centers and are key neuropeptides responsible for generating and maintaining wakefulness.
- Two receptors respond to orexin signaling: Orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R) both have partially overlapping nervous system distributions.
- **Suvorexant** is a potent and selective antagonist of OX1R and OX2R and was the first drug in this class approved by FDA for the treatment of insomnia.
- It is orally bioavailable, has good brain penetration, and has high receptor occupancy.

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonbenzodiazepine Hypnotics				
Zolpidem: Oral tablet	2.5 (1.4–4.5)	1.6 (0.5–1.5)	None	5 (age >65 yrs) 5–10 (age <65 yr)
Zolpidem: Extended release (Ambien CR)	2.8 (1.6–4.5)	1.5 (1.5–2.0)	None	6.25–12.5
Zolpidem: Sublingual (Intermezzo)	2.5 (1.4–3.6)	0.6 (0.6–1.3)		women: 1.75; men: 3.5
Zolpidem: Sublingual (Edluar)	2.7 (1.5–6.7)	1.4 (0.5–3.0)		5–10
Zolpidem: Oral spray (Zolpimist)	2.8 (1.7–8.4)	0.9		10
Zopiclone[§] (Imovane)	5–6		None	3.75 (age >65 yr) 7.5 (age <65 yrs)
Zaleplon (Sonata)	1 (0.8–1.3)	1 (0.5–2)	None	5–10
Eszopiclone (Lunesta)	6 (5–8)	1.5 (0.5–2)	None	2–3 (age <65 yr); 1–2 (age >65 yr)
Ramelteon, tasimelteon	1–2.6[¶]	0.75 (0.5–1.5)	M-II	8
Doxepin	15 (10–30)	3.5 (1.5–4)		3–6 (Silenor) 10–50[**] (generic)
Suvorexant (dual orexin receptor antagonist)	12	0.5–6.0	None	10–20

(the first hypnotic by the FDA without a limit on duration of administration).

Binding affinity of DORAs across mammalian species

	Compound	OX_1R						OX_2R					
		Mouse	Rat	Rabbit	Dog	Rhesus monkey	Human	Mouse	Rat	Rabbit	Dog	Rhesus monkey	Human
Binding (K_i in nM)[b]	Suvorexant	0.62	0.56	1.2	0.41	2.1	0.55	0.65	0.36	0.32	0.48	0.68	0.35
	DORA-12[d]	1.9	2.1	3.8	2.0	7.5	1.8	0.37	0.45	0.31	0.43	0.29	0.20
	Filorexant	2.9	2.5	2.6	2.7	12.5	2.5	0.56	0.22	0.28	0.36	0.44	0.31
	DORA-22[d]	21	13.2	9.1	22	69.7	9.7	1.14	0.44	0.75	0.36	1.23	0.61
	Almorexant						2.7						0.19

Annu. Rev. Pharmacol. Toxicol. 2017.57:21.1–21.25

OREXIN ANTAGONISTS

- Suvorexant’s peak concentrations occur at a median of 2 hours (30 minutes to 6 hours) under fasted conditions.
- The mean absolute bioavailability of 10 mg is 82%.
- It is extensively bound (>99%) to plasma proteins and has a terminal half-life of 9 to 12 hours,22 with some next morning residual effects.
- CYP3A4 and, to a lesser extent, CYP2C19 are the major enzymes involved in suvorexant metabolism.
- In patients with primary insomnia, 4 weeks of suvorexant treatment improved sleep efficiency and wake after sleep onset.
- Total sleep time also improved with greater time spent in REM and stage 2 sleep.
- During 1-year treatment with suvorexant, insomniac patients reported subjective improvements in total sleep time, time to sleep onset, WASO, and sleep quality.

OREXIN ANTAGONISTS

- The most common adverse events reported with suvorexant are somnolence, fatigue, and dry mouth.
- The key safety concerns are residual sedation, rapid onset of somnolence if administered during the daytime, motor impairment, driving impairment, and hypnogogic hallucinations.
- At higher dosages (50 and 100 mg), the medication significantly decreased reaction time and reduced subjective alertness tested the morning after drug administration.
- Although effects resembling cataplexy are a theoretical concern, given the role of deficient orexin neurotransmission in narcolepsy cataplexy, these effects were not found in clinical trials.
- Adverse events appeared to be dose- and plasma-exposure dependent.
- It is possible that these residual effects are related not only to half-life but also to a combination of pharmacokinetic (slow elimination or metabolism) and pharmacodynamic effects (slow equilibration and off rates).
- Moreover, endogenous orexin production appears to follow a circadian pattern with a peak in the late waking period, which could lead to more potent effects of orexin receptor antagonists during daytime than nighttime hours.

(**Curr Topics Behav Neurosci, Springer 2016**)

suvorexant

- The recent Phase III clinical trials performed with suvorexant (lasting 3, 6 or 12 months with a possible extension up to 14 months) represent the largest and longest company-sponsored clinical trials ever reported in insomnia (Michelson D et al. WJ (2014) Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 13:461–471).
- Suvorexant (Belsomra) received approval in 2014 from the US FDA.
- It is clear from the long-term clinical studies carried out with suvorexant that this DORA had no marked effect on food intake or weight status.

(**Curr Topics Behav Neurosci, Springer 2016**)

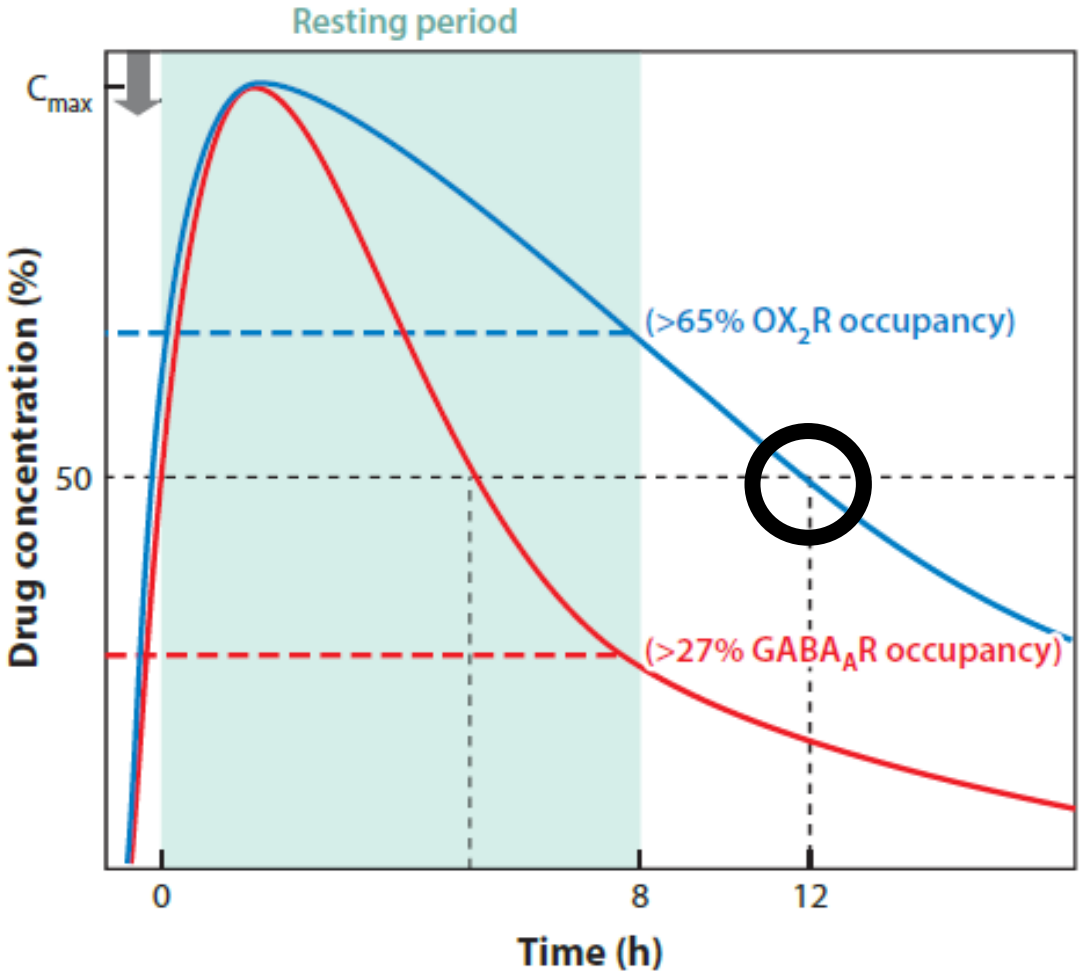
Suvorexant for the treatment of primary insomnia: A systematic review and meta-analysis

- A total of four randomized trials involving 3076 patients with primary insomnia were included in the analysis.
- Analysis suggested that suvorexant was associated with significant improvements in subjective time to sleep onset, subjective total sleep time, and subjective quality of sleep at 1 mo and 3 mo.
- Somnolence, fatigue, and abnormal dreams were the most common adverse effects.
- We concluded that suvorexant was associated with improvement in some sleep parameters and some adverse effects.

A. Kuriyama, H. Tabata / Sleep Medicine Reviews 35 (2017) 1-7

Receptor occupancies required for sleep efficacy

Endogenous orexin production appears to follow a circadian pattern with a peak in the late waking period, which could lead to more potent effects of orexin receptor antagonists during daytime than nighttime hours.



Receptor occupancies required for sleep efficacy are greater for OX2R receptor blockade by DORAs (>65%) relative to GABAAR activation by GABAAR modulators (>27%). Greater occupancies required by DORAs necessitate longer plasma half-lives for 8 h of sleep maintenance relative to GABAAR modulators. Abbreviations: Cmax, maximal plasma concentration; DORA, dual orexin receptor antagonist; GABAAR, γ-aminobutyric acid A receptor; OX2R, orexin 2 receptor.

Annu. Rev. Pharmacol. Toxicol. 2017,57:1–21

Orexin OX2 Receptor Antagonists as Sleep Aids (2-SORA: Selective orexin 2 receptor antagonist)

- **In the clinic, all dual orexin receptor antagonists (DORAs) promote sleep primarily by increasing rapid eye movement (REM) and are almost devoid of effects on slow wave (SWS) sleep.**
- **At present, there is no consensus on whether the sole promotion of REM sleep has a negative impact in patients suffering from insomnia.**
- **Based on receptor KO studies, it would appear that the OX1R plays a minor role in sleep/wake regulation by itself, whereas the role of the OX2R is more prominent.**
- **An OX2R antagonist may produce more balanced sleep than a DORA.**
- **The OX2R is the primary target of orexin receptor antagonists in sleep modulation.**
- **An OX2R antagonist should, in theory, have a lower narcoleptic/cataplexic potential.**
- **In the clinic, the situation remains equivocal, since OX2R antagonists are in early stages of development.**

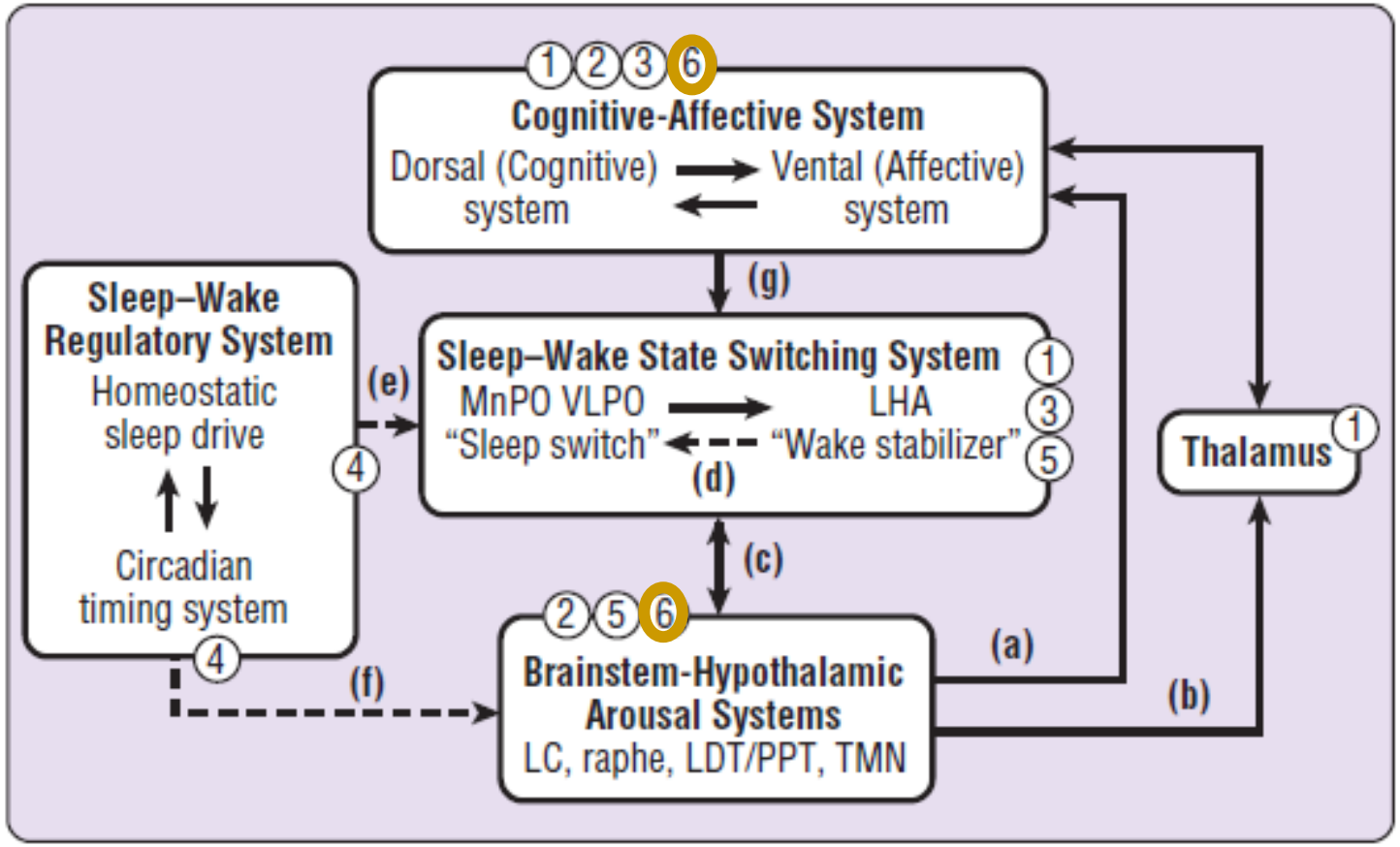
(Curr Topics Behav Neurosci, Springer 2016)

Table 1 Selective orexin 2 receptor antagonists inducing sleep

Compound	Institute/ company	Binding or functional affinity (pK_D, pK_b, pIC_{50})			Species tested	Sleep features	Clinical status
		Method	hOX_1R	hOX_2R			
MIN-202/ JNJ-42847922	Janssen/J&J/ Minerva	Radioligand binding, calcium	6.1 6.3	8.0 8.8	Mouse, rat, humans	Balanced in mice, main effects on NREM and NREM latency; no effect on REM latency. Inactive in OX_2R KO, balanced in humans	Phase I/II
JNJ-10397049	Janssen/J&J	Radioligand binding, calcium	5.5 NA	8.3 7.9	Rat	Balanced when applied alone, but REM latency decreased and REM duration increased in the presence of OX_1R antagonists GSK-1059865 or SB-408124, replicating effects of the DORA SB-649868	Research
MK-3697	Merck	Radioligand binding, calcium	5.44 5.7	8.96 7.8	Mouse, rat, dog	Balanced in mice and rats. Inactive in OX_2R KO. Affects only SWS in dogs	Clinical candidate
MK-1064	Merck	Radioligand binding, calcium	5.8 5.75	9.3 7.75	Mouse, rat, dog, rhesus monkey	Balanced: increases in NREM and REM in mice, limited effects on REM in dogs and monkeys	Clinical candidate
MK-8133	Merck	Calcium	5.31	7.55	Mouse, rat, dog	Balanced: In mice no effect on REM, increased SWS. Inactive in OX_2R KO. In rat, both SWS and REM increased. In dog, limited effect on REM, increased NREM	Clinical candidate
2-SORA-18	Merck	Radioligand binding, calcium	7.02 6.53	10.15 7.92	Rat	Balanced, main effects on delta sleep > REM	Research

(Curr Topics Behav Neurosci, Springer 2016)

SLEEP-WAKE REGULATION
RELEVANT TO SLEEP-PROMOTING DRUGS



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Classes of antidepressant drugs

Class	Generic name of antidepressants	Mode of action
Tricyclic antidepressants (TCAs)	Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine, Desipramine, Nortriptyline, Protriptyline, Amoxapine, Maprotiline	Inhibition of both serotonin and noradrenaline reuptake
Monoamine oxidase inhibitors (MAOIs)		
Irreversible	Iproniazid, Isocarboxazid, Phenelzine, Tranylcypromine	Inhibition of MAO-A and MAO-B
Reversible (Type A)	Moclobemide, Brofaromine	Inhibition of MAO-A (the only MAO implicated in antidepressant effects)
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, Paroxetine, Citalopram, Escitalopram, Fluvoxamine, Sertraline	Selective inhibition of serotonin reuptake
Noradrenaline reuptake inhibitors (NRIs)	Atomoxetine, Reboxetine	Selective inhibition of noradrenaline reuptake
Mixed reuptake inhibitors		
Serotonin–noradrenaline reuptake inhibitiors (SNRIs)	Venlafaxine, Duloxetine	Inhibition of both serotonin and noradrenaline reuptake
Noradrenaline-dopamine reuptake inhibitor (NDRI)	Bupropion	Inhibition of both noradrenaline and dopamine reuptake
Serotonin-2 antagonist and reuptake inhibitors (SARIs)	Nefazodone, Trazodone	Blockade of 5-HT2 receptors and inhibition of serotonin reuptake
Noradrenaline and specific serotonergic antidepressant (NaSSA)	Mirtazapine	Blockade of 5-HT2 receptors and potent antagonist for 5-HT3 and noradrenergic $\alpha 2$ receptors
Modern antidepressant	Agomelatine	Agonist of melatonergic (MT(1) and MT(2)) receptors and antagonist for 5-HT_{2C} receptors

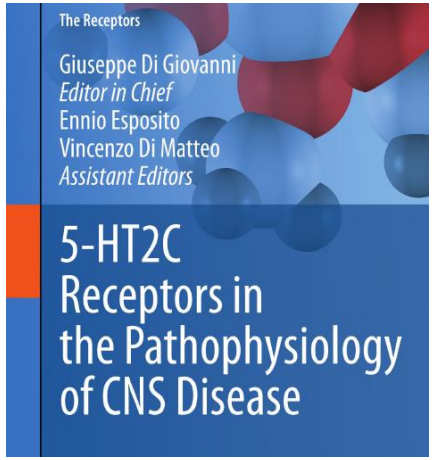
Current Opinion in Neurobiology 2011, 21:858–865

5HT 2 RECEPTORS

Chapter 20
The Role of 5-HT$_{2A/2C}$ Receptors in Sleep and Waking

Jaime M. Monti and Héctor Jantos

(G. Di Giovanni et al. (eds.), *5-HT2C Receptors in the Pathophysiology of CNS Disease*, Springer 2011)



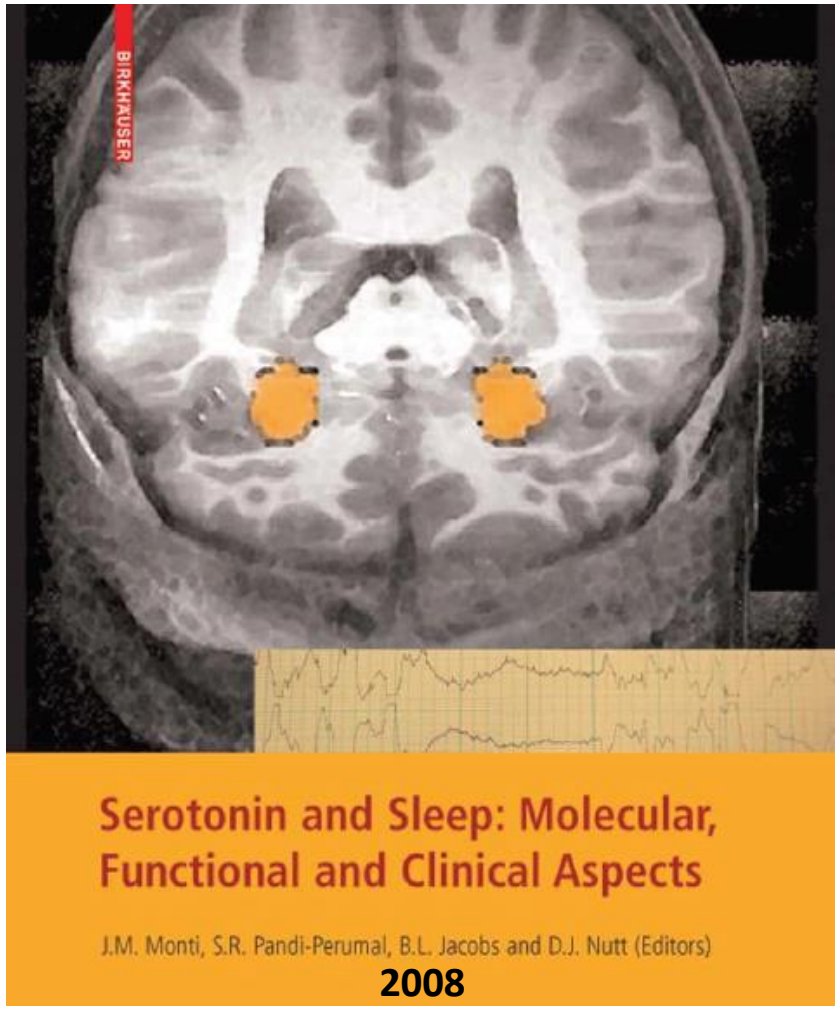


Table 1. Serotonin receptor subtypes

Receptor	Type of receptor	Effector mechanisms	Subtypes	Location in the basal ganglia	Speculated function
5-HT_1	G protein linked	Inhibits adenylyl cyclase, opens K^+ channels	5-HT_{1A}	Caudate-putamen, subthalamic nucleus	Anxiety, depression
			5-HT_{1B}	Caudate-putamen, substantia nigra, globus pallidus	Locomotion
			5-HT_{1D}	Substantia nigra	Locomotion
			5-HT_{1E}	Caudate-putamen	
			5-HT_{1F}	Caudate-putamen	
5-HT_2	G protein linked	Stimulation of phospholipase C, closing of K^+ channels	5-HT_{2A}	Nucleus accumbens, caudate-putamen	
			5-HT_{2B}	None detected in the basal ganglia	
			5-HT_{2C}	Nucleus accumbens, caudate-putamen, substantia nigra, subthalamus	
5-HT_3	Ligand-gated cation channel	Na^+ current	5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}	GABAergic projection neurons of caudate-putamen	Anxiety, depression, emesis
5-HT_4	G protein linked	Stimulation of adenylyl cyclase	5-HT_4	GABAergic projection neurons of caudate-putamen	Anxiety, depression
5-HT_5	G protein linked	Inhibits adenylyl cyclase	5-HT_{5A}, 5-HT_{5B}	Caudate-putamen	Motor control, feeding, anxiety, depression, learning, memory
5-HT_6	G protein linked	Stimulation of adenylyl cyclase	5-HT_6	Dendrites of GABAergic striatopallidal and striatonigral neurons	Dopamine transmission
5-HT_7	G protein linked	Stimulation of adenylyl cyclase	5-HT_7	Caudate-putamen, nucleus accumbens	Locomotion, circadian rhythms

- Serotonergic neurotransmission effects CNS systems through the binding of serotonin to one of 14 described receptors, which are grouped into seven families (5-HT1R to 5-HT7R).
- The 5-HT2 receptors form a closely related subgroup of G-protein coupled receptors and show the typical heptahelical structure of an integral membrane protein monomer.
- They are currently classified as 5-HT2A, 5-HT2B, 5-HT2C.
- In humans, 5-HT2B R mRNA was detected in the whole brain, and in particular in the cerebellum, the occipital cortex and the frontal cortex.
- The amino acid sequence of the 5-HT2 receptors shares a high degree (>70%) of identity within the transmembrane segments.

Serotonin 5-HT2 Receptor

In vitro binding profiles of ligands for 5-HT_{2A}R, 5-HT_{2B}R, and 5-HT_{2C}R

Ligand	5-HT_2 Receptor Family					
	h5-HT_{2A}R		h5-HT_{2B}R		h5-HT_{2C}R	
Agonists[a]	Affinity K_i	Potency EC_{50}	Affinity K_i	Potency EC_{50}	Affinity K_i	Potency EC_{50}
	nM					
5-HT	16	31	13	2	4.8	6
DOI	0.78	0.9	39	1.4	6.7	7.9
Lorcaserin	112	168	174	943	15	9
MK 212	1023	N.E.	617	295	98	214
Ro 60-0175	36.3	447	5.4	0.9	6.0	32
WAY 163909	212	N.E.	2101	185	10.5	8

In vitro binding profiles of ligands for 5-HT_{2A}R, 5-HT_{2B}R, and 5-HT_{2C}R

Ligand	5-HT_2 Receptor Family		
	Affinity K_i		
Antagonists[a]	h5-HT_{2A}R	h5-HT_{2B}R	h5-HT_{2C}R
		nM	
Ketanserin	8.1	741	62
M100907	1.9	1000	30
Pimavanserin	0.05	N.D.	1.6
SB 242084	851	145	7.1
SB 243213	160	100	1.0

Pharmacol Rev 67:176–197, 2015

Table 42-1 Pharmacokinetic Properties of Sedating Antidepressant Drugs*

Drug	Drug Class	Time to Maximal Concentration (h)	Metabolism (CYP Enzymes)	Elimination Half-Life (h) (Range)	Usual Dose (mg)	
					Antidepressant	Hypnotic†
Doxepin	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	20 (10–30)	100–300	3, 6
Amitriptyline	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	30 (5–45)	100–300	10–150
Trimipramine	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	25 (15–40)	100–300	25–150
Trazodone	Phenylpiperazine	1–2	3A4, 2D6	9 (3–14)	200–600	25–150
Nefazodone	Phenylpiperazine	1	3A4, 2D6, 2C19	2–4 (6–18 for active metabolites)	150–450	50–150
Mirtazapine	Noradrenergic and specific serotonergic antidepressant	1–3	3A4, 2D6, 1A2	25 (13–40)	15–45	7.5–30

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

TRAZODONA

- Trazodone produces sedation by blocking the 5HT-2A/2C receptor.
- Trazodone is the most highly prescribed drug for insomnia.
- This is despite the fact that the efficacy of trazodone for treatment of insomnia had been studied in only small populations for insomnia in depressed individuals, usually with limited subjective sleep evaluations of sleep duration, sleep latency, or nocturnal awakenings and without objective polysomnographic data.
- In a 2-week, parallel group study in non depressed primary insomniacs, comparing trazodone 50 mg and zolpidem 10 mg, only zolpidem maintained a signifi cantly shorter sleep latency than the placebo group, with no differences in sleep duration among the groups at week 2.
- *Side effects*: Potential adverse reactions include dizziness, dry mouth, nausea/vomiting, constipation, headache, orthostatic hypotension, ventricular arrhythmias/ torsades de pointes, and, rarely, priapism. This should caution physicians against routine use of trazodone for insomnia, especially in the elderly.

M.S. Badr (ed.), *Essentials of Sleep Medicine,* Springer 2012

Table 42-1 Pharmacokinetic Properties of Sedating Antidepressant Drugs*

Drug	Drug Class	Time to Maximal Concentration (h)	Metabolism (CYP Enzymes)	Elimination Half-Life (h) (Range)	Usual Dose (mg)	
					Antidepressant	Hypnotic†
Doxepin	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	20 (10–30)	100–300	3, 6
Amitriptyline	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	30 (5–45)	100–300	10–150
Trimipramine	Tricyclic	2–8	Major: 2D6, 2C19 Minor: 1A2, 3A4	25 (15–40)	100–300	25–150
Trazodone	Phenylpiperazine	1–2	3A4, 2D6	9 (3–14)	200–600	25–150
Nefazodone	Phenylpiperazine	1	3A4, 2D6, 2C19	2–4 (6–18 for active metabolites)	150–450	50–150
Mirtazapine	Noradrenergic and specific serotonergic antidepressant	1–3	3A4, 2D6, 1A2	25 (13–40)	15–45	7.5–30

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

Affinities of various 5-HT_2 ligands toward 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors.

	Receptor subtype		
	5-HT_{2C}	5-HT_{2B}	5-HT_{2A}
5-HT_2 antagonists			
Agomelatin	708	251	4467
S32212	6.6	105	5.8
Mesulergine	1.8	3.5	46
LY 53857	4.2	6.9	1.7
SR 46349B	7.9	nd	9.2
Ritanserin	6.6	2.1	4.6
Mianserin	5.5	12	18
Ketanserin	62	741	8.1
Mirtazapine	13	200	6.3
Cyproheptadine	2.1	nd	8.7
SCH-23390	5.5 (A)	nd	20

Values correspond to Ki (nM).

MIRTAZAPINA

- **Mechanism of Action:** The primary mechanism of action of mirtazapine is antagonism at central pre-synaptic alpha2-receptors. The drug is a potent antagonist at 5-HT2 (particularly subtypes 2A and 2C) and 5-HT3 receptors, and exhibits significant antagonism at H1-receptors.
- **Pharmacokinetics:** Plasma protein binding is approximately 85% over a concentration range of 0.01 to 10 mcg/mL. Steady-state plasma concentrations are reached within 5 days. The elimination half-life is long and ranges from 20 to 40 hours across age and gender subgroups. Metabolism: CYP2D6, CYP1A2, CYP3A.
- The dose range is 15 mg/day to 45 mg/day.

(Drug Information Provided By Gold Standard, 2017)

Table 42-2 Receptor Pharmacology of Sedating Antidepressant Drugs*

Drug	Receptor Effects†						
	NE Reuptake	5-HT Reuptake	5-HT_2 Receptor Antagonism	α_1 Antagonism	M_1 Antagonism (Anticholinergic)	H_1 Antagonism (Antihistamine)	Other Effects
Doxepin	+	0/+	+	+++	++	+++	
Amitriptyline	+	++	+	+++	+++	++	
Trimipramine	0	0	+	+++	++	+++	
Trazodone	0	+	++	++	0	0/+	5-HT_{1A}, 5-HT_{1C}, and α_2 antagonism
Nefazodone	0	++	++	++	0	+	
Mirtazapine	0/+	0	++	+	+	+++	α_2 and 5-HT_1 antagonism

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

The effects of second generation antipsychotic drugs on sleep variables in healthy subjects and patients with schizophrenia

Jaime M. Monti [a, *], Pablo Torterolo [b], Seithikurippu R. Pandi Perumal [c]

Relative receptor affinities of second generation antipsychotic drugs.

Receptor	D_1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	α_1	α_2	H_1	m_1
Clozapine	+	+	−	+++	++	++	++	+++	+	+++	+++
Risperidone	+	+++	−	+++	++	−	+++	+++	++	+	−
Olanzapine	++	++	−	+++	++	+	−	++	+	+++	+++
Quetiapine	−	+	−	++	−	−	−	+++	−	++	++
Ziprasidone	+	+++	+++	+++	+++	+	++	++	−	+	−
Paliperidone	+	++	+	+++	+	−	−	++	++	+	−

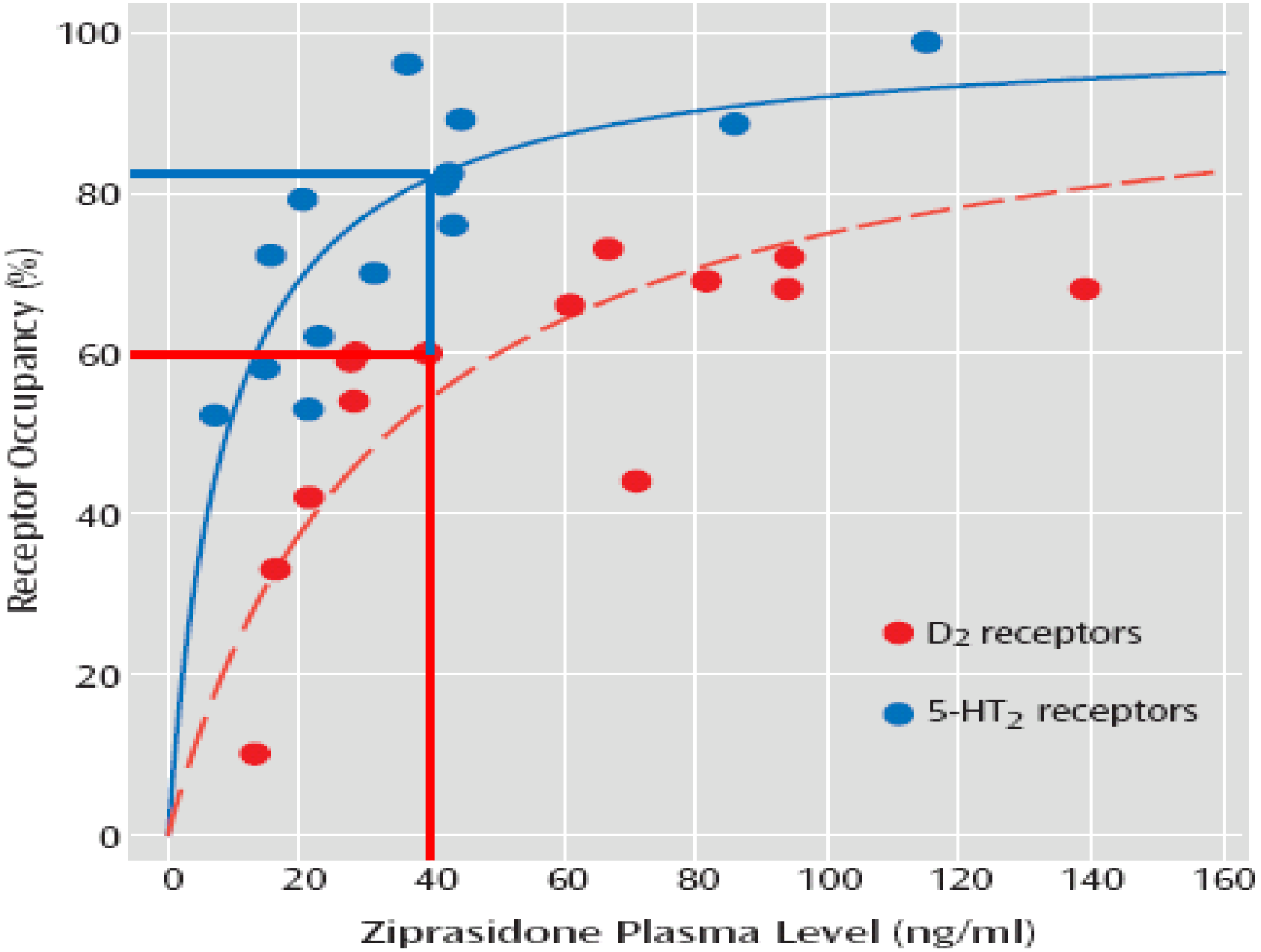
Effects of clozapine, risperidone, olanzapine, quetiapine and ziprasidone on sleep parameters in healthy subjects.

Treatment	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
S2 sleep latency (min)	n.s.	n.s	Decrease[a]	Decrease[a]	n.s.
Wake time after sleep onset (min)	−	n.s. or decrease[a]	Decrease[a]	Decrease[a]	Decrease[a]
Total sleep time (min)	n.s. or increase[a]	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Sleep efficiency (%)	−	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Stage 1 sleep (min)	n.s. or decrease[a]	n.s.	Decrease[a]	n.s.	Decrease[a]
Stage 2 sleep (min)	n.s.	n.s. or increase[a]	n.s.	n.s.	Increase[a]
Stage 3 sleep (min)	n.s.	−	−	−	−
Stage 4 sleep (min)	n.s. or decrease[a]	−	−	−	−
Slow wave sleep (min or %)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep latency (min)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep (min or %)	n.s. or decrease[a]	n.s. or decrease[a]	n.s. or decrease[a]	n.s.	Decrease[a]

Table 1. Affinity of Ziprasidone and Other Antipsychotics for Human Receptors

Receptor	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Haloperidol
D_1	130	580	52	1300	290	120
D_2	3.1	2.2	20	180	130	1.4
D_3	7.2	9.6	50	940	240	2.5
D_4	32	8.5	50	2200	47	3.3
5-HT_{1A}	2.5	210	2100	230	140	3600
5-HT_{1D}*	2.0	170	530	>5100	1700	>5000
5-HT_{2A}	0.39	0.29	3.3	220	8.9	120
5-HT_{2C}	0.72	10	10	1400	17	4700
5-HT_6	76	2000	10	4100	11	6000
5-HT_7	9.3	3.0	250	1800	66	1100
α_1	13	1.4	54	15	4.0	4.7
α_2	310	5.1	170	1000	33	1200
H_1	47	19	2.8	8.7	1.8	440
M_1	5100	2800	4.7	100	1.8	1600

Affinity values, K_i in nM.
Values are geometric means of at least 3 determinations.
*Bovine.
Adapted from Zorn et al (2).


Receptor Occupancy (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
Ziprasidone Plasma Level (ng/ml)
D2 receptors
5-HT2 receptors

Eventos Adversos†

Estudos 125 y 126

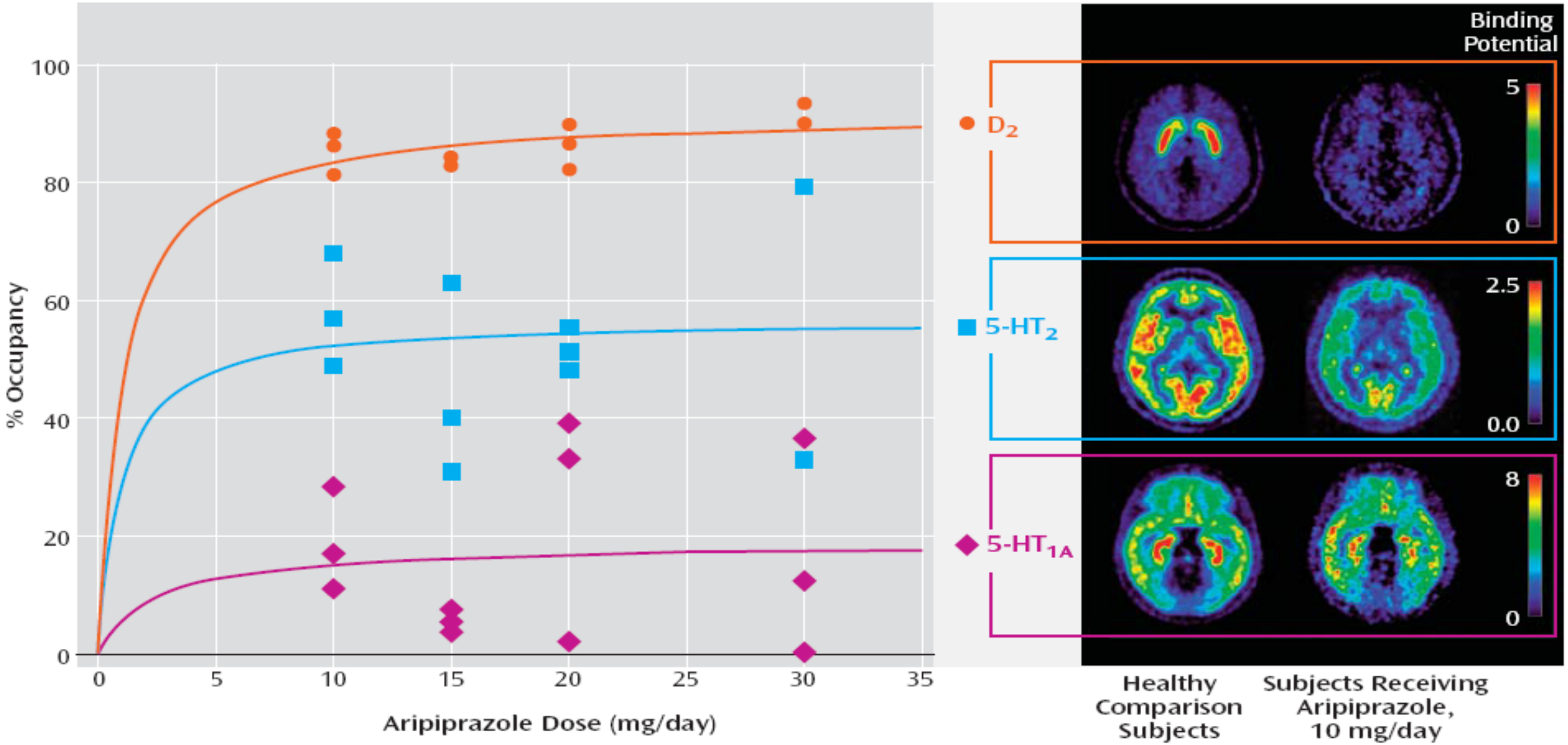
ZIPRASIDONA i/m

	Ziprasidona Estudio 125		Ziprasidona Estudio 126	
	2 mg (n=54)	10 mg (n=63)	2 mg (n=38)	20 mg (n=41)
Número (%) de pacientes con Eventos Adversos.	19 (35.2%)	27 (42.9%)	14 (36.8%)	18 (43.9%)
Discontinuación por eventos adversos	1 (5.2%)	2 (7.4%)	1 (7.1%)	0 (0%)
Dolor local	7 (13%)	5 (7.9%)	1 (2.6%)	3 (7.3%)
Astenia	0 (0%)	0 (0%)	2 (5.3%)	0 (0%)
Mareos	2 (3.7%)	2 (3.2%)	1 (2.5%)	4 (9.6%)
Somnolencia	2 (3.7%)	5 (7.9%)	5 (13.2%)	8 (19.5%)
Insomnio	0 (0%)	0 (0%)	2 (5.3%)	0 (0%)
Cefalea	3 (5.6%)	8 (12.7%)	0 (0%)	2 (4.9%)
Diarrea	1 (1.9%)	2 (3.2%)	2 (5.3%)	0 (0%)
Nauseas	1 (1.9%)	5 (7.9%)	3 (7.9%)	5 (12.2%)

†≥5% de pacientes en cada grupo
‡Transitorios y no dieron luegar a discontinuación

Data on file, Pfizer

FIGURE 1. Relationship Between Aripiprazole Dose and Occupancy at D_2, 5-HT_{1A}, and 5-HT_2 Receptors in the Putamen and Temporal Cortex in Patients With Schizophrenia or Schizoaffective Disorder[a]



Ziprasidona 2.5G/Aripiprasol 3G: un cambio de paradigma en el manejo de la esquizofrenia.

- Control de la psicopatología nuclear
- Efectos antidepresivos, ansiolíticos y neuroprotectores
- **SIN SEDACION**, paciente activo, con motivación (una puerta abierta a la rehabilitación)
- SIN LOS EFECTOS ADVERSOS DE LOS OTROS ANTIPSICOTICOS ATIPICOS, no producen (o la significación clínica es menor): obesidad, dislipemias, diabetes tipo II

(A. LISTA VARELA. 2007)

The effects of second generation antipsychotic drugs on sleep variables in healthy subjects and patients with schizophrenia

Jaime M. Monti [a, *], Pablo Torterolo [b], Seithikurippu R. Pandi Perumal [c]

Relative receptor affinities of second generation antipsychotic drugs.

Receptor	D_1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	α_1	α_2	H_1	m_1
Clozapine	+	+	−	+++	++	++	++	+++	+	+++	+++
Risperidone	+	+++	−	+++	++	−	+++	+++	++	+	−
Olanzapine	++	++	−	+++	++	+	−	++	+	+++	+++
Quetiapine	−	+	−	++	−	−	−	+++	−	++	++
Ziprasidone	+	+++	+++	+++	+++	+	++	++	−	+	−
Paliperidone	+	++	+	+++	+	−	−	++	++	+	−

Effects of clozapine, risperidone, olanzapine, quetiapine and ziprasidone on sleep parameters in healthy subjects.

Treatment	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
S2 sleep latency (min)	n.s.	n.s	Decrease[a]	Decrease[a]	n.s.
Wake time after sleep onset (min)	−	n.s. or decrease[a]	Decrease[a]	Decrease[a]	Decrease[a]
Total sleep time (min)	n.s. or increase[a]	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Sleep efficiency (%)	−	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Stage 1 sleep (min)	n.s. or decrease[a]	n.s.	Decrease[a]	n.s.	Decrease[a]
Stage 2 sleep (min)	n.s.	n.s. or increase[a]	n.s.	n.s.	Increase[a]
Stage 3 sleep (min)	n.s.	−	−	−	−
Stage 4 sleep (min)	n.s. or decrease[a]	−	−	−	−
Slow wave sleep (min or %)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep latency (min)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep (min or %)	n.s. or decrease[a]	n.s. or decrease[a]	n.s. or decrease[a]	n.s.	Decrease[a]

Table 41-1 Pharmacokinetic Properties and Dosages of Some Hypnotic Drugs Used in the Treatment of Insomnia

	Half-Life (h)	T_{MAX} (h)*	Pharmacologically Active Metabolites	Dose (mg)
Nonhypnotics Sometimes Used to Aid Sleep‖				
Clonazepam (Klonopin)	20–40	1–2.5	4-Amino derivative	0.5–1**
Diazepam (Valium)	30–100		*N*-desmethyl	2–10**
Chlordiazepoxide (Librium)	24–28		*N*-desmethyl (chlordiazepoxide, demoxepam, oxazepam)	10–25**
Alprazolam	6–20	0.6–1.4		0.5–1**
Lorazepam	10–20	0.7–1		0.5–1**
Quetiapine (Seroquel)	6	1–2	Quetiapine sulfoxide	25–50**
Trazodone (Desyrel)	9 (7–15)	1–2	*m*-CPP	25–50**

The effects of second generation antipsychotic drugs on sleep variables in healthy subjects and patients with schizophrenia

Jaime M. Monti [a, *], Pablo Torterolo [b], Seithikurippu R. Pandi Perumal [c]

Relative receptor affinities of second generation antipsychotic drugs.

Receptor	D_1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	α_1	α_2	H_1	m_1
Clozapine	+	+	−	+++	++	++	++	+++	+	+++	+++
Risperidone	+	+++	−	+++	++	−	+++	+++	++	+	−
Olanzapine	++	++	−	+++	++	+	−	++	+	+++	+++
Quetiapine	−	+	−	++	−	−	−	+++	−	++	++
Ziprasidone	+	+++	+++	+++	+++	+	++	++	−	+	−
Paliperidone	+	++	+	+++	+	−	−	++	++	+	−

Effects of clozapine, risperidone, olanzapine, quetiapine and ziprasidone on sleep parameters in healthy subjects.

Treatment	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
S2 sleep latency (min)	n.s.	n.s	Decrease[a]	Decrease[a]	n.s.
Wake time after sleep onset (min)	−	n.s. or decrease[a]	Decrease[a]	Decrease[a]	Decrease[a]
Total sleep time (min)	n.s. or increase[a]	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Sleep efficiency (%)	−	n.s.	Increase[a]	n.s. or increase[a]	n.s. or increase[a]
Stage 1 sleep (min)	n.s. or decrease[a]	n.s.	Decrease[a]	n.s.	Decrease[a]
Stage 2 sleep (min)	n.s.	n.s. or increase[a]	n.s.	n.s.	Increase[a]
Stage 3 sleep (min)	n.s.	−	−	−	−
Stage 4 sleep (min)	n.s. or decrease[a]	−	−	−	−
Slow wave sleep (min or %)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep latency (min)	n.s.	n.s.	Increase[a]	n.s.	Increase[a]
REM sleep (min or %)	n.s. or decrease[a]	n.s. or decrease[a]	n.s. or decrease[a]	n.s.	Decrease[a]

Table 42-4 Summary of Other Drugs Used to Treat Insomnia*

Drug	Drug Type	Time to Maximal Concentration	Metabolism	Elimination Half-Life	Mechanism of Action
Olanzapine	Thienobenzodiazepine antipsychotic	4–6 h	CYP1A2, CYP2D6	20–54 h	Antagonizes H_1, α_1, α_2, M_1, 5-HT_2, D_2 receptors
Quetiapine	Dibenzothiazepine antipsychotic	1–2 h	CYP3A4	6 h	Antagonizes H_1, α_1, M_1, 5-HT_2, D_2 receptors
Gamma–hydroxybutyrate (GHB)	Endogenous four-carbon molecule	30–45 min	Metabolized to GABA, succinic semialdehyde, H_2O and CO_2	20–70 min	May act directly as neurotransmitter, increase brain dopamine levels

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

PREGABALINA

Table 7.2 (continued)

Generic name	Trade name	FDA indication	Receptor-binding profile							t_{max} (h)	$t_{1/2}$ (h)	Metabolism[a]	Dose range for insomnia (mg)
			$GABA_A$ specificity	MT_1–MT_2	Anti-H_1	Anti-$5HT_2$	Anti-alpha$_1$	Anti-dopamine	Anti-mACh				
Trazodone	Desyrel	Depression			+	+++	+++			1–2	7–15	3A4, 2D6, 1A2	25–150
Antipsychotics													
Olanzapine	Zyprexa	Schizophrenia bipolar disorder			+++	+++	++	++	+++	4–6	30	1A2	2.5–20
Quetiapine	Seroquel	Schizophrenia			++	+	+++	+		1–2	7	2D6, 3A4	25–250
Anticonvulsants													
Gabapentin	Neurontin	Seizures, neuropathic pain								2–3.5	5–7		300
Pregabalin	Lyrica	Seizures, neuropathic pain								1.5	6.3		100
Tiagabine	Gabitril	Seizures	GAT_1 inhibition							0.75	2–9	3A	2–12
Other													
Melatonin	Melatonin	None		+++							1–3	1A2, 2C19	0.1–75
Prazosin	Minipress	Hypertension					+++			3	2–3		2–20

$GABA_A$ γ[gamma]-aminobutyric acid type A receptor agonist, *MT_1–MT_2* melatonin 1 and 2 receptor agonist, *anti-H1* histamine 1 receptor antagonist, *anti-$5HT_2$* serotonin type 2 receptor antagonist, *anti-dopamine* dopamine receptor antagonist, *anti-mACh* muscarinic anticholinergic receptor antagonist, t_{max} time to peak concentration, $t_{1/2}$ elimination half-life, *UG* uridine 5′-diphospho-glucuronosyltransferase, *AO* aldehyde oxidase, *GAT_1* GABA transporter 1

[a]All entries beginning with numbers refer to specific CYP enzymes in the cytochrome P-450 system

Pregabalin Mechanism of Action

- Pregabalin is
  - Not active at $GABA_A$ or $GABA_B$ receptors
  - Not metabolically converted to GABA
  - Not a GABA agonist or antagonist
  - Not able to alter GABA uptake or degradation

- Pregabalin is a potent $\alpha_2\delta$ ligand

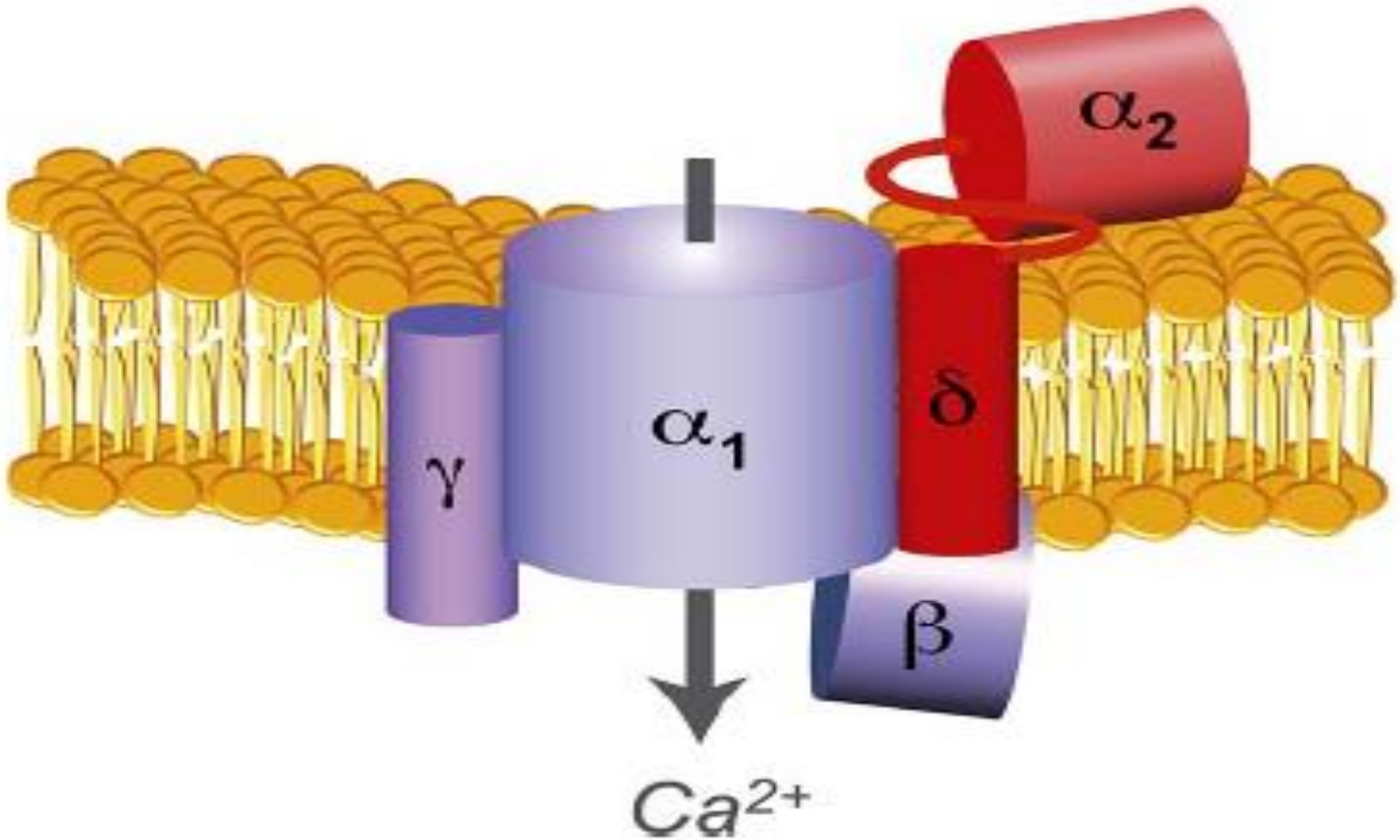
Gee et al. 1996, Fink et al. 2002, Dooley et al. 2000, Maneuf et al. 2001, Bialer et al. 1999, Welty et al. 1997

Ancillary subunits

$\beta_1, \beta_2, \beta_3, \beta_4$

γ_1 through γ_8

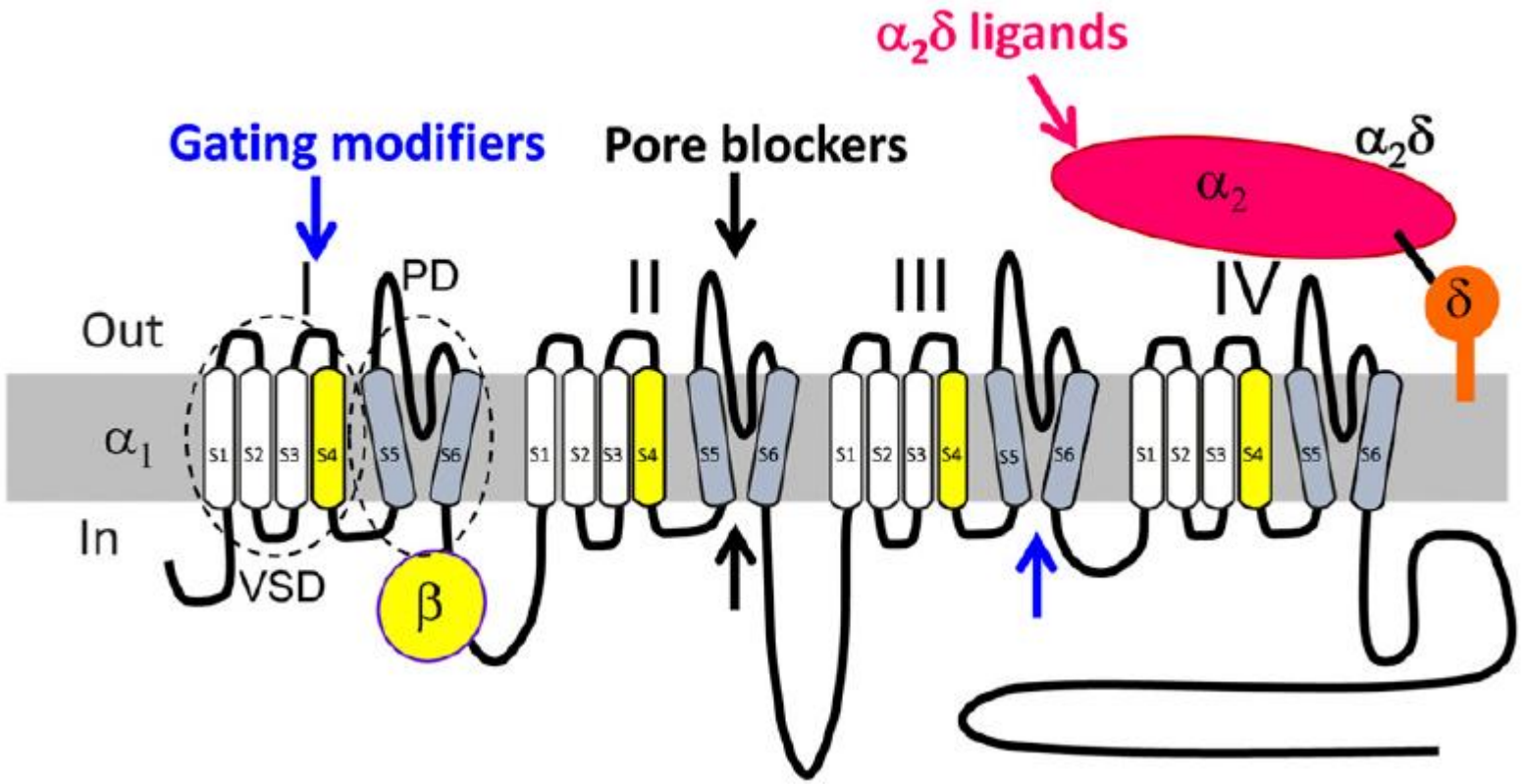
α_2-δ_1 through α_2-δ_4



Neuronal α_1 subunits

HVA	$Ca_v1.2$	L-type
	$Ca_v1.3$	L-type
	$Ca_v1.4$	L-type
	$Ca_v2.1$	P/Q-type
	$Ca_v2.2$	N-type
	$Ca_v2.3$	R-type
LVA	$Ca_v3.1$	T-type
	$Ca_v3.2$	T-type
	$Ca_v3.3$	T-type

Voltage-gated calcium channel subunit topology showing major drug binding mechanisms.



Pharmacol Rev 67:821–870, 2015

Canales de Ca^{2+}

Los canales de calcio están constituidos por múltiples unidades proteicas

La sub unidad $\alpha_2\ \delta$ regula la apertura del canal

Hay cuatro genes que codifican para 4 subtipos de sub $\alpha_2\ \delta$

Todas las sub unidades $\alpha_2\ \delta$ tiene un peso mol. de 180 k Da

La expresión de los genes por la sub unidad $\alpha_2\ \delta$ difieren en los distintos tejidos:

- $\alpha_2\ \delta$ T1: ampliamente distribuida (SNC, SNA, otros)
- $\alpha_2\ \delta$ T2: cerebro, músculo, pulmón, corazón
- $\alpha_2\ \delta$ T3: cerebro
- $\alpha_2\ \delta$ T4: hipófisis, g. suprarrenal

(Taylor LP CNS Drugs Rew 10(2): 183-188, 2004)

Canales de Ca^{2+}

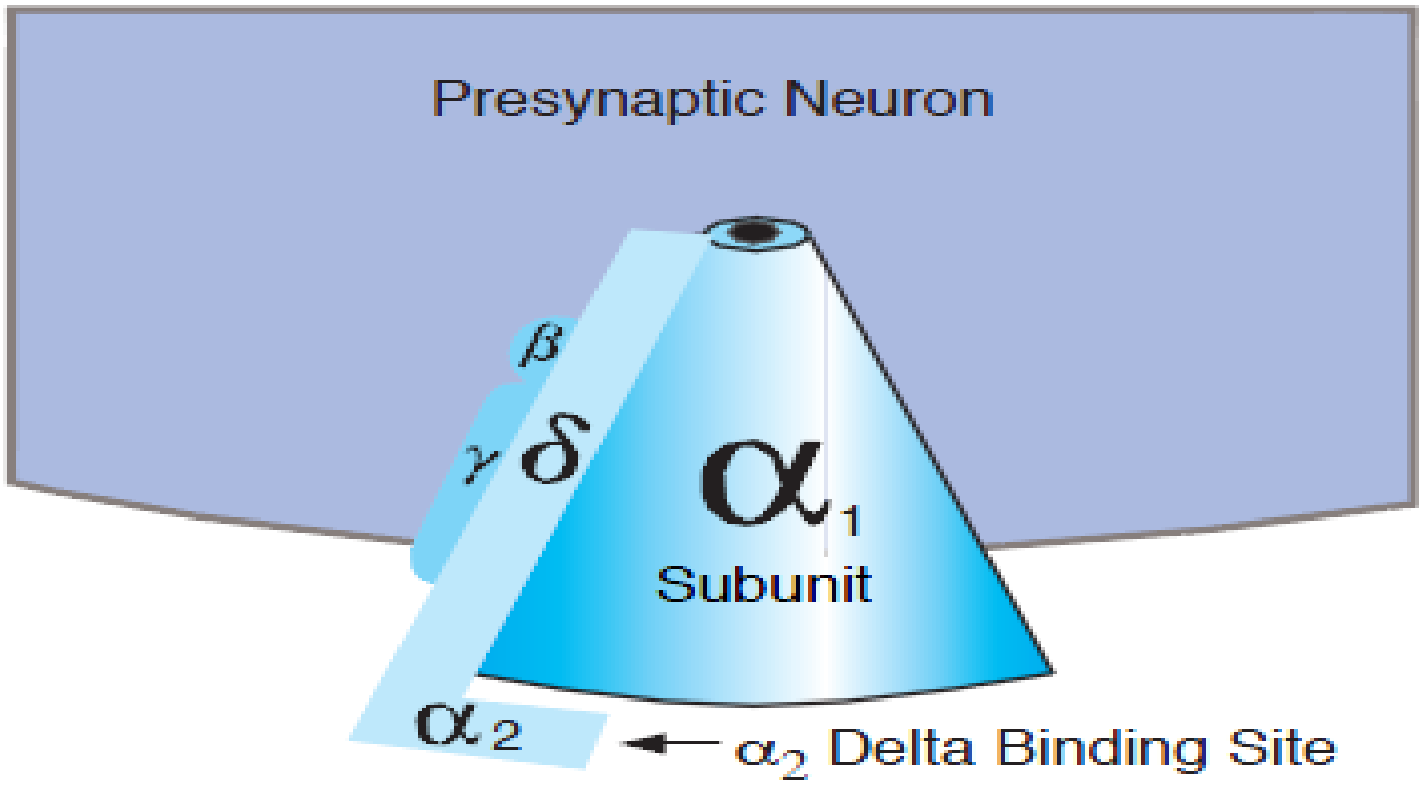
Pregabalina se liga con alta afinidad solo a los tipos 1 y 2 de las sub unidades α_2 δ

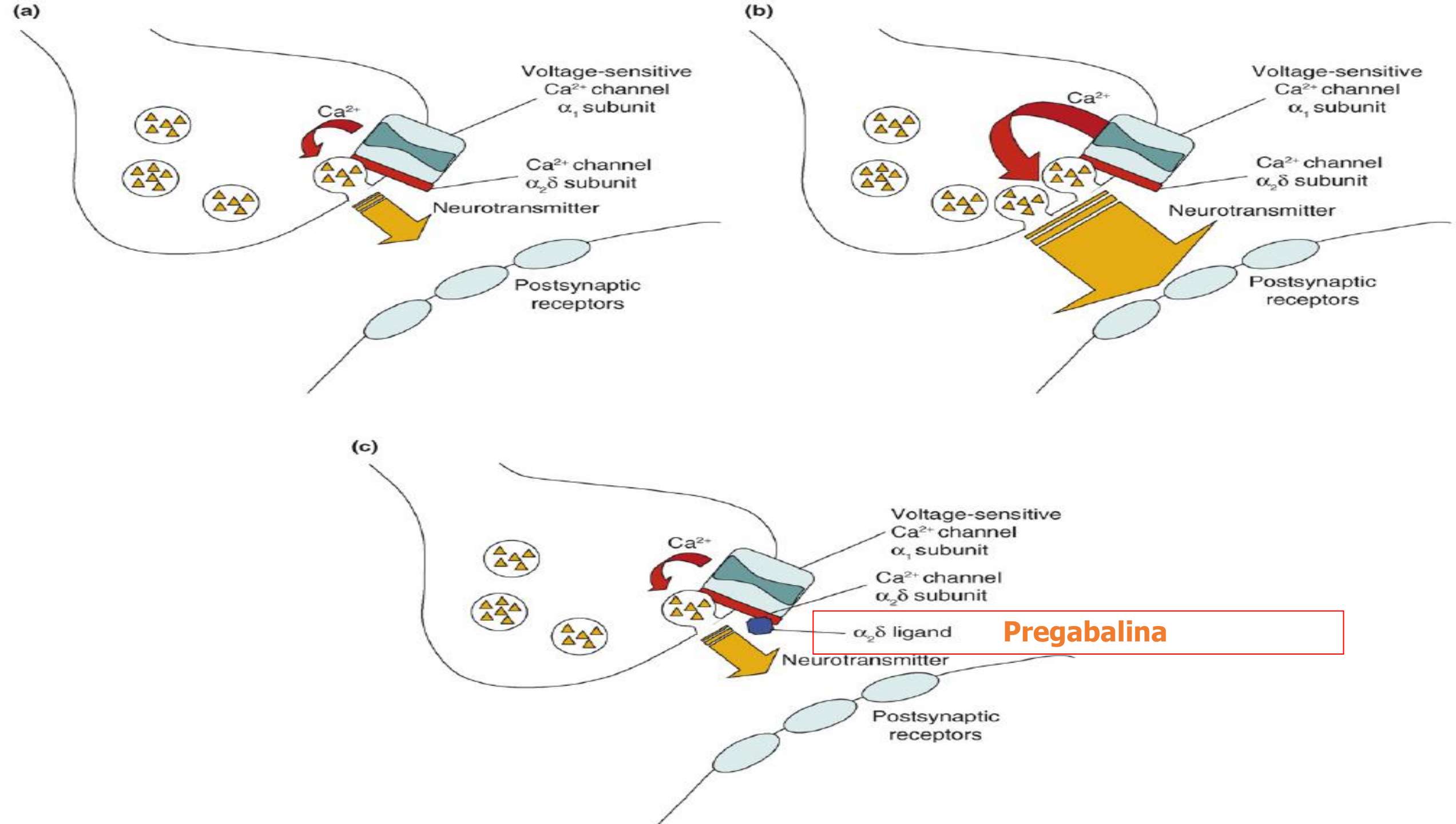
Tiene una afinidad en el entorno de 30-40 nM

Pregabalina interactuando con la **sub unidad α_2 δ tipo 1** disminuye la liberación de NT cuando estos sistemas están sobreactivados.

Taylor LP CNS Drugs Rew 10(2): 183-188, 2004

Figure 2. Calcium Channel With Multiple Subunits




(a)
Voltage-sensitive
Ca2+ channel
α1 subunit
Ca2+
Ca2+ channel
α2δ subunit
Neurotransmitter
Postsynaptic
receptors
(b)
Ca2+
Voltage-sensitive
Ca2+ channel
α1 subunit
Ca2+ channel
α2δ subunit
Neurotransmitter
Postsynaptic
receptors
(c)
Ca2+
Voltage-sensitive
Ca2+ channel
α1 subunit
Ca2+ channel
α2δ subunit
α2δ ligand
Pregabalina
Neurotransmitter
Postsynaptic
receptors

Pregabalin: Prescribing Information

Indications

- Pregabalin is indicated for the treatment of peripheral neuropathic pain in adults
- Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization
- Pregabalin is indicated for the treatment of Generalized Anxiety Disorder (GAD) in adults

Contraindication

- Hypersensitivity to the active substance or to any of the excipients

Pregabalin: Prescribing Information

Adverse events

- **The most common adverse events in the entire clinical development program were dizziness and somnolence**

Dosing

- **The effective pregabalin starting dose is 150 mg/day (**peripheral neuropathic pain**). Based on individual patient response and tolerability, the dose may be increased up to 600 mg/day over a 2-week period**

Renal impairment

- **Pregabalin dosage reduction is necessary in patients with renal impairment (Clcr < 60 mL/min).**

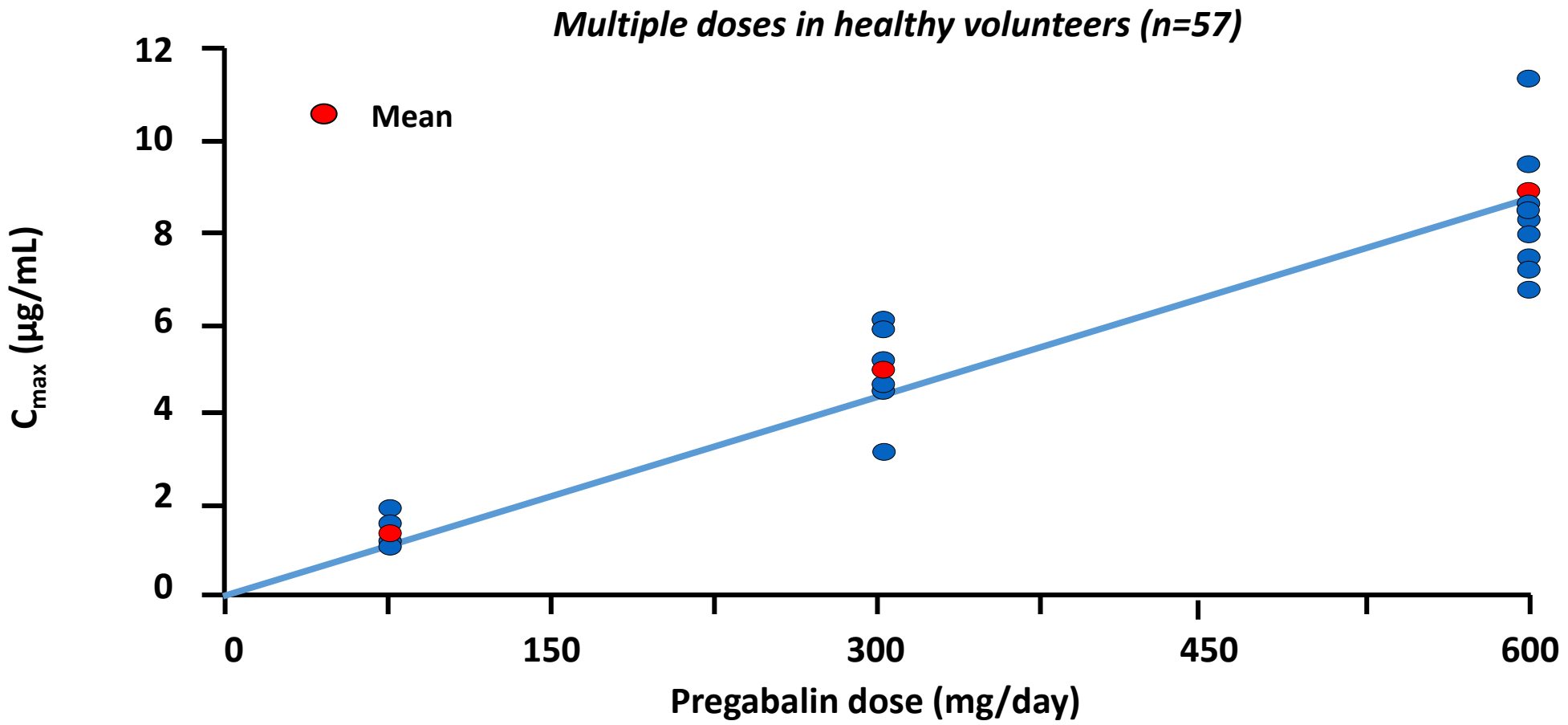
Pharmacodynamic interactions

- **Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam**

Pregabalin: Pharmacokinetic Profile

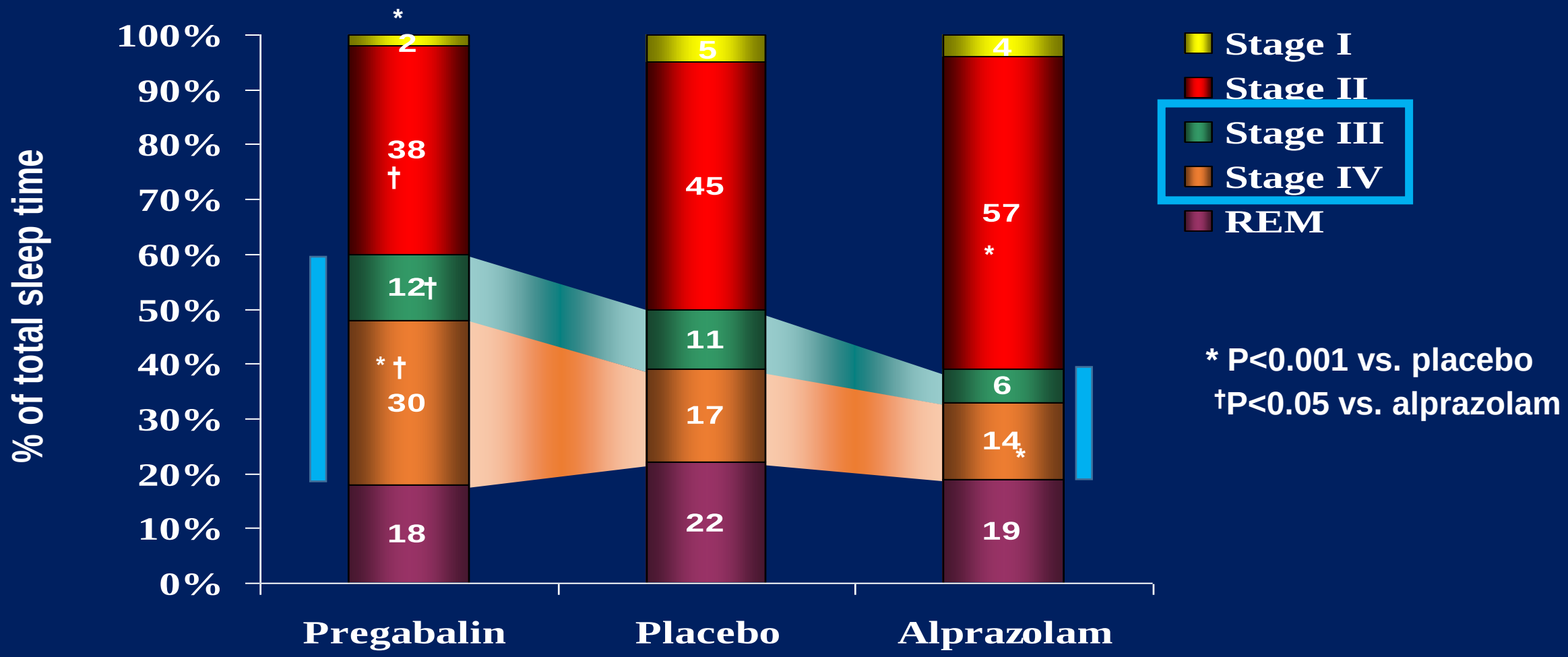
Variable	Properties	Clinical relevance
Absorption	$T_{max} \leq 1$ h	Rapid attainment of plasma levels
Bioavailability	$\geq 90\%$ No food effect	Consistent across dose range Administration with or without food
Pharmacokinetics (150–600 mg/day)	Linear PK Dose-proportional C_{max} & AUC	Dose-related increase in clinical response in neuropathic pain and epilepsy trials
Plasma half-life	6.3 h	Twice daily dosing (three times daily dosing an option)*
Steady state	24 – 48 h	Potentially fast dose adjustment
Protein binding	No	No displacement of protein-bound drugs
Metabolised	No (<2%)	No hepatic effects
Renal excretion	98% unchanged	Dose adjustment in renal impairment

Pregabalin Absorption is Linear Across Dosing Range



Pregabalin and Alprazolam vs. Placebo

Pregabalin:
Novel Sleep Architecture Benefits



* P<0.001 vs. placebo
†P<0.05 vs. alprazolam

Data on file, Pfizer

AGENDA DE LA PRESENTACIÓN

INTRODUCCIÓN:

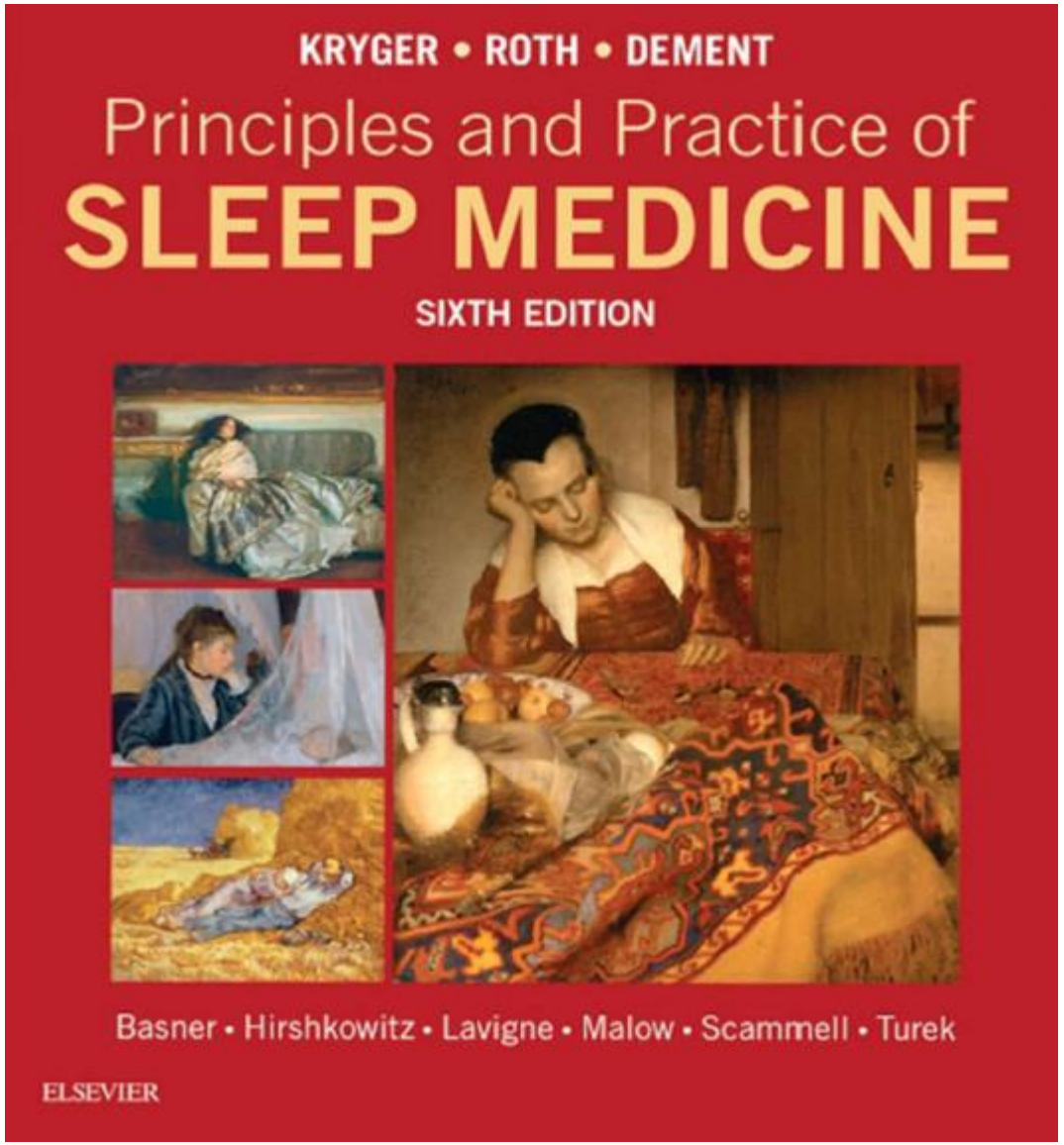
HIPNÓTICOS: bioquímica y farmacología

ACTIVADORES: bioquímica y farmacología

USOS EN LA PRÁCTICA CLÍNICA:

DESARROLLOS FUTUROS:

CONCLUSIONES:



Chapter 43

Wake-Promoting Medications: Basic Mechanisms and Pharmacology

Seiji Nishino; Emmanuel Mignot

Chapter 44

Wake-Promoting Medications: Efficacy and Adverse Effects

Mihaela Bazalakova; Ruth M. Benca

Wake-Promoting Medications: Basic Mechanisms and Pharmacology

- The term central nervous system (CNS) stimulant is a loosely defined scientific term.
- In *Drugs and the Brain* by S. Snyder, stimulants are “drugs that have an alerting effect; they improve the mood and quicken the intellect.”
- In *Handbook of Sleep Disorders* by J. D. Parkes, CNS stimulation implies “an increase in neuronal activity due to enhanced excitability, with a change in the normal balance between excitatory and inhibitory influences. This may result from blockage of inhibition, enhancement of excitation, or both.”
- In *A Primer of Drug Action* by R. M. Julien, the term “psychomotor stimulants (psychostimulants)” is used, and “psychostimulants” are said to induce excitement, alertness, euphoria, a reduced sense of fatigue, and increased motor activity. Psychostimulants include dopamine (DA) uptake blockers, DA-releasing agents, adenosine receptor blockers, and acetylcholine receptor stimulants.
- In *The Pharmacological Basis of Therapeutics* by Goodman and Gilman, the term “indirect sympathomimetic amines” refers to amphetamines as the “most potent compounds with respect to stimulation of the CNS.”
- In this chapter, the generic term ***CNS stimulants*** **will be used for all wake-promoting compounds of potential use in the treatment of excessive daytime sleepiness**.

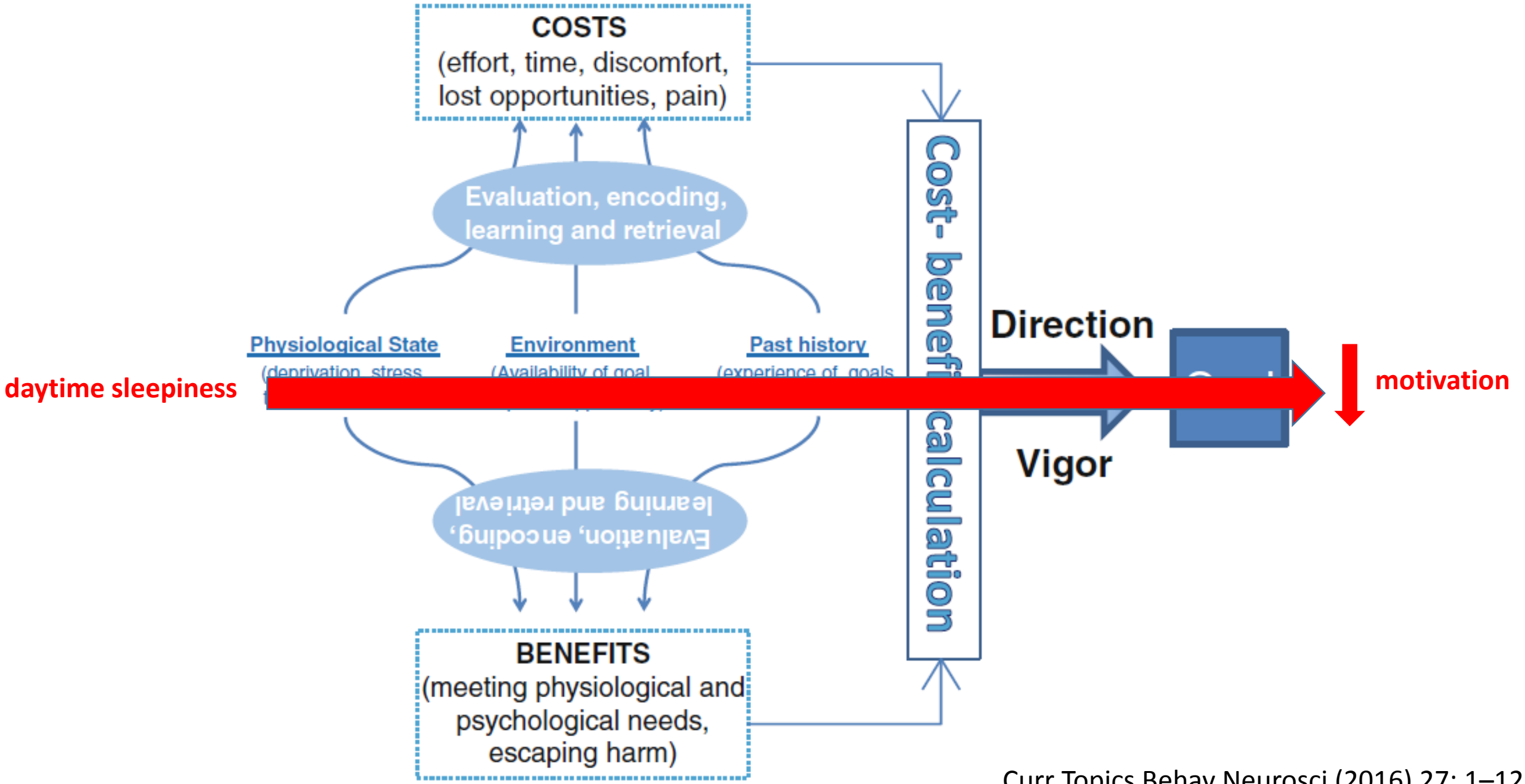
Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier

How Motivation Might Work in the Brain

- **Motivation** is conceptualized to consist of both a goal-directed, directional component and **an arousal, activational component**.
- There is generally a hierarchical structure to motivation in the sense that general arousal factors such as sleep–wake cycles will affect many different motives, that activation of specific motives (e.g., hunger, thirst, social motives) can activate many specific actions that could lead to many specific outcomes within a general class of goals.
- Many different factors influence motivation, including the organism's internal physiological states, the current environmental conditions, as well as the organism's past history and experiences.

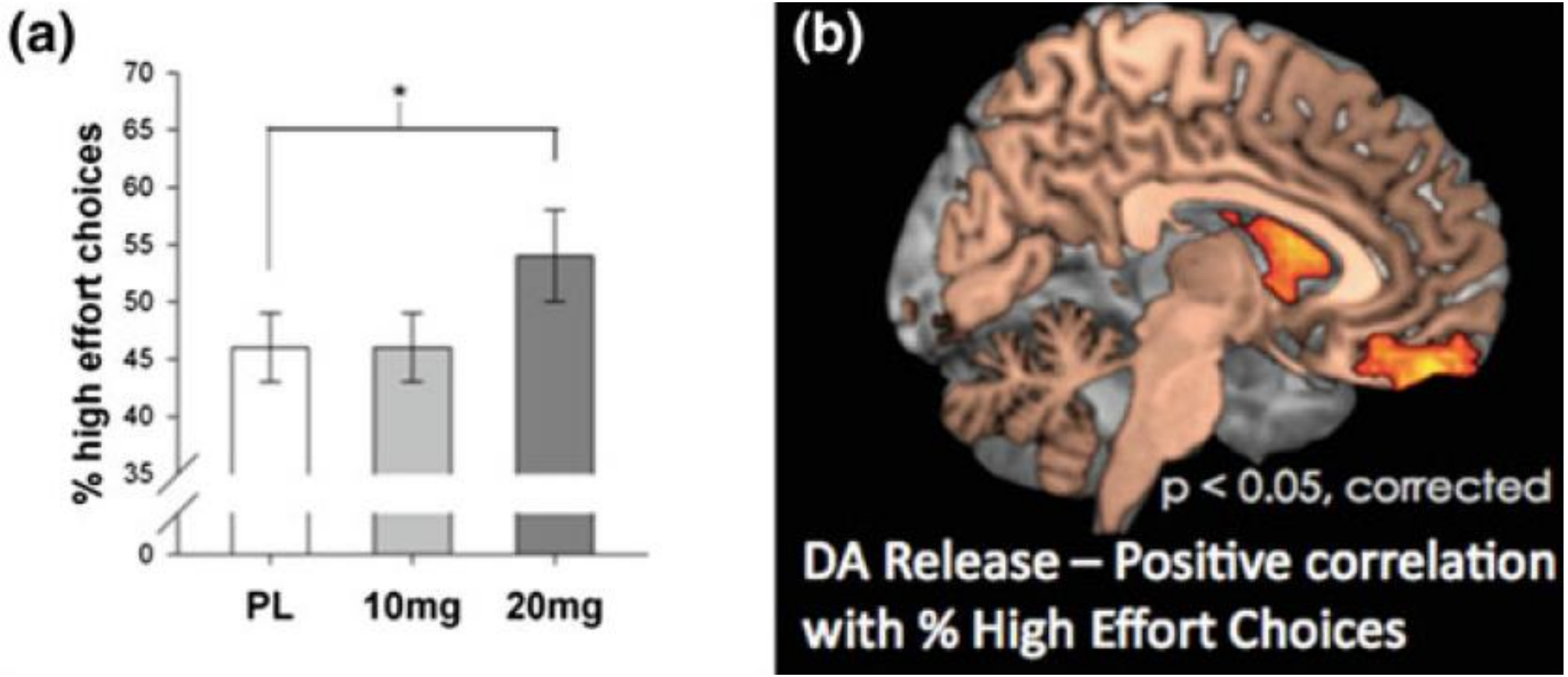
Curr Topics Behav Neurosci (2016) 27: 1–12

The influencing factors and processes that are involved in motivation.



Curr Topics Behav Neurosci (2016) 27: 1–12

studies in humans



Administration of amphetamine produces a dose-dependent increase in willingness to expend greater effort for larger rewards

Curr Topics Behav Neurosci (2016) 27: 337–355

Chapter 43

Wake-Promoting Medications: Basic Mechanisms and Pharmacology

Seiji Nishino; Emmanuel Mignot

- Almost all the currently available stimulants used to treat excessive daytime sleepiness in clinical practice (amphetamines, amphetamine-like stimulants, and modafinil-armodafinil) act presynaptically to increase dopaminergic transmission, either by stimulating dopamine release or by blocking dopamine reuptake.
- These effects are believed to be critically involved in the mediation of the wake-promoting effects of these compounds.
- Some (e.g., amphetamine) stimulants also increase adrenergic neurotransmission.
- Selective adrenergic uptake inhibitors have limited wake-promoting effects but potently reduce REM sleep or cataplexy.
- Increased adrenergic neurotransmission may play a minor role in stimulant-induced wake-promoting effects.

Table 43-1 Commonly Used Pharmacologic Compounds for Excessive Daytime Sleepiness

Stimulant Compound	Usual Daily Doses*	Half-Life (hr)	Side Effects, Notes
Amphetamines and Amphetamine-like CNS Stimulants			
D-Amphetamine sulfate (schedule II)	5–60 mg (15, 100 mg)	16–30	Irritability, mood changes, headaches, palpitations, tremors, excessive sweating, insomnia
Methamphetamine HCl† (schedule II)	5–60 mg (15, 80 mg)	9–15	Same as D-amphetamine; may have a greater central over peripheral effects than D-amphetamine‡
Methylphenidate HCl (schedule II)	10–60 mg (30, 100 mg)	~3	Same as amphetamines; better therapeutic index than D-amphetamine with less reduction of appetite or increase in blood pressure; short duration of action
Pemoline (schedule IV)	20–115 mg (37.5, 150 mg)	11–13	Less sympathomimetic effect, milder stimulant, slower onset of action; occasionally produces liver toxicity; had been withdrawn from the U.S. market
Dopamine and Norepinephrine Uptake Inhibitor			
Mazindol (schedule IV)	2–6 mg (NA)	10–13	Weaker CNS stimulant effects; anorexia, dry mouth, irritability, headaches, gastrointestinal symptoms; reported to have less potential for abuse
Other Agents for Treatment of EDS			
Modafinil§ (schedule IV)	100–400 mg (NA)	9–14	No peripheral sympathomimetic action; headaches, nausea; reported to have less potential for abuse
Armodafinil (schedule IV)	100–300 mg (NA)	10–15	Similar to those of modafinil
MAO Inhibitors with Alerting Effect			
Selegiline	5–40 mg (NA)	2	Low abuse potential; partial (10%-40%) interconversion to amphetamine
Xanthine Derivative			
Caffeine¶	100–200 mg (NA)	3–7	Weak stimulant effect; 100 mg of caffeine roughly equivalent to one cup of coffee; palpitations, hypertension

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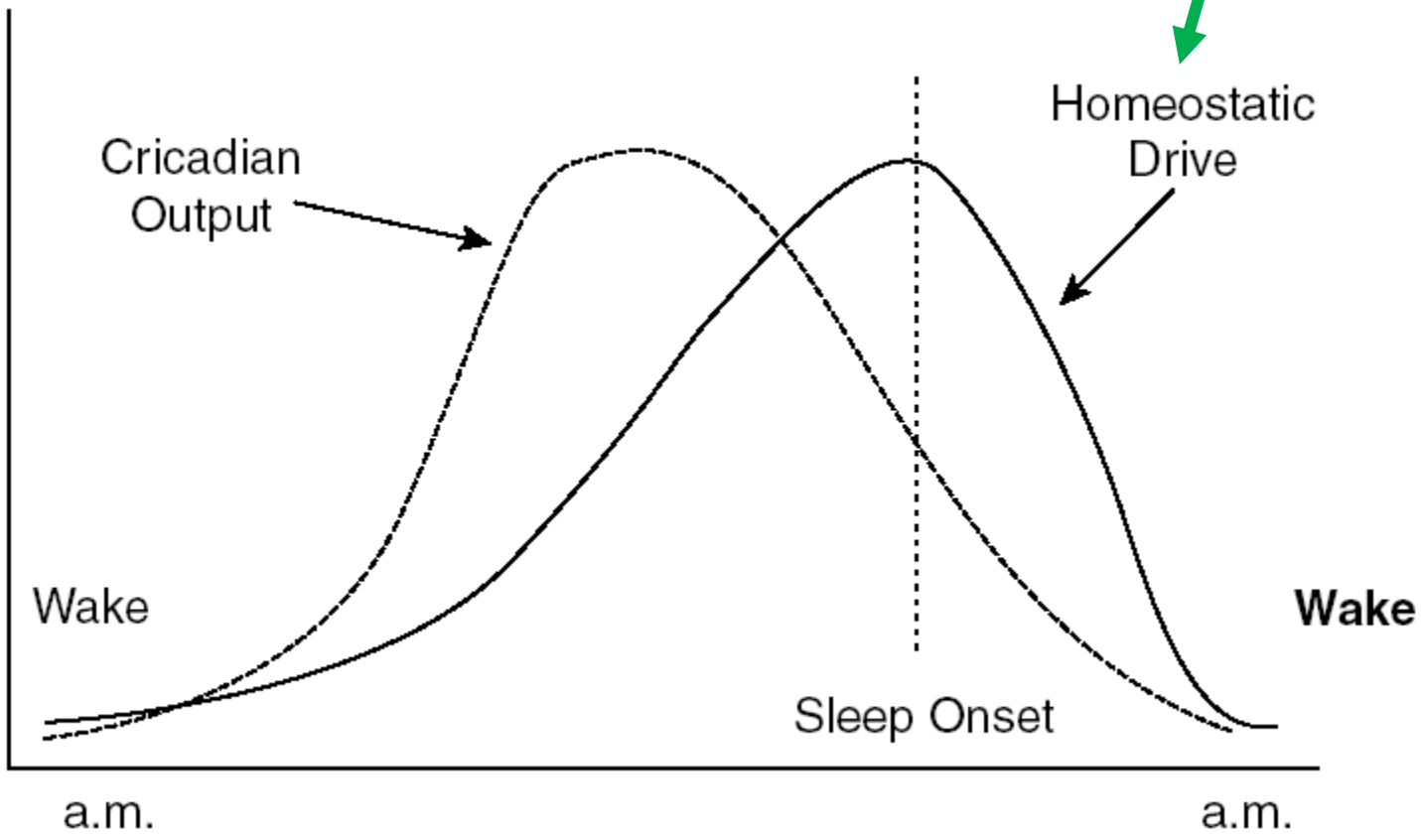
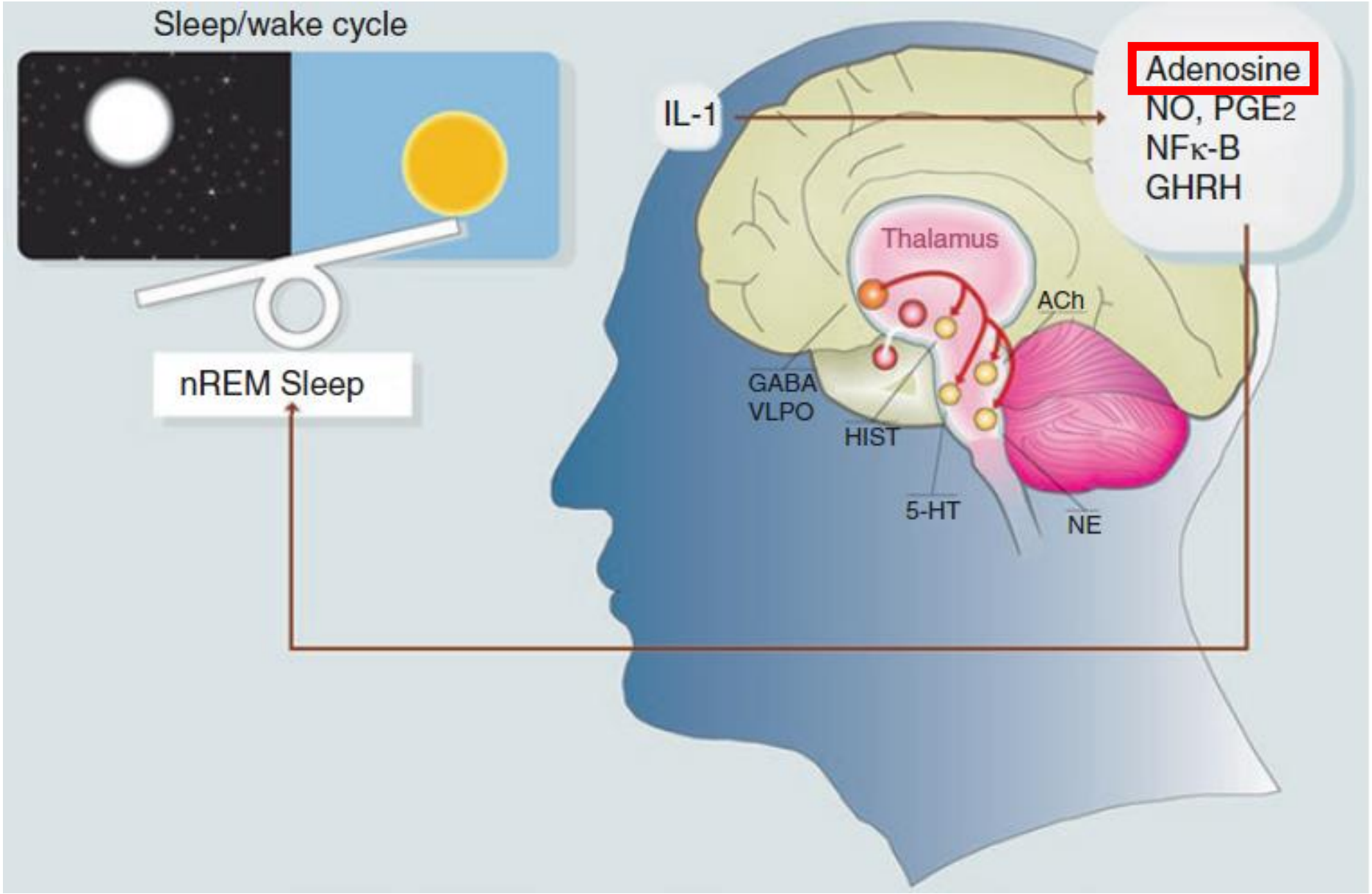
Metabolitos: **adenosina**, GABA, PGD2, IL1, TNFalfa



Interaction of circadian and homeostatic factors in sleep–wake regulation.

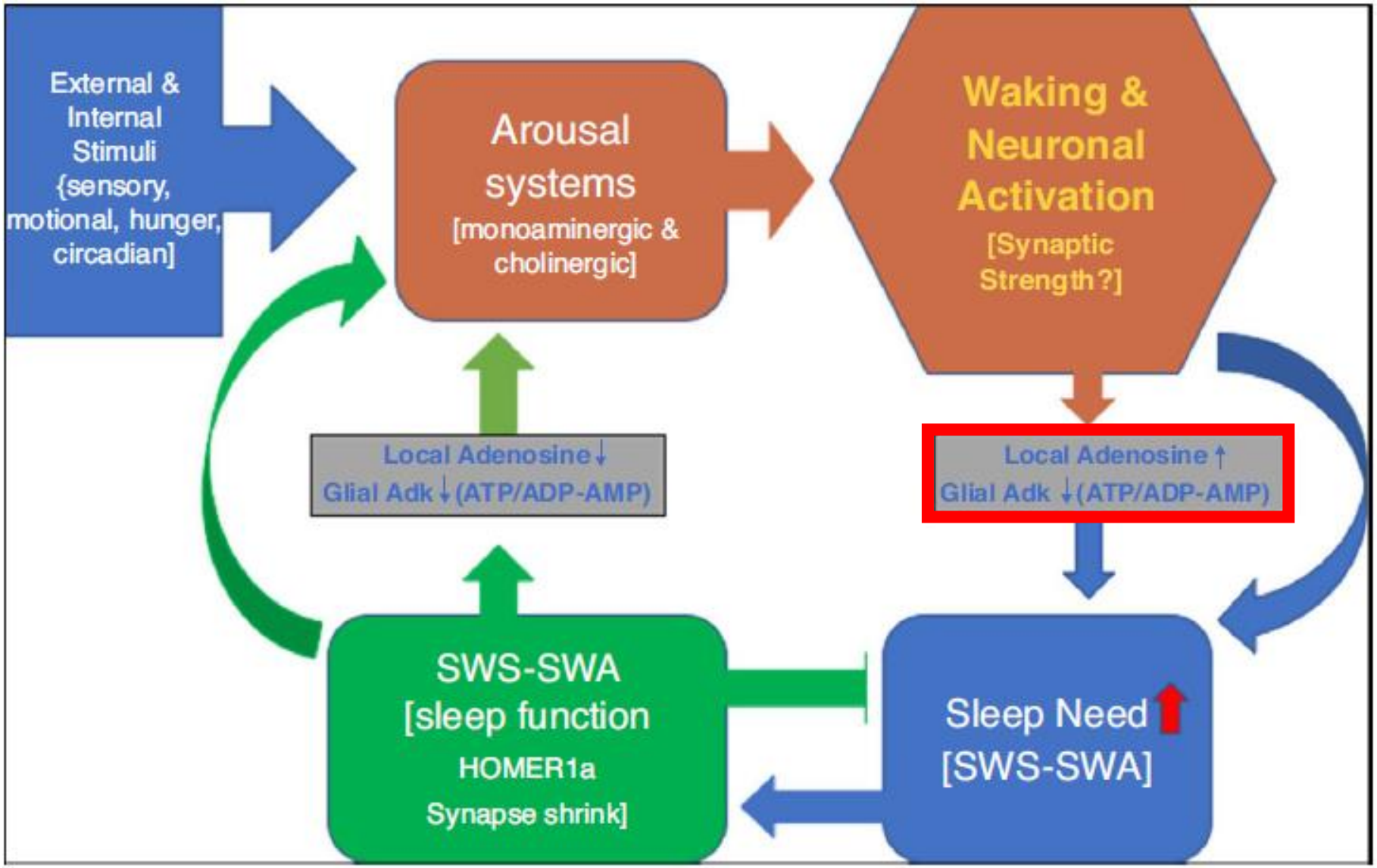
Effect of humoral signals on slow-wave sleep



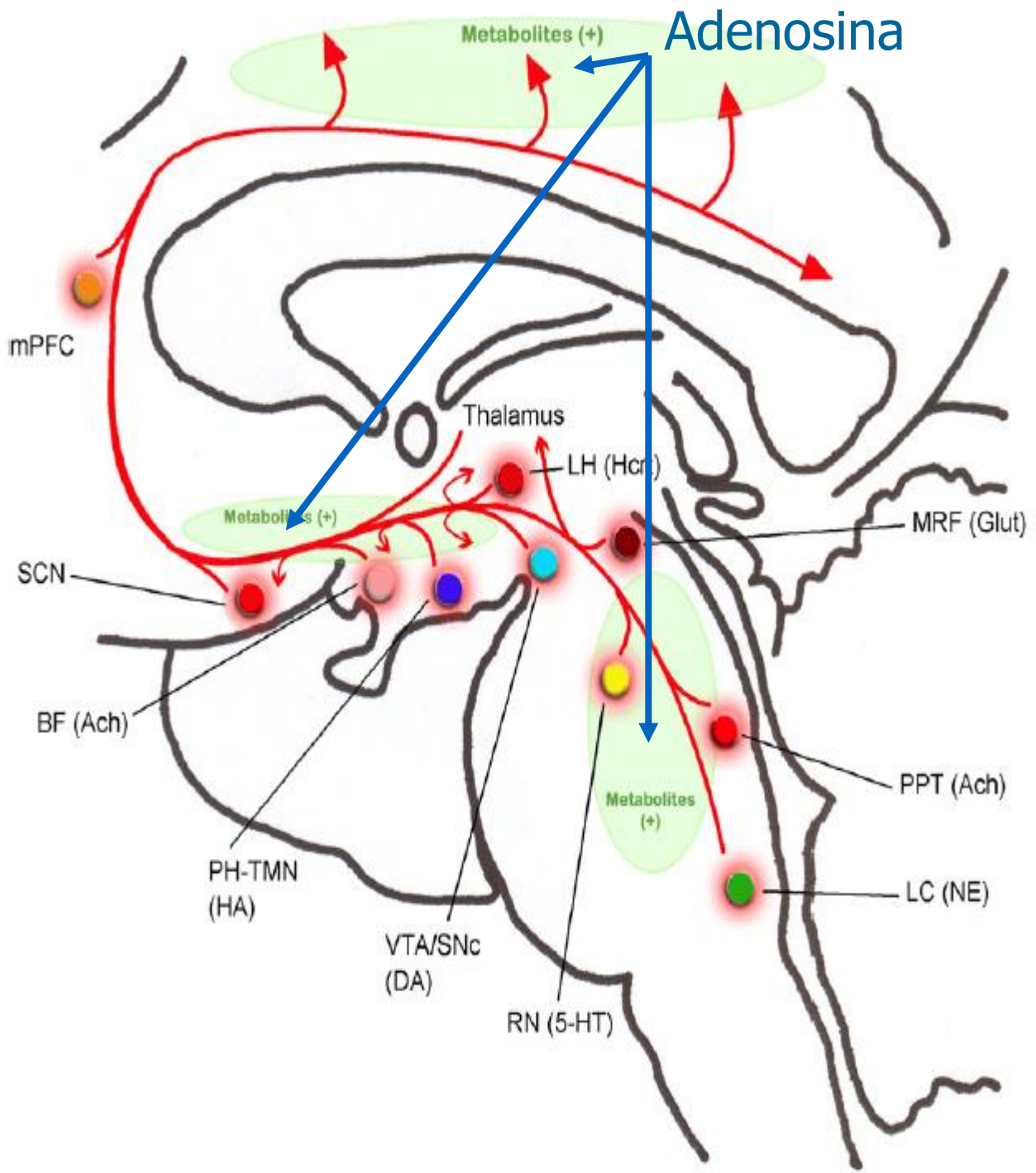
D.P. Cardinali, *Autonomic Nervous System*, Springer 2018

The adenosine-mediated, neuronal-glial, homeostatic sleep response

Sleep-homeostasis related SWA (slow wave activity) results from a buildup of extracellular adenosine that acts at neuronal adenosine A1 receptors to facilitate SWA and is metabolized by adenosine kinase found in glia. This local neuronal-glial circuit for homeostatic SWA is primarily under the requisite control of two genes, the Adora1 and Adk.



Current Opinion in Neurobiology 2017, 44:236–242


Adenosina
Metabolites (+)
mPFC
Thalamus
LH (Hcrt)
MRF (Glut)
SCN
BF (Ach)
PPT (Ach)
PH-TMN
(HA)
VTA/SNc
(DA)
RN (5-HT)
LC (NE)

Regulation of Adenosine Levels

- Adenosine is formed by hydrolysis of adenosine monophosphate (AMP) or S-adenosylhomocysteine
- Adenosine is formed from S-adenosylhomocysteine by the enzyme S-adenosylhomocysteine hydrolase, which can also act to trap adenosine in the presence of excess L-homocysteine.
- This takes place intracellularly and the fact that the enzyme is bidirectional ensures the constant presence of a finite concentration of adenosine in the cell.
- The formation of adenosine from 5’-AMP can occur both intracellularly and extracellularly, mediated by different enzymes.
- The intracellular 5’nucleotidase generates adenosine, which can be used to generate AMP by adenosine kinase.
- This bidirectional reaction ensures the constant presence of a finite intracellular concentration of adenosine in the range of 10 to a few hundred nanomolar (nM) under physiologic conditions.

Neuronal and glial-derived adenosine

- Adenosine reduces excitatory neurotransmission by stimulating inhibitory A1 receptors.
- The A1 receptor appears to be required for disruption of hippocampal long-term potentiation by a spontaneous low-frequency EEG pattern, which is typical for deep NREM sleep and could provide a stimulus for plasticity reversal.
- Prolonged A1 receptor activation also induces dynamic changes in the synaptic expression of NMDA R that may reversibly adjust the threshold for plasticity induction.
- Adenosine actively promotes sleep by stimulating excitatory A2A receptors in ventro-lateral preoptic area of the hypothalamus.

Curr Topics Behav Neurosci (2015) 25: 331–366

CAFFEINE PHARMACOLOGY

- In humans, the principal metabolic pathway for caffeine is catalyzed by the cytochrome P450 (CYP) enzyme CYP1A2 in the liver and accounts for approximately 95% of its initial breakdown.
- The process begins with removal of a methyl group to form the primary metabolite paraxanthine; however, theobromine and theophylline are also formed in smaller concentrations.
- The half-life of caffeine in healthy adults is approximately 4–5 hours.
- A1 and A2a ARs in the brain are responsible for the behavioral effects of caffeine.

Annu. Rev. Food Sci. Technol. 2016. 7:117–37

CAFFEINE PHARMACOLOGY

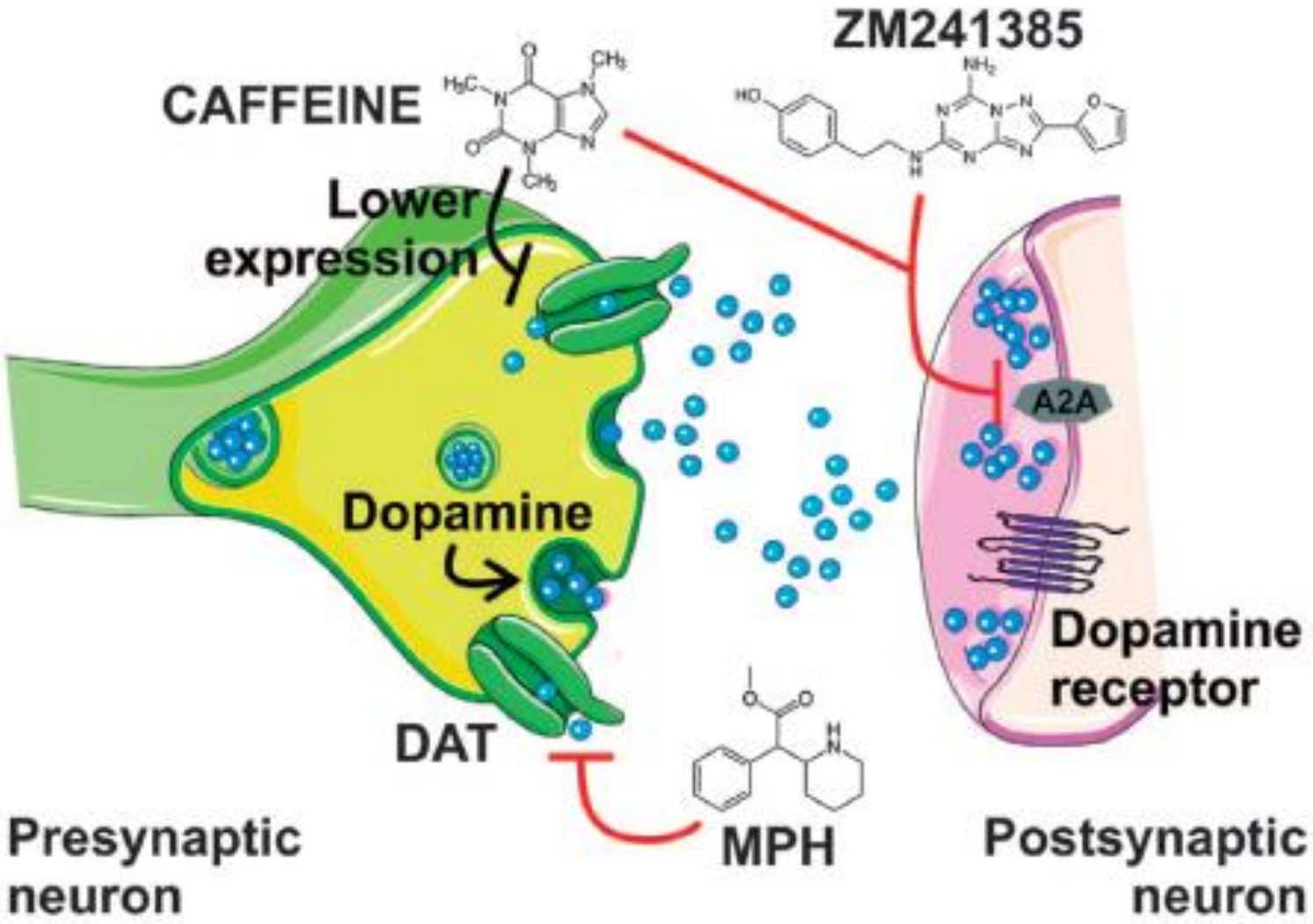
- The American Academy of Sleep Medicine examined the efficacy and safety of caffeine use during sleep loss and concluded that caffeine can:
- (*a*) increase alertness and improve performance after acute restriction of sleep (at doses of 75–150 mg) and
- (*b*) provide similar benefit after a night or more of total sleep loss (at doses
- of 200–600 mg).
- The major disruptive effects of caffeine on sleep are unlikely to occur more than 8 hours after administration, and prolonged administration of caffeine is not recommended because of the increasing likelihood of side effects (e.g., interference with sleep, increased anxiety and blood pressure) with high doses.

Annu. Rev. Food Sci. Technol. 2016. 7:117–37

CAFFEINE PHARMACOLOGY

- In summary, extensive research exists that demonstrates beneficial behavioral effects of caffeine.
- Most neurobehavioral studies find that the desirable benefits of caffeine are common and can be achieved at dose levels that appear to warrant no concern.
- Negative effects are very rare and may largely be restricted to consumption of high doses by susceptible individuals.

Annu. Rev. Food Sci. Technol. 2016. 7:117–37



Caffeine augments responsiveness to MPH, probably by reducing DAT expression. Moreover, **caffeine inhibits ADO receptors**.

Molecular Psychiatry (2017), 1 – 13

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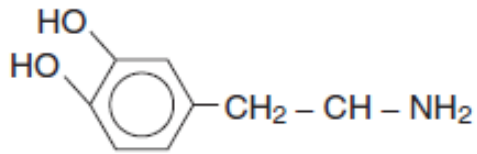
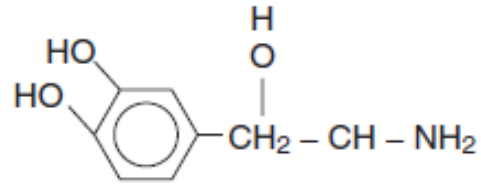
Chemical structures of amphetamine-like stimulants, modafinil, armodafinil, and xanthine derivatives compared with catecholamine.

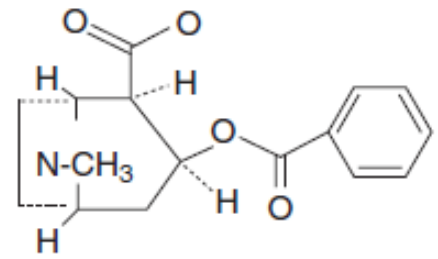
Dopamine



Norephinephrine

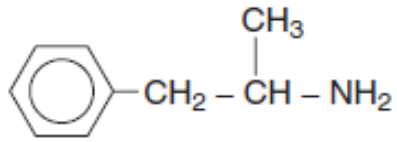


Cocaine

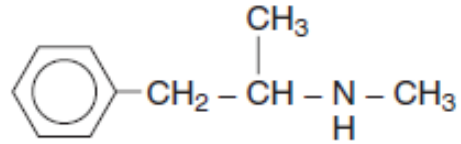


Amphetamines

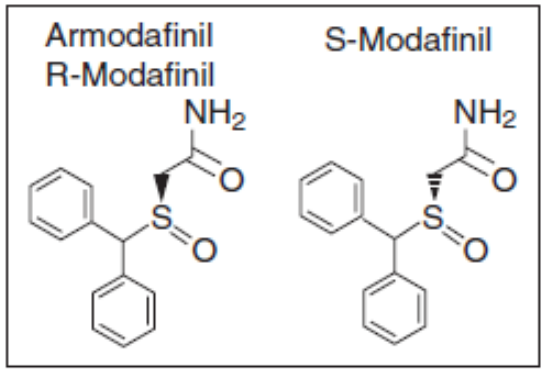
Amphetamine



Methamphetamine

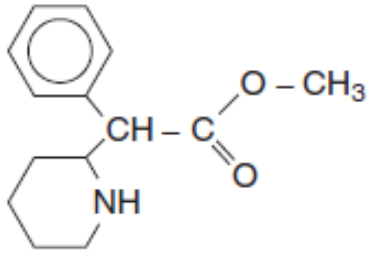


Modafinil

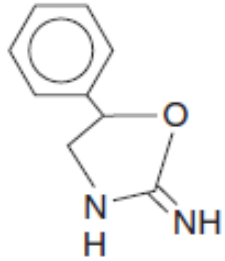


Amphetamine-like stimulants

Methylphenidate

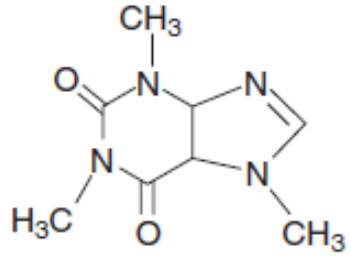


Pemoline



Xanthine derivative

Caffeine



Historia del desarrollo de modafinilo

- CRL 40476 (modafinilo) fue seleccionado como un metabolito estable de adrafinilo en abril de 1976 en el Lab. Louis Lafon, Paris.
- Se demuestra su perfil farmacológico único, como estimulante no catecolaminérgico y promotor de vigilia en diferentes modelos animales.
- Estudios en voluntarios sanos confirman el aumento de la vigilia y sus propiedades neurocognitivas positivas.
- Se demuestra su eficacia en pacientes con trastornos del sueño (narcolepsia, hipersomnia, somnolencia diurna por diferentes causas).

Modafinil, A Unique Wake-Promoting Drug: A Serendipitous Discovery in Search of a Mechanism of Action

F Rambert, J F Hermant, and D Schweizer, Cephalon France, Maisons-Alfort, France

Historia del desarrollo de modafinilo

- En la búsqueda de su mecanismo de acción se demuestra que modafinilo modula la actividad catecolaminérgica, serotoninérgica, histaminérgica y colinérgica.
- Sin embargo, no interactúa, a las concentraciones cerebrales en la cuales produce su acción en el hombre, con ningún componente molecular de estos sistemas de neurotransmisión-neuromodulación.

Modafinil, A Unique Wake-Promoting Drug: A Serendipitous Discovery in Search of a Mechanism of Action

F Rambert, J F Hermant, and D Schweizer, Cephalon France, Maisons-Alfort, France

Historia del desarrollo de modafinilo

- En el año 1998 se descubren los sistemas peptidérgicos que usan orexina A y B (o hipocretinas 1 y 2) en el hipotálamo.

- Y se observa que modafinilo aumenta la actividad de estos sistemas neuronales.

Modafinil, A Unique Wake-Promoting Drug: A Serendipitous Discovery in Search of a Mechanism of Action

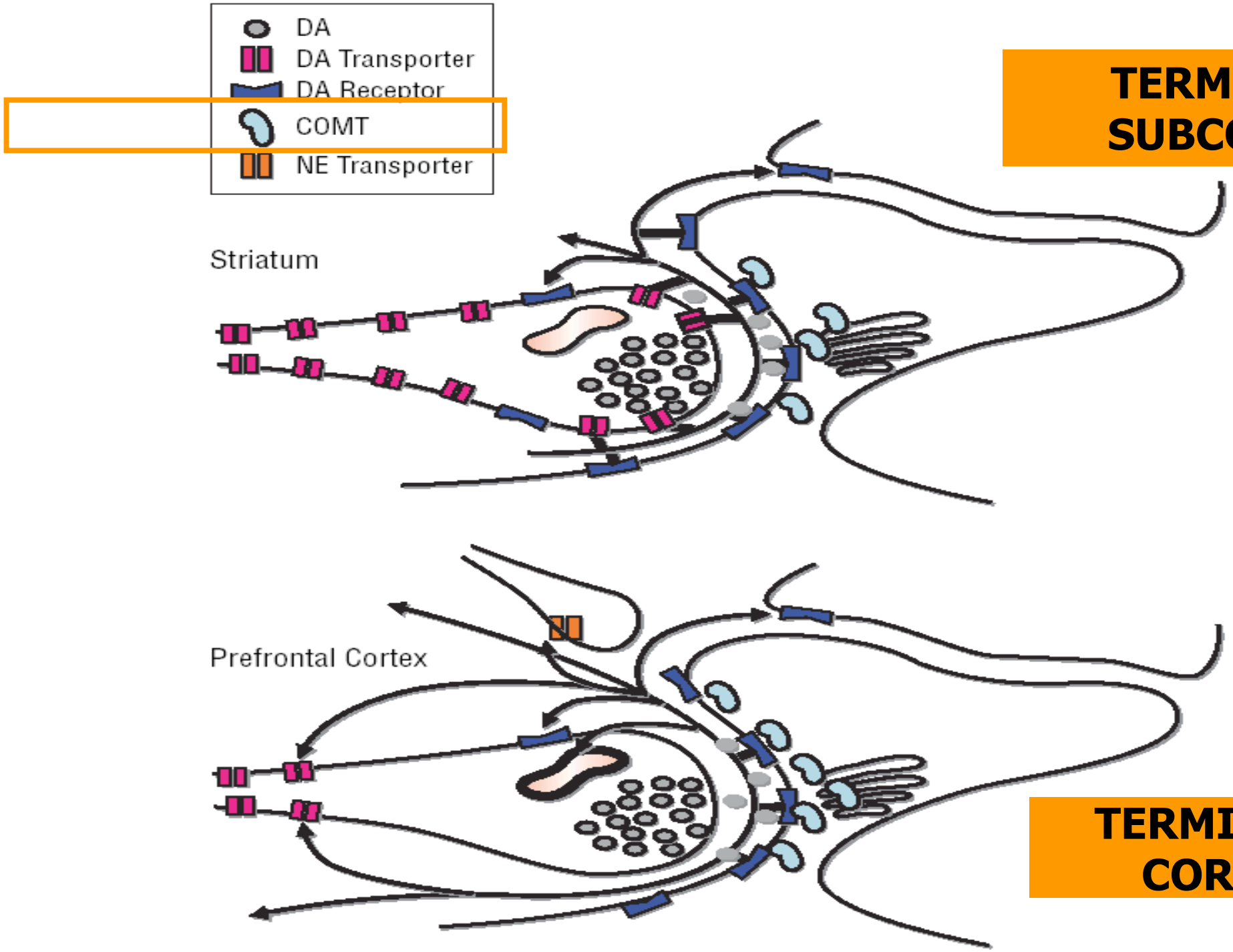
F Rambert, J F Hermant, and D Schweizer, Cephalon France, Maisons-Alfort, France

FARMACOLOGIA PRECLINICA

Mechanism of Action

- The mechanism of action of modafinil-armodafinil is the subject of controversy, although in our opinion, it is, as in the case of other stimulants, most likely related to DAT inhibition.
- Modafinil has not been shown to bind to or inhibit receptors or enzymes for most known neurotransmitters, with the exception of the DAT protein.
- In vitro, modafinil binds to the DAT and inhibits dopamine reuptake.

Principles and Practice of Sleep Medicine (Sixth Edition). Meir Kryger, Thomas Roth, William Dement. 2016 Elsevier



TERMINALES DA SUBCORTICALES

TERMINALES DA CORTICALES

Table 1 | Affinity of modafinil compared to other dopamine reuptake inhibitors.

Agent/drug	DAT-binding affinity: competitive displacement of ^{3}H-WIN 35,428 (K_i)					DAT functional assays: inhibition of ^{3}H-DA reuptake (IC_{50})		
	(10)[a]	(13)[b]	(11)[c]	(14)[d,f]	(12)[e]	(12)[e]	(14)[d]	(15)[c]
Modafinil (nM)	1930	3800	2143	4800	2300	13,000	4043	6390
Cocaine (nM)	46.2	–	163.6	187	450	230	487	–
Methylphenidate (nM)	–	–	21.2	–	–	–	–	25.4
Bupropion (nM)	383	310	319.5	–	–	–	–	1088
Nomifensine (nM)	36.9	44	–	–	–	–	–	–
β-CFT (nM)	–	–	15.4	–	–	–	–	–
GBR 12909 (nM)	–	–	53.2	12	–	–	4.3	–
Benztropine (nM)	–	–	75.3	–	–	–	–	213

β-CFT, (−)-2-β-Carbomethoxy-3-β-(4-fluorophenyl)tropane (also known as WIN 35,428); DAT, dopamine transporter; IC_{50}, concentration that inhibits 50%; K_i, inhibition constant.

MODAFINIL MECH OF ACTION

- If modafinil is a DAT inhibitor, and the blockade of DATs by modafinil is central to its wake-promoting effects, several predictions can be made and tested experimentally.
- First, one would expect tha genetical ablation of the DAT would nullify the wake- promoting effect of modafinil. In fact, the wake-promoting effect of modafinil is abolished in mice genetically deficient for DAT.
- Second, one would expect modafinil administration to elevate extracellular DA concentrations *in vivo*, and it does. Modafinil administration increased extracellular DA concentrations.
- Elevating microdialyzate DA concentration in the mouse nucleus accumbens at systemic doses of 30–300mg/kg **(2.100-21.000 mg for human current doses).**

Frontiers in Neurology | Sleep and Chronobiology , 2013|Vol 4|Article139

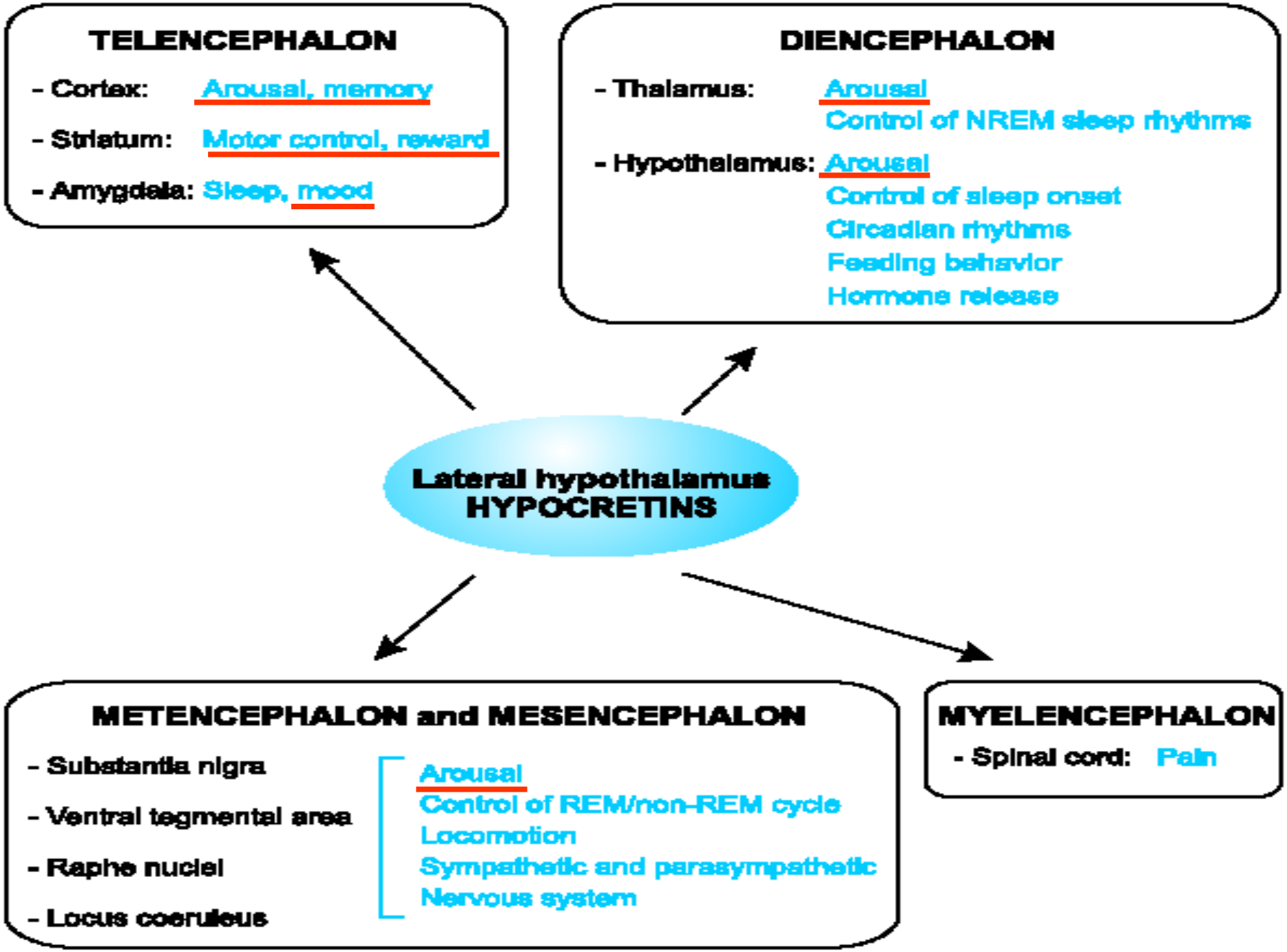
Hypocretin analogues, or substances that activate hypocretin release, may prove to be useful pharmacological treatments for narcolepsy. Indeed, modafinil, the drug that is most widely prescribed for narcolepsy, enhances the activity of hypocretin neurons.[83,84] Psychostimulants such as amphetamine increase *c-fos* immunoreactivity in hypocretin neurons.[83,84]

Mechanism of Action

- **Pharmacodynamics**
- Modafinil is a stimulant drug marketed as a 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy. The orexin neurons are activated by modafinil.
- **Mechanism of action**
- The exact mechanism of action is unclear, although *in vitro* studies have shown it to inhibit the reuptake of dopamine by binding to the dopamine reuptake pump, and lead to an increase in extracellular dopamine.
- Modafinil activates glutamatergic circuits while inhibiting GABA.
- It is possible that modafinil acts by a synergistic combination of mechanisms including direct inhibition of dopamine reuptake, indirect inhibition of noradrenalin reuptake in the VLPO and orexin activation.
- Modafinil has partial alpha 1B-adrenergic agonist effects by directly stimulating the receptors.

IUPHAR/BPS
Guide to PHARMACOLOGY

(website accessed 7 november, 2017)


TELENCEPHALON
- Cortex: Arousal, memory
- Striatum: Motor control, reward
- Amygdala: Sleep, mood
DIENCEPHALON
- Thalamus: Arousal
Control of NREM sleep rhythms
- Hypothalamus: Arousal
Control of sleep onset
Circadian rhythms
Feeding behavior
Hormone release
Lateral hypothalamus
HYPOCRETINS
METENCEPHALON and MESENCEPHALON
- Substantia nigra
- Ventral tegmental area
- Raphe nuclei
- Locus coeruleus
Arousal
Control of REM/non-REM cycle
Locomotion
Sympathetic and parasympathetic
Nervous system
MYELENCEPHALON
- Spinal cord: Pain

Thus, the medial wing of the orexin population may be driven by metabolic and homeostatic inputs, whereas the lateral wing may receive information related to reward and motivated behaviors. It will be important to determine whether there are differences in the outputs of these fields that reflect these connections and apparent roles. However, by their projections to the cerebral cortex, motor neurons and the extrapyramidal system, both wings of the orexin population may provide an impetus through which motivated states influence whether specific behaviors will be suppressed or expressed.

The hypocretinergic system is located in a key area for homeostatic control of diverse physiological functions, as revealed by anatomical studies.[3,5,40] In addition to being key regulators of the sleep–wake cycle, peptides have been shown to influence many diverse functions and consummatory behaviors. Thus, the hypocretin peptides may be important molecules to change the set point that is associated with allostasis.

FARMACOLOGIA CLINICA

Pharmacokinetics

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing.

Table I. Pharmacokinetics (mean values) of oral modafinil 200mg in six healthy men following a single dose (day 1) and once-daily administration for 7 days[3]

Parameter	Day 1	Day 7
C_{max} (μg/mL)	4.8	6.4
t_{max} (h)	2.3	2.7
AUC_{∞} (μg • h/mL)	74.0	
AUC_{τ} (μg • h/mL)		79.0
V/F (L/kg)	0.8	0.8
$t_{1/2}$ (h)		17.0
CL/F (mL/min)	46.0	44.0
CL_R (mL/min)	2.3	

USO DE MODAFINILO EN ADULTOS

TRASTORNOS DEL SUEÑO

FATIGA

DEPRESION

ADHD

ADICCIONES

SOMNOLENCIA

TRASTORNOS DEL SUEÑO
(narcolepsia, somnolencia diurna)
FATIGA

Modafinil

A Review of its Use in Excessive Sleepiness Associated With Obstructive Sleep Apnoea/Hypopnoea Syndrome and Shift Work Sleep Disorder

Gillian M. Keating and *Michael J. Raffin*

In conclusion, oral modafinil promotes wakefulness in patients with OSA/HS and SWSD. It is an effective adjunctive therapy in patients with residual excessive sleepiness associated with OSA/HS who are receiving nCPAP. In SWSD, the drug improves night-time wakefulness without disrupting daytime sleep. Modafinil is generally well tolerated in patients with OSA/HS or SWSD and has a low abuse potential. Thus, modafinil is a valuable new treatment option for use in patients with excessive sleepiness associated with OSA/HS (as an adjunct to nCPAP) or SWSD.

CNS Drugs 2005; 19 (9): 785-803

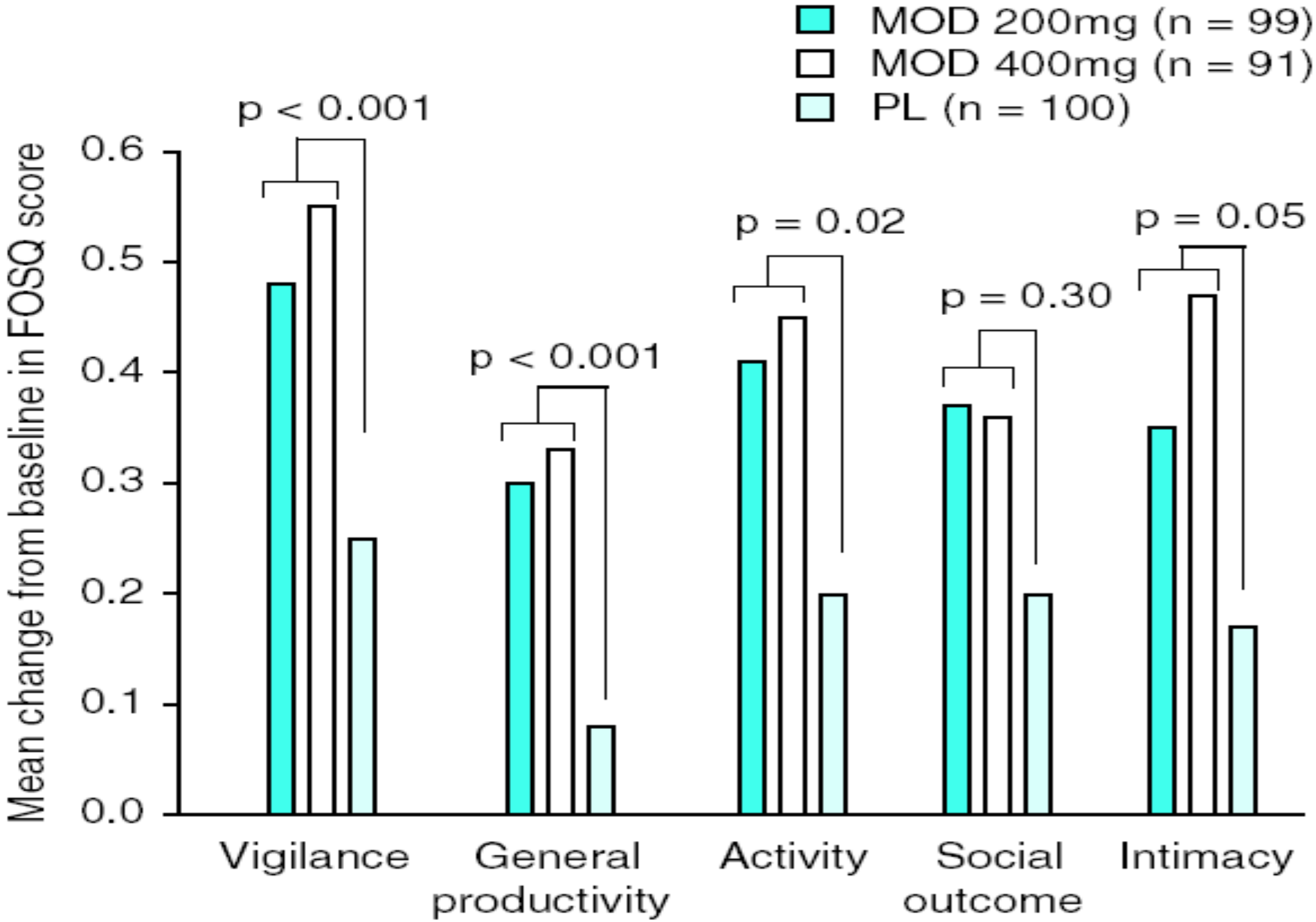

MOD 200mg (n = 99)
MOD 400mg (n = 91)
PL (n = 100)
p < 0.001
p < 0.001
p = 0.02
p = 0.30
p = 0.05
Mean change from baseline in FOSQ score
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Vigilance
General productivity
Activity
Social outcome
Intimacy

Table IV. Incidence of adverse events in patients with obstructive sleep apnoea/hypopnoea syndrome who received modafinil (MOD). Results of three randomised, double-blind studies of parallel-group[53,73] or crossover[52] design. Treatment duration was 2,[52] 4[53] or 12[73] weeks

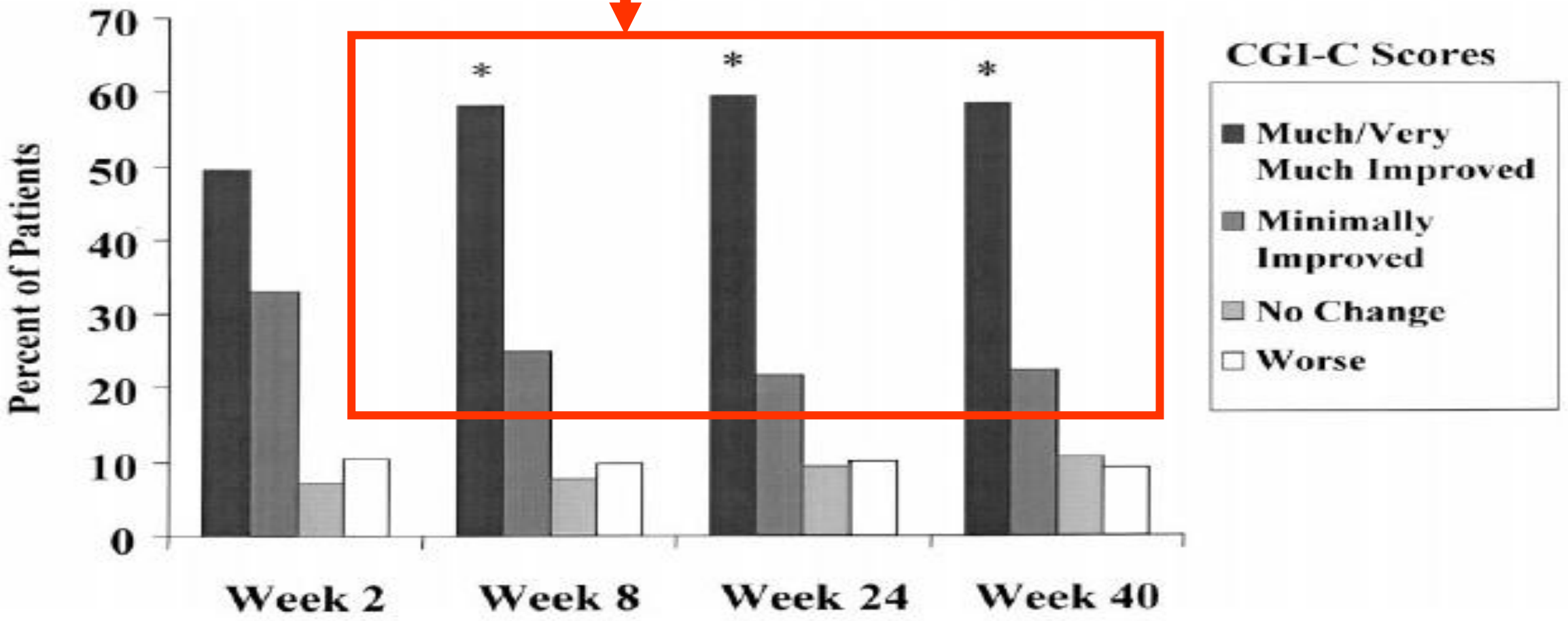
Adverse event[a] (% of patients)	Black and Hirshkowitz[73]			Pack et al.[53]		Kingshott et al.[52]	
	MOD 200mg od (n = 103)	MOD 400mg od (n = 99)	PL (n = 103)	MOD 400mg od (n = 77)	PL (n = 80)	MOD 400mg od (n = 31)[b]	PL (n = 31)[b]
Headache	23	26	13*	23	11*	16	16
Infection	19	10	22				
Nausea	10	10	2**	6	4	16	0
Anxiety	6	8	2	6	1		
Accidental injury	8	5	8				
Diarrhoea	8	5	8				
Hypertension	4	8	2				
Nervousness	6	6	2	12	3*		
Dizziness	6	5	3	6	3		
Insomnia	7	4	1	5	1		
Rhinitis	6	5	8	8	3		
Dry mouth						10	0

Efficacy and safety of modafinil for improving daytime wakefulness in patients treated previously with psychostimulants

Jonathan R.L. Schwartz[a,*], Neil T. Feldman[b], June M. Fry[c], John Harsh[d]

Sleep Medicine 4 (2003) 43–49

Más del 80% responden y mantienen el efecto terapéutico en el tiempo !!!!



Incidence of treatment-related adverse events reported by ≥2.5% of patients[a]

Adverse event (AE)	All patients ($N = 478$)[b]		Dose of modafinil when the AE occurred[c]					
			200 mg ($N = 147$)		300 mg ($N = 163$)		400 mg ($N = 388$)	
	N	%	*N*	%	*N*	%	*N*	%
Headache	61	12.8	18	12.2	12	7.4	40	10.3
Nervousness	37	7.7	14	9.5	18	11.0	16	4.1
Nausea	24	5.0	7	4.8	6	3.7	13	3.4
Anxiety	21	4.4	10	6.8	7	4.3	9	2.3
Dry mouth	15	3.1	6	4.1	6	3.7	10	2.6
Somnolence	14	2.9	4	2.7	5	3.1	11	2.8
Cataplexy	13	2.7	5	3.4	1	0.6	10	2.6
Insomnia	13	2.7	6	4.1	2	1.2	6	1.5
Diarrhea	12	2.5	2	1.4	5	3.1	7	1.8

ORIGINAL RESEARCH ARTICLE

CNS Drugs 2007; 21 (5): 407-416
1172-7047/07/0005-0407/$44.95/0

Effect of Adjunctive Modafinil on Wakefulness and Quality of Life in Patients with Excessive Sleepiness-Associated Obstructive Sleep Apnoea/Hypopnoea Syndrome

A 12-Month, Open-Label Extension Study

Max Hirshkowitz[1] and *Jed Black*[2]

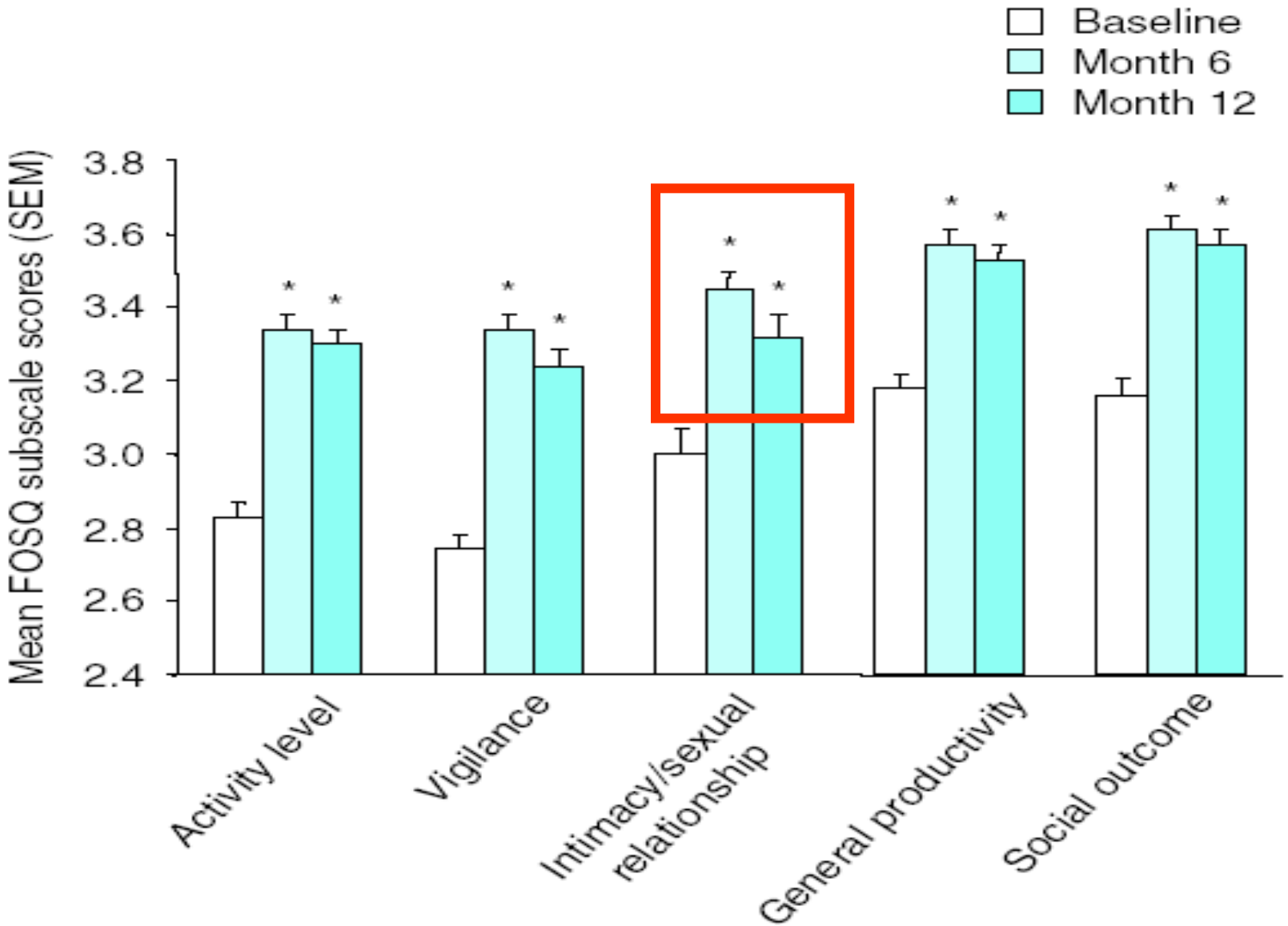


Fig. 2. Mean (SEM) increase (improvement) in the Functional Outcomes of Sleep Questionnaire (FOSQ) subscale scores at baseline and months 6 and 12 in patients treated with modafinil 200–400mg once daily. * $p < 0.0001$ vs baseline.

Table II. Adverse events occurring in ≥5% of patients

Adverse event	No. of patients (%) [n = 266]
Infection	30 (11.3)
Headache	25 (9.4)
Nervousness	24 (9.0)
Accidental injury	21 (7.9)
Pain	20 (7.5)
Sinusitis	19 (7.1)
Rhinitis	18 (6.8)
Anxiety	15 (5.6)
Depression	15 (5.6)
Dizziness	14 (5.3)
Insomnia	14 (5.3)

Conclusion

In this 12-month, open-label extension, the efficacy of adjunctive modafinil on wakefulness and functional status was maintained and quality of life improved during long-term use in patients with OSA/HS experiencing residual sleepiness who were receiving nCPAP therapy. Long-term use of modafinil was well tolerated, with a safety profile equivalent to that observed during shorter-term studies in patients receiving nCPAP therapy.

- **Modafinil is an enzymatic inductor of P450 cytochrome activity.**
- **Hence, it increases the metabolism of oral contra-ceptives.**
- **Consequently an oral contraceptive containing at least 50 mg of ethinylestradiol must be prescribed if modafinil is used.**

USO EN PERSONAS SANAS, ASINTOMÁTICAS, COMO POTENCIADOR COGNITIVO??????????

Towards responsible use of cognitive-enhancing drugs by the healthy*

Henry Greely, Barbara Sahakian, John Harris, Ronald C. Kessler, Michael Gazzaniga, Philip Campbell, and Martha J. Farah

"We should welcome new methods of improving our brain function."

As for an appeal to the "natural", the lives of almost all living humans are deeply unnatural; our homes, our clothes and our food — to say nothing of the medical care we enjoy — bear little relation to our species' "natural" state. Given the many cognitive-enhancing tools we accept already, from writing to laptop computers, why draw the line here and say, thus far but no further?

Based on our considerations, we call for a presumption that mentally competent adults should be able to engage in cognitive enhancement using drugs.

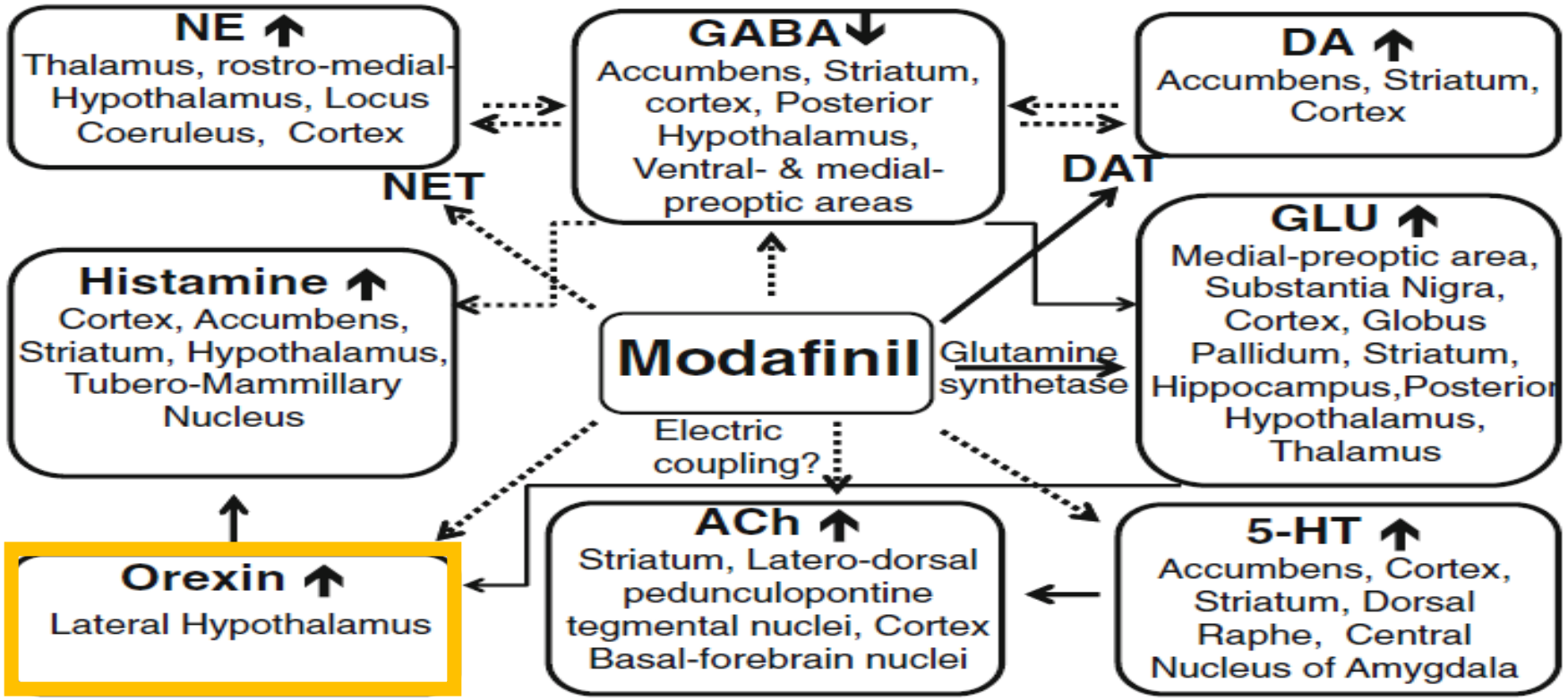
S.A. Hays et al. (eds.), *Nanotechnology, the Brain, and the Future*,
Springer Science+Business Media Dordrecht 2013

Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review

- Modafinil is an FDA-approved eugeroic that directly increases cortical catecholamine levels, indirectly up regulates cerebral serotonin, glutamate, orexin, and histamine levels, and indirectly decreases cerebral gamma-amino-butrytic acid levels.
- In addition to its approved use treating excessive somnolence, modafinil is thought to be used widely off-prescription for cognitive enhancement.
- **Modafinil appears to consistently engender enhancement of attention, executive functions, and learning.**
- **Importantly, we did not observe any preponderances for side effects or mood changes.**

European Neuropsychopharmacology (2015) 25, 1865–1881

The neurobiology of modafinil as an enhancer of cognitive performance



Psychopharmacology (2013) 229:415–434

Enhancing Effect in Healthy Non-sleep-Deprived Individuals

- Modafinil enhanced cognitive function with very low abuse liability, it has already been introduced in various professions requiring prolonged wakefulness, such as workers in the forced army and health care. Indeed, approximately 90% of Modafinil users are healthy individuals with no sleep disorders aiming to enhance their attentional capacity.

- In sum, in healthy non-sleep-deprived individuals, Modafinil appears to increase specifically attention and cognitive control and this effect seems to be more pronounced in challenging task conditions and in low performing individuals.

L.S. Colzato, Theory-Driven Approaches to Cognitive Enhancement, Springer 2017

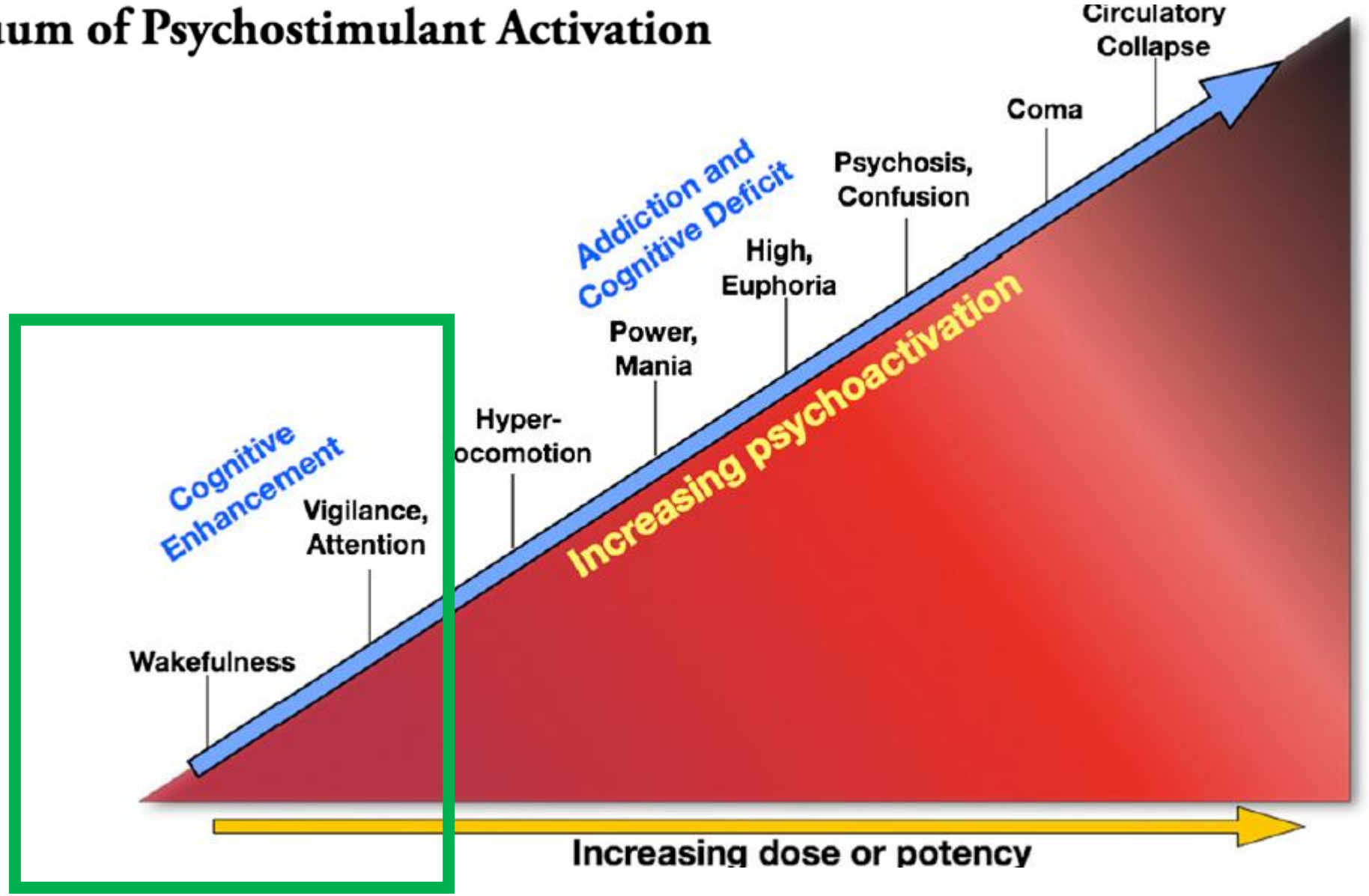
Enhancing Effect in Healthy Sleep-Deprived Individuals

- **In sum, administration of Modafinil shows promising potential to maintain cognitive function in sleep-deprived individuals: however, caution may be needed given a possible overconfidence effect.**

Cost 100 mg (30 pills): $923.99.

L.S. Colzato, Theory-Driven Approaches to Cognitive Enhancement, Springer 2017

Continuum of Psychostimulant Activation



Increasing cognitive activation as stimulant dose increases initially produces increased wakefulness and cognitive enhancement. These are the desired therapeutic effects. As dose increases, a sense of power and euphoria can ensue; these are the effects addicts seek and are accompanied by cognitive deficits. Higher doses can result in overdose, psychosis, coma, and eventual circulatory collapse.

Pharmacol Rev 66:193–221, 2014

AGENDA DE LA PRESENTACIÓN

INTRODUCCIÓN:

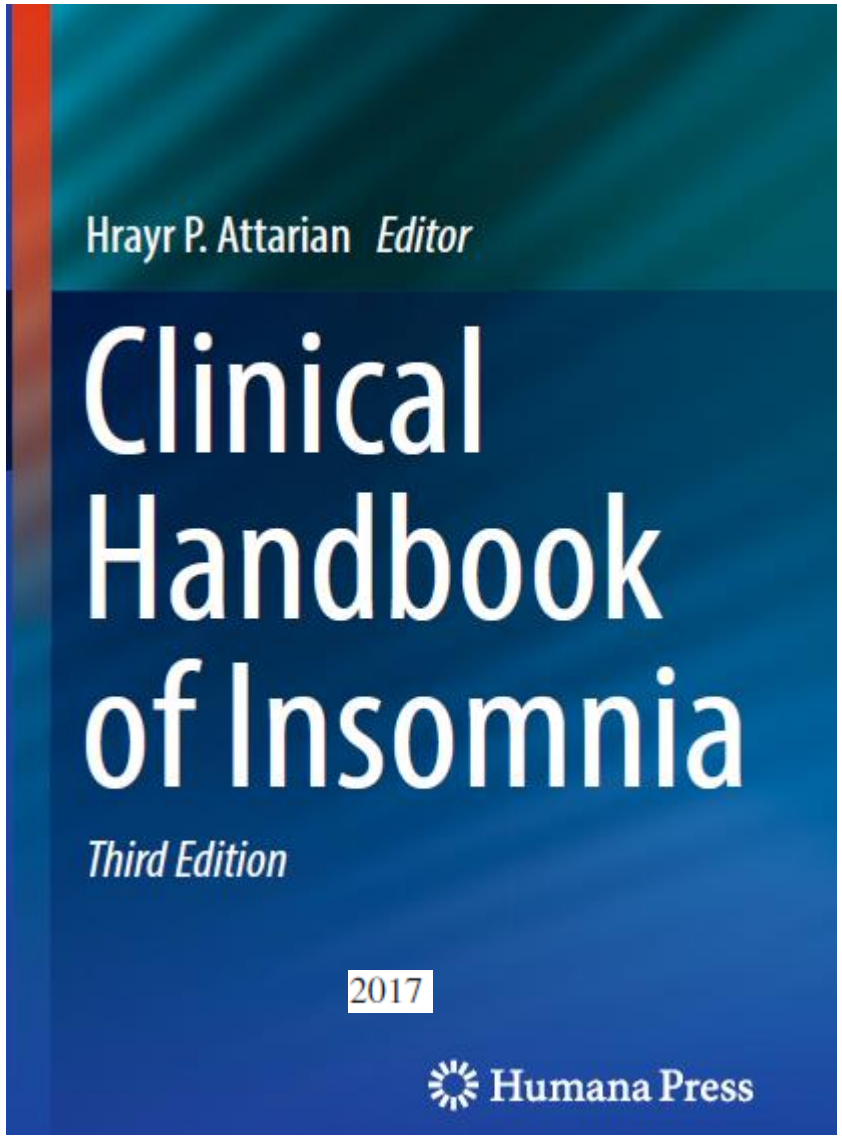
HIPNÓTICOS: bioquímica y farmacología

ACTIVADORES: bioquímica y farmacología

USOS EN LA PRÁCTICA CLÍNICA:

DESARROLLOS FUTUROS:

CONCLUSIONES:


Hrayr P. Attarian Editor
Clinical Handbook of Insomnia
Third Edition
2017
Humana Press

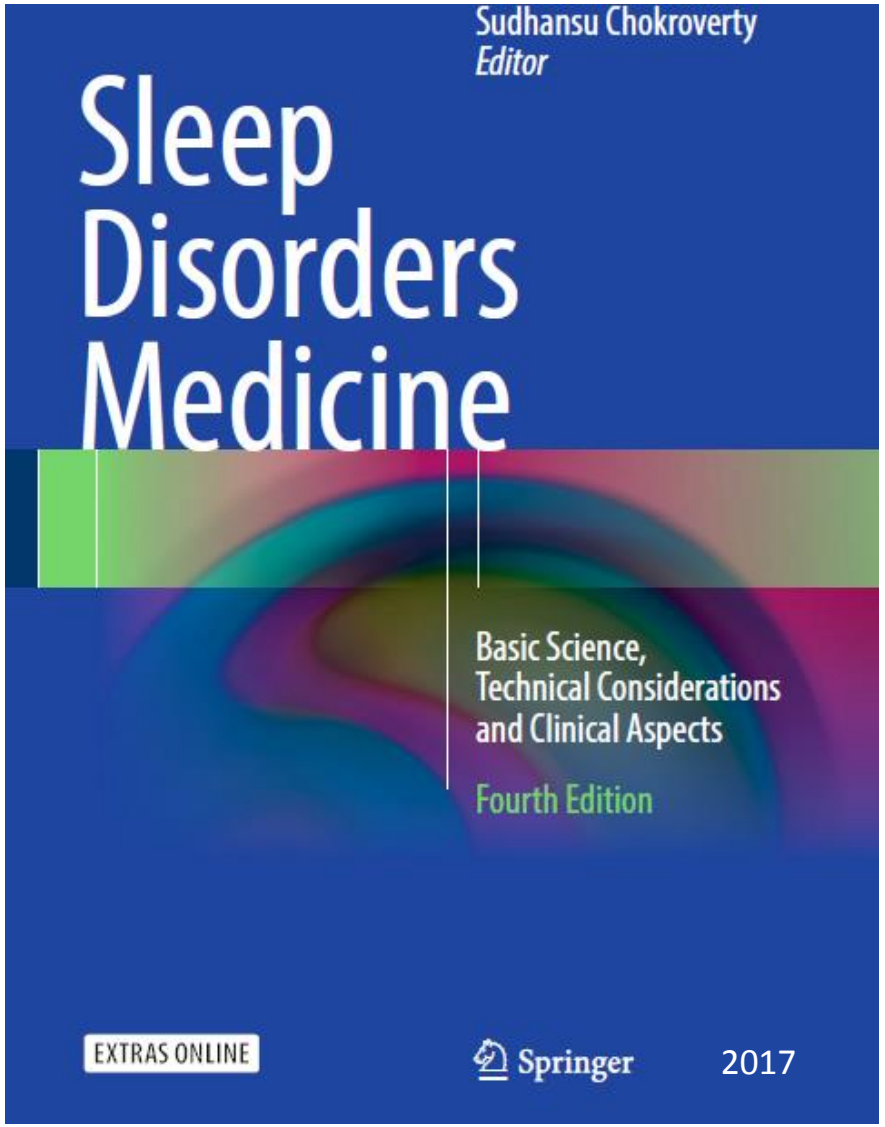

Sudhansu Chokroverty Editor
Sleep Disorders Medicine
Basic Science, Technical Considerations and Clinical Aspects
Fourth Edition
EXTRAS ONLINE
Springer
2017

Table 7.1 Pharmacology of drugs with FDA indication for insomnia

Generic name	Trade name	FDA indication	Receptor-binding profile					t_{max} (h)	$t_{1/2}$ (h)	Metabolism[a]	Dose range for insomnia (mg)
			$GABA_A$ specificity	MT_1–MT_2	Anti-OX_1–OX_2	Anti-H_1	Anti-mACh				
Benzodiazepine receptor agonists											
Estazolam	Prosom	Insomnia	Nonspecific					1.5–2	10–24	3A4	1–2
Flurazepam	Dalmane	Insomnia	Nonspecific					0.5–1.5	48–120[b]	3A4	15–30
Quazepam	Doral	Insomnia	Nonspecific					2	39–73[b]	2C19, 3A4	7.5–15
Temazepam	Restoril	Insomnia	Nonspecific					1–3	8–20	3A4, UGT	15–30
Triazolam	Halcion	Insomnia	Nonspecific					1–3	2–6	3A4, 3A5	0.125–0.25
Eszopiclone	Lunesta	Insomnia	Nonspecific					1.3–1.6	6–7	3A4, 2E1	1–3
Zaleplon	Sonata	Insomnia	$\alpha_1 > \alpha_{2,3,5}$					1.1	1	AO, 3A4	5–20
Zolpidem	Ambien	Insomnia	$\alpha_1 \gg \alpha_{2,3,5}$						1.5–2.4	3A4, 2C9	5–10
Zolpidem modified release	Ambien CR	Insomnia	$\alpha_1 \gg \alpha_{2,3}$ no α_5					1.7–2.5	1.6–4.5	3A4, 2C9	6.25–12.5
Zolpidem sublingual	Intermezzo	Insomnia	$\alpha_1 \gg \alpha_{2,3}$ no α_5					0.3–1.3	1.5–2.4	3A4, 2C9	1.75–3.5
Zolpidem sublingual	Edluar	Insomnia	$\alpha_1 \gg \alpha_{2,3}$ no α_5					0.5–3	2.6–2.8	3A4, 2C9	5–10
Zolpidem oral spray	Zolpimist	Insomnia	$\alpha_1 \gg \alpha_{2,3}$ no α_5					0.9	2.7–2.8	3A4, 2C9	5–10
Melatonin receptor agonist											
Ramelteon	Rozerem	Insomnia		+++				0.7–0.9	0.8–2	1A2, 2PC, 3A4	8

Generic name	Trade name	FDA indication	Receptor-binding profile					t_{max} (h)	$t_{1/2}$ (h)	Metabolism[a]	Dose range for insomnia (mg)
			$GABA_A$ specificity	MT_1–MT_2	Anti-OX_1–OX_2	Anti-H_1	Anti-mACh				
Orexin receptor antagonist											
Suvorexant	Belsomra	Insomnia			+++			0.5–6	12	3A, 2C19	5–20
Histamine receptor antagonists											
Doxepin	Silenor	Insomnia				+++		3.5	15.3–31[b]	2C10, 2D6, 1A2, 2C9	3–6
Diphenhydramine	Benadryl	Allergy, sleep aid				+++	+++	2–3	5–11	2D6, 1A2, 2CP, 2C19	25–50
Doxylamine	Unisom	Allergy, sleep aid				+++	+++	1.5–2.5	10–12	2D6, 1A2, 2CP	25

$GABA_A$ γ[gamma]-aminobutyric acid type A receptor agonist, *MT_1–MT_2* melatonin 1 a| 2 receptor agonist, anti-*OX_1–OX_2* orexin 1 and 2 receptor antagonist, *anti-H_1* histamine 1 receptor antagonist, *anti-mACh* muscarinic anticholinergic receptontagonist, t_{max} time to peak concentration, $t_{1/2}$ elimination half-life, *AO* aldehyde oxidase

[a]All entries beginning with numbers refer to specific CYP enzymes in the cytochrome 450 system

Table 7.2 Pharmacology of drugs used "off-label" for insomnia

Generic name	Trade name	FDA indication	Receptor-binding profile							t_{max} (h)	$t_{1/2}$ (h)	Metabolism[a]	Dose range for insomnia (mg)
			$GABA_A$ specificity	MT_1–MT_2	Anti-H_1	Anti-$5HT_2$	Anti-alpha$_1$	Anti-dopamine	Anti-mACh				
Benzodiazepines													
Alprazolam	Xanax	Anxiety	Nonspecific							1–3	12–14	3A4, 3A55, 2C19	0.25–1.0
Alprazolam extended release	Xanax XR	Anxiety	Nonspecific							1–2	6.3–27	3A4, 3A55, 2C19	0.5–3
Chlordiazepoxide	Librium	Anxiety, alcohol withdrawal	Nonspecific							0.5–4	5–100	2B, 2C19, 3A4	5–10
Clonazepam	Klonopin	Anxiety, seizures	Nonspecific							1–2	35–40	2B, 3A4	0.25–2.0
Diazepam	Valium	Anxiety, muscle spasm, seizures	Nonspecific							0.5–2	20–50	2B, C19, CYP3A4	2–10
Lorazepam	Ativan	Anxiety	Nonspecific							1–3	12–15	UGT	0.25–2
Antidepressants													
Amitriptyline	Elavil	Depression			++	+	+++		+++	2–8	5–45	2D6, 2C19, 1A2, 3A4	25–150
Doxepin	Sinequan	Depression, anxiety			+++	+	+++		++	2–8	10–30	2D6, 2C19, 1A2, 3A4	10–150
Trimipramine	Surmontil	Depression			+++	+	+++		++	2–8	15–40	2D6, 2C19, 1A2, 3A4	25–150
Mirtazapine	Remeron	Depression			+++	+++	++			0.25–2	20–40	2D6, 3A4	7.5–30

Benzodiazepine half-lives and dose equivalence

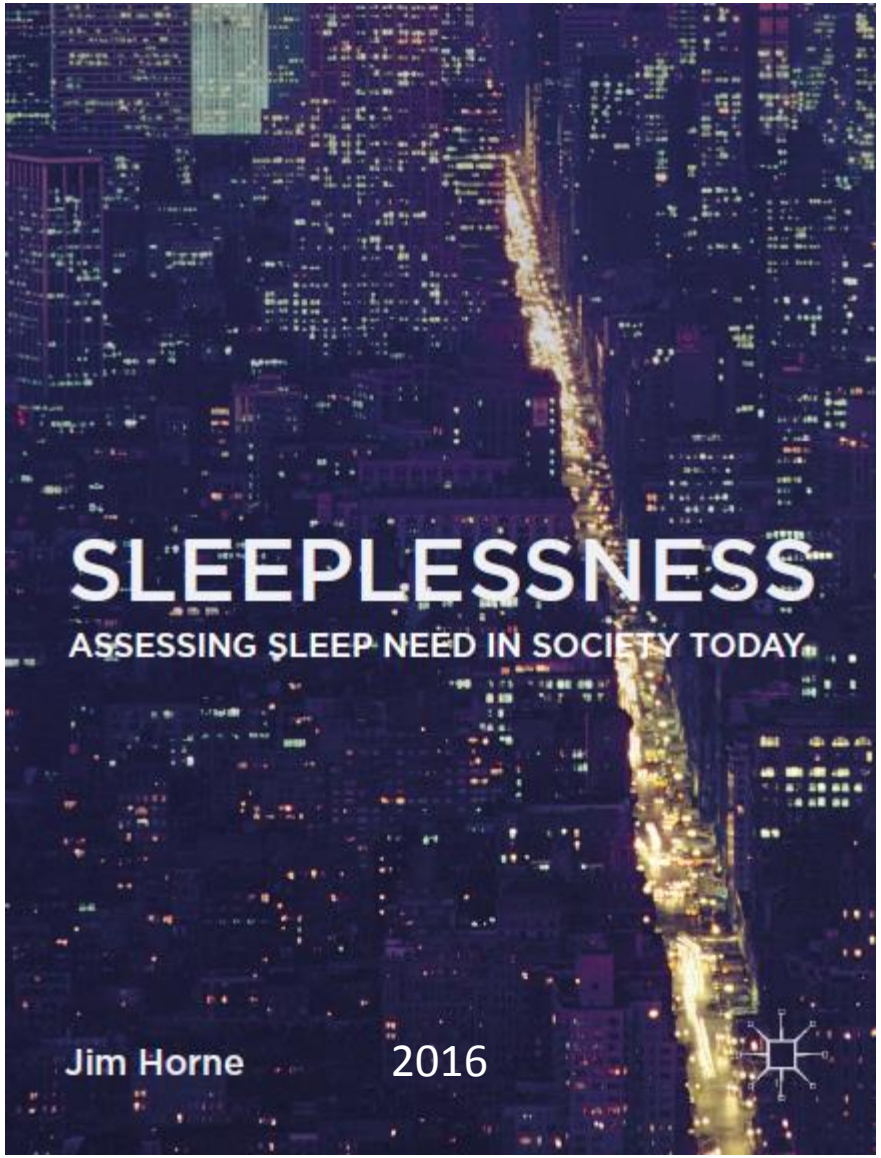
Benzodiazepine with examples of common brand names	Half-life	Dose equivalent to diazepam 5 mg
Alprazolam:	Short–intermediate	0.5
Bromazepam:	Short–intermediate	3
Clobazam:	Intermediate	10
Clonazepam:	Intermediate	0.25
Diazepam:	Long	5
Flunitrazepam:	Intermediate	0.5
Lorazepam:	Short–intermediate	1
Nitrazepam:	Intermediate	5
Oxazepam:	Short	15
Temazepam:	Short	10

Table 7.2 (continued)

Generic name	Trade name	FDA indication	Receptor-binding profile							t_{max} (h)	$t_{1/2}$ (h)	Metabolism[a]	Dose range for insomnia (mg)
			$GABA_A$ specificity	MT_1–MT_2	Anti-H_1	Anti-$5HT_2$	Anti-alpha$_1$	Anti-dopamine	Anti-mACh				
Trazodone	Desyrel	Depression			+	+++	+++			1–2	7–15	3A4, 2D6, 1A2	25–150
Antipsychotics													
Olanzapine	Zyprexa	Schizophrenia bipolar disorder			+++	+++	++	++	+++	4–6	30	1A2	2.5–20
Quetiapine	Seroquel	Schizophrenia			++	+	+++	+		1–2	7	2D6, 3A4	25–250
Anticonvulsants													
Gabapentin	Neurontin	Seizures, neuropathic pain								2–3.5	5–7		300
Pregabalin	Lyrica	Seizures, neuropathic pain								1.5	6.3		100
Tiagabine	Gabitril	Seizures	GAT_1 inhibition							0.75	2–9	3A	2–12
Other													
Melatonin	Melatonin	None		+++							1–3	1A2, 2C19	0.1–75
Prazosin	Minipress	Hypertension					+++			3	2–3		2–20

$GABA_A$ γ[gamma]-aminobutyric acid type A receptor agonist, *MT_1–MT_2* melatonin 1 and 2 receptor agonist, *anti-H1* histamine 1 receptor antagonist, *anti-$5HT_2$* serotonin type 2 receptor antagonist, *anti-dopamine* dopamine receptor antagonist, *anti-mACh* muscarinic anticholinergic receptor antagonist, t_{max} time to peak concentration, $t_{1/2}$ elimination half-life, *UG* uridine 5′-diphospho-glucuronosyltransferase, *AO* aldehyde oxidase, *GAT_1* GABA transporter 1

[a]All entries beginning with numbers refer to specific CYP enzymes in the cytochrome P-450 system


SLEEPLESSNESS
ASSESSING SLEEP NEED IN SOCIETY TODAY
Jim Horne
2016

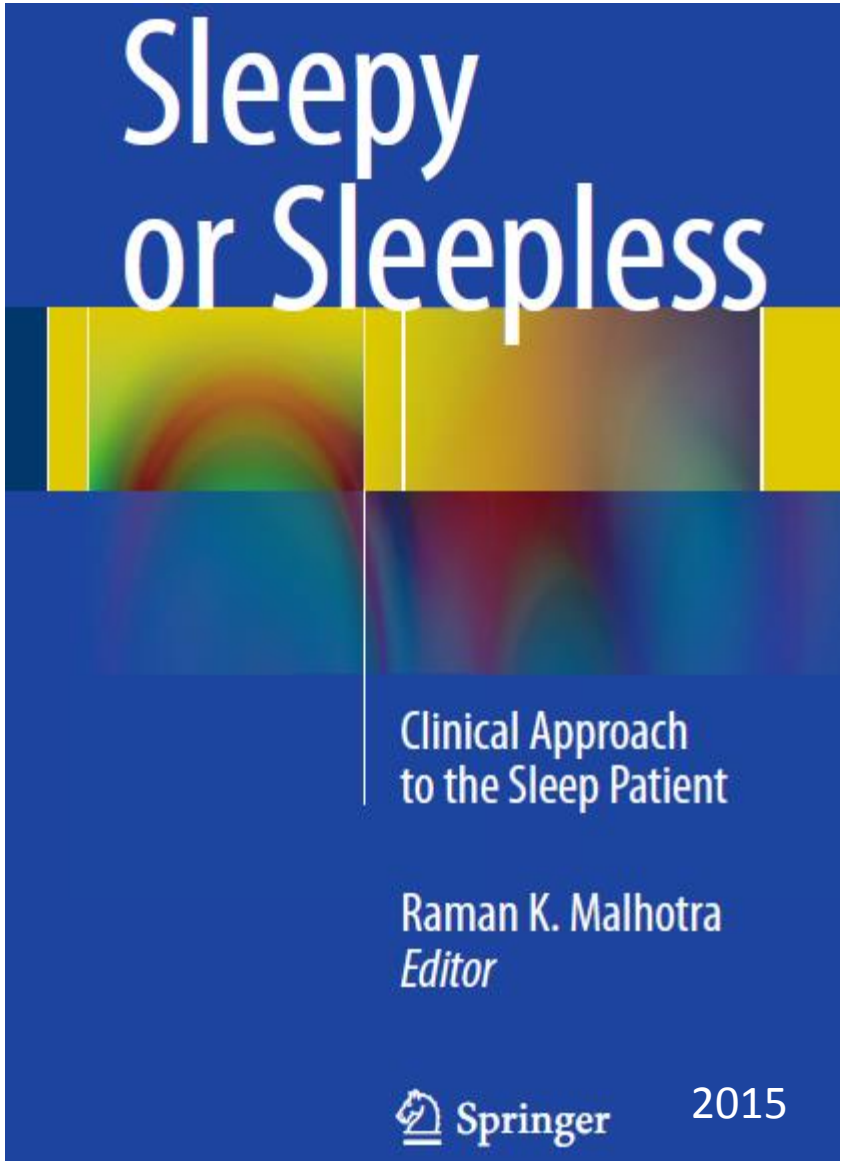
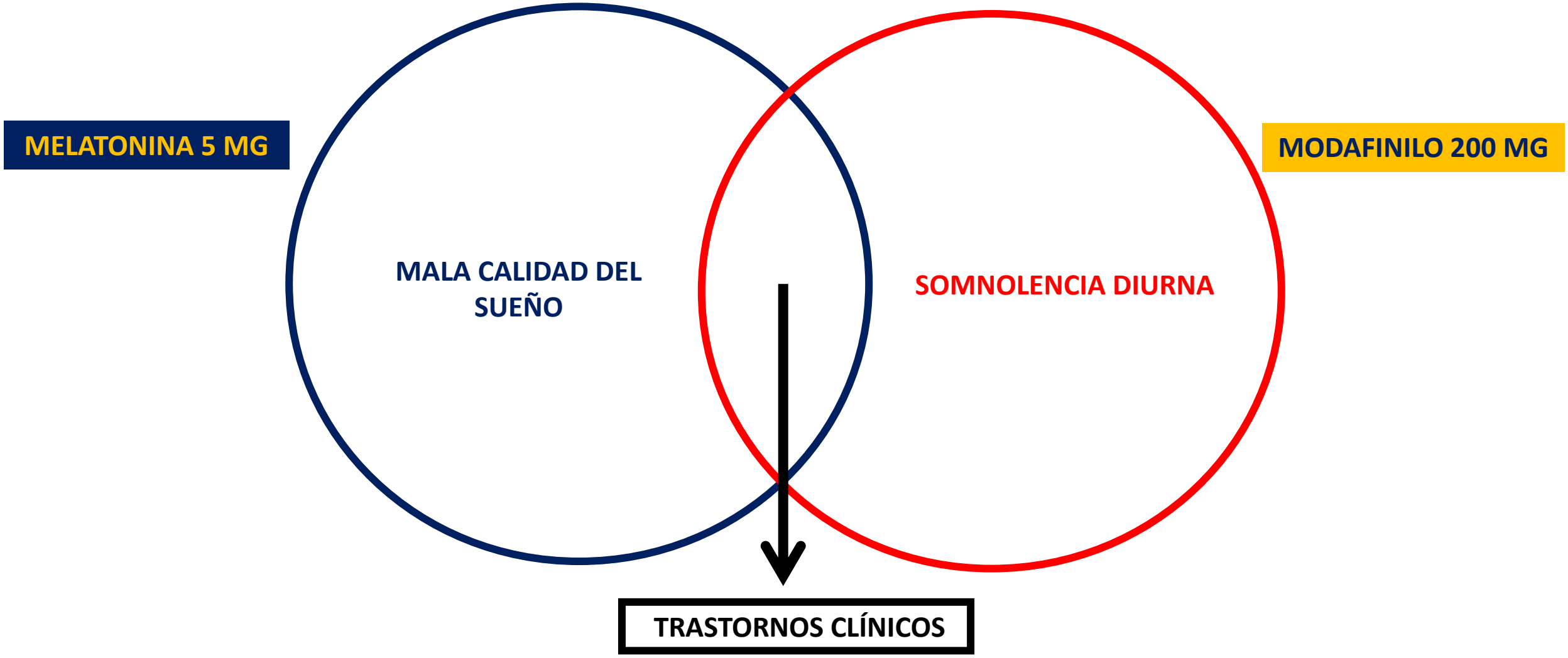

Sleepy or Sleepless
Clinical Approach to the Sleep Patient
Raman K. Malhotra
Editor
Springer
2015

Table 43-1 Commonly Used Pharmacologic Compounds for Excessive Daytime Sleepiness

Stimulant Compound	Usual Daily Doses*	Half-Life (hr)	Side Effects, Notes
Amphetamines and Amphetamine-like CNS Stimulants			
D-Amphetamine sulfate (schedule II)	5–60 mg (15, 100 mg)	16–30	Irritability, mood changes, headaches, palpitations, tremors, excessive sweating, insomnia
Methamphetamine HCl† (schedule II)	5–60 mg (15, 80 mg)	9–15	Same as D-amphetamine; may have a greater central over peripheral effects than D-amphetamine‡
Methylphenidate HCl (schedule II)	10–60 mg (30, 100 mg)	~3	Same as amphetamines; better therapeutic index than D-amphetamine with less reduction of appetite or increase in blood pressure; short duration of action
Pemoline (schedule IV)	20–115 mg (37.5, 150 mg)	11–13	Less sympathomimetic effect, milder stimulant, slower onset of action; occasionally produces liver toxicity; had been withdrawn from the U.S. market
Dopamine and Norepinephrine Uptake Inhibitor			
Mazindol (schedule IV)	2–6 mg (NA)	10–13	Weaker CNS stimulant effects; anorexia, dry mouth, irritability, headaches, gastrointestinal symptoms; reported to have less potential for abuse
Other Agents for Treatment of EDS			
Modafinil§ (schedule IV)	100–400 mg (NA)	9–14	No peripheral sympathomimetic action; headaches, nausea; reported to have less potential for abuse
Armodafinil (schedule IV)	100–300 mg (NA)	10–15	Similar to those of modafinil
MAO Inhibitors with Alerting Effect			
Selegiline	5–40 mg (NA)	2	Low abuse potential; partial (10%-40%) interconversion to amphetamine
Xanthine Derivative			
Caffeine¶	100–200 mg (NA)	3–7	Weak stimulant effect; 100 mg of caffeine roughly equivalent to one cup of coffee; palpitations, hypertension

EN LA PRÁCTICA CLÍNICA DIARIA



AGENDA DE LA PRESENTACIÓN

INTRODUCCIÓN:

HIPNÓTICOS: bioquímica y farmacología

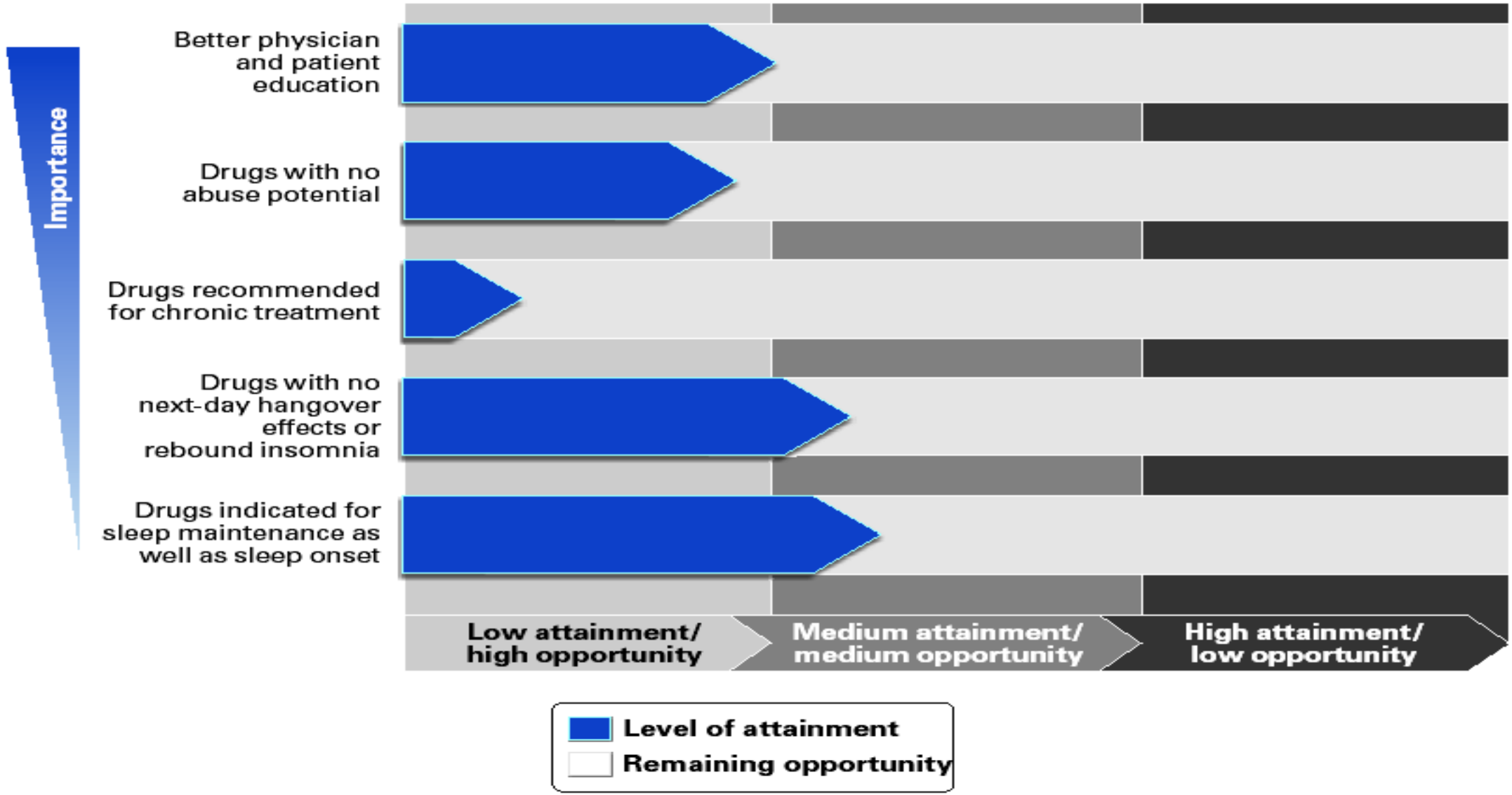
ACTIVADORES: bioquímica y farmacología

USOS EN LA PRÁCTICA CLÍNICA:

DESARROLLOS FUTUROS:

CONCLUSIONES:

Unmet Needs: Attainment and Remaining Opportunity in Insomnia



The Perfect Sleeping Pill?

- A good “sleeping pill” should reduce the time to enter NREM sleep (reduce “sleep latency”) and allow only limited awakenings, and most researchers assume that sleep-promoting medication should aim to reproduce the sleep EEG profile and architecture found in natural sleep.
- Other practical considerations are that a sleeping pill compound should occupy its receptor sites quickly and have a short half-life so that it on the one hand increases sleep time but on the other does not give “hangover effects” such as daytime sleepiness or reduced daytime alertness.
- The ideal sleep-promoting compound should also have low addictive potential and not cause rebound insomnia when the drug is withdrawn.
- **Zolpidem meets most of these requirements well**.

Handbook of Experimental Pharmacology
Springer 2017

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DESARROLLOS FUTUROS:

CONCLUSIONES:

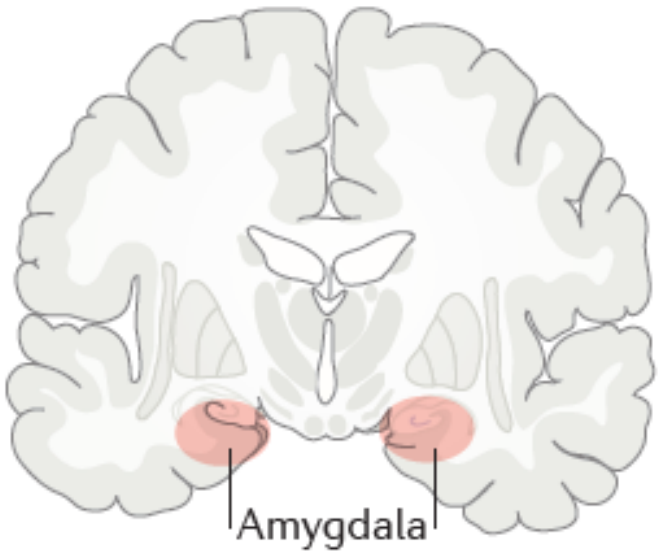
Sleep deprivation

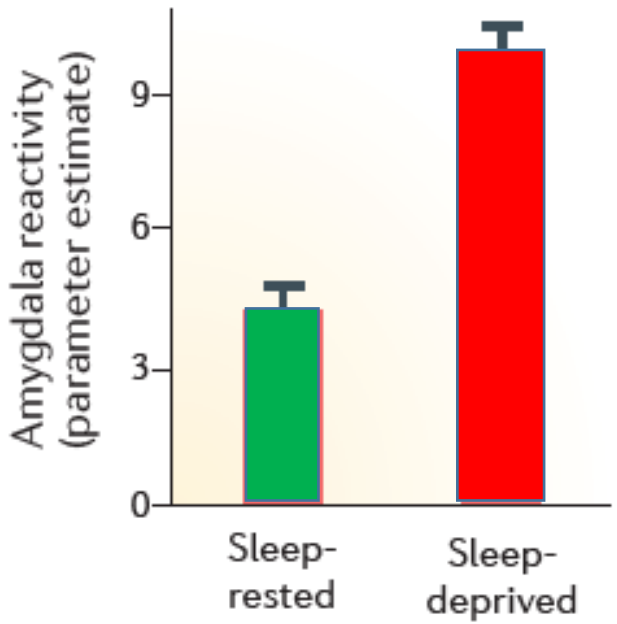
- Sleep deprivation (SD) has become a relevant health problem in modern societies.
- We can be sleep deprived due to **lifestyle habits** or due to sleep disorders, such as insomnia, obstructive sleep apnea (OSA) and neurological disorders.
- One of the common element of sleep disorders is the condition of chronic SD, which has complex biological consequences.
- SD is capable of inducing different biological effects, such as neural autonomic control changes, increased oxidative stress, altered inflammatory and coagulatory responses and accelerated atherosclerosis.
- All these mechanisms links SD and cardiovascular and metabolic disorders.
- Epidemiological studies have shown that short sleep duration is associated with increased incidence of cardiovascular diseases, such as coronary artery disease, hypertension, arrhythmias, diabetes and obesity, after adjustment for socioeconomic and demographic risk factors and comorbidities.

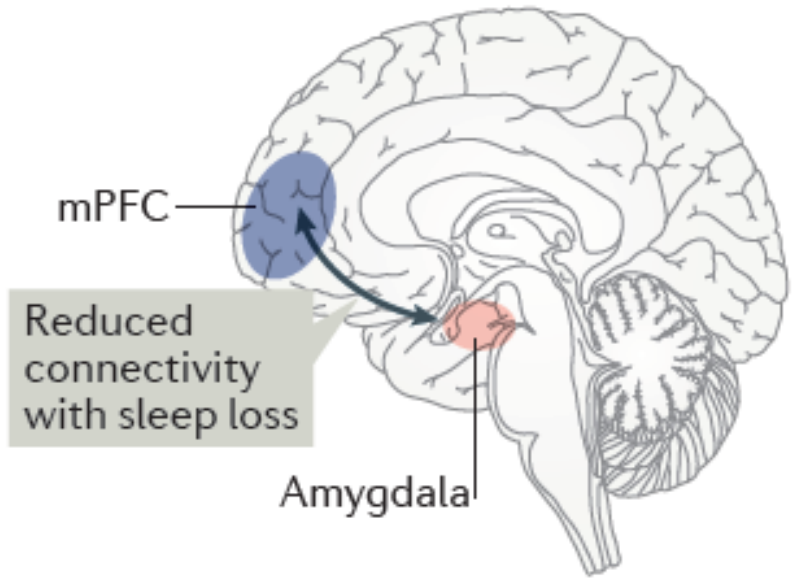
E. Tobaldini et al. / Neuroscience and Biobehavioral Reviews 74 (2017) 321–329

The sleep-deprived human brain

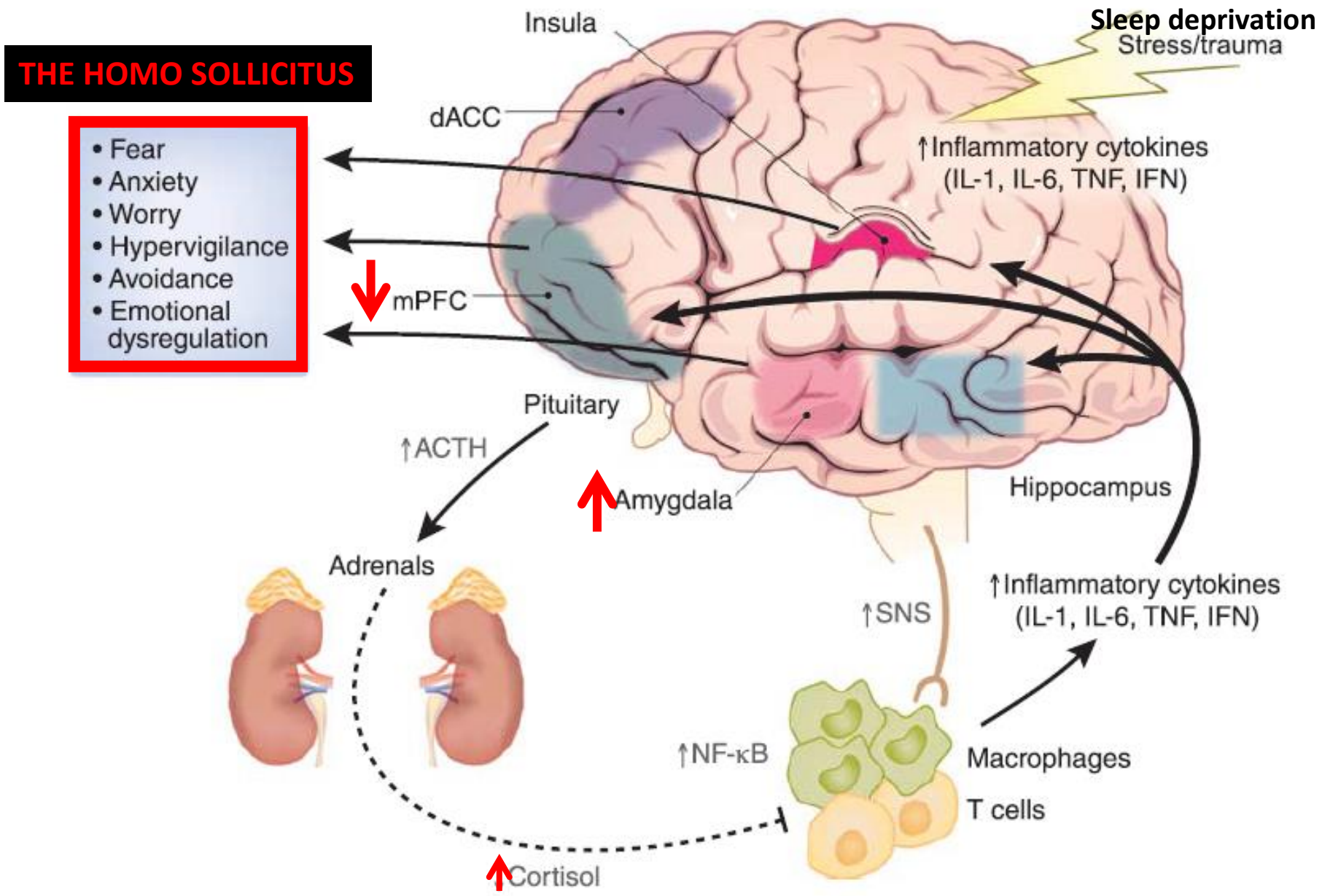
Adam J. Krause[1], Eti Ben Simon[1], Bryce A. Mander[1], Stephanie M. Greer[2], Jared M. Saletin[1], Andrea N. Goldstein-Piekarski[2] and Matthew P. Walker[1,2]







(THE HOMO SOLLICITUS, A. LISTA, 2018)



Neuropsychopharmacology (2017) 42, 254–270

GRACIAS!!!!

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Noviembre 2017

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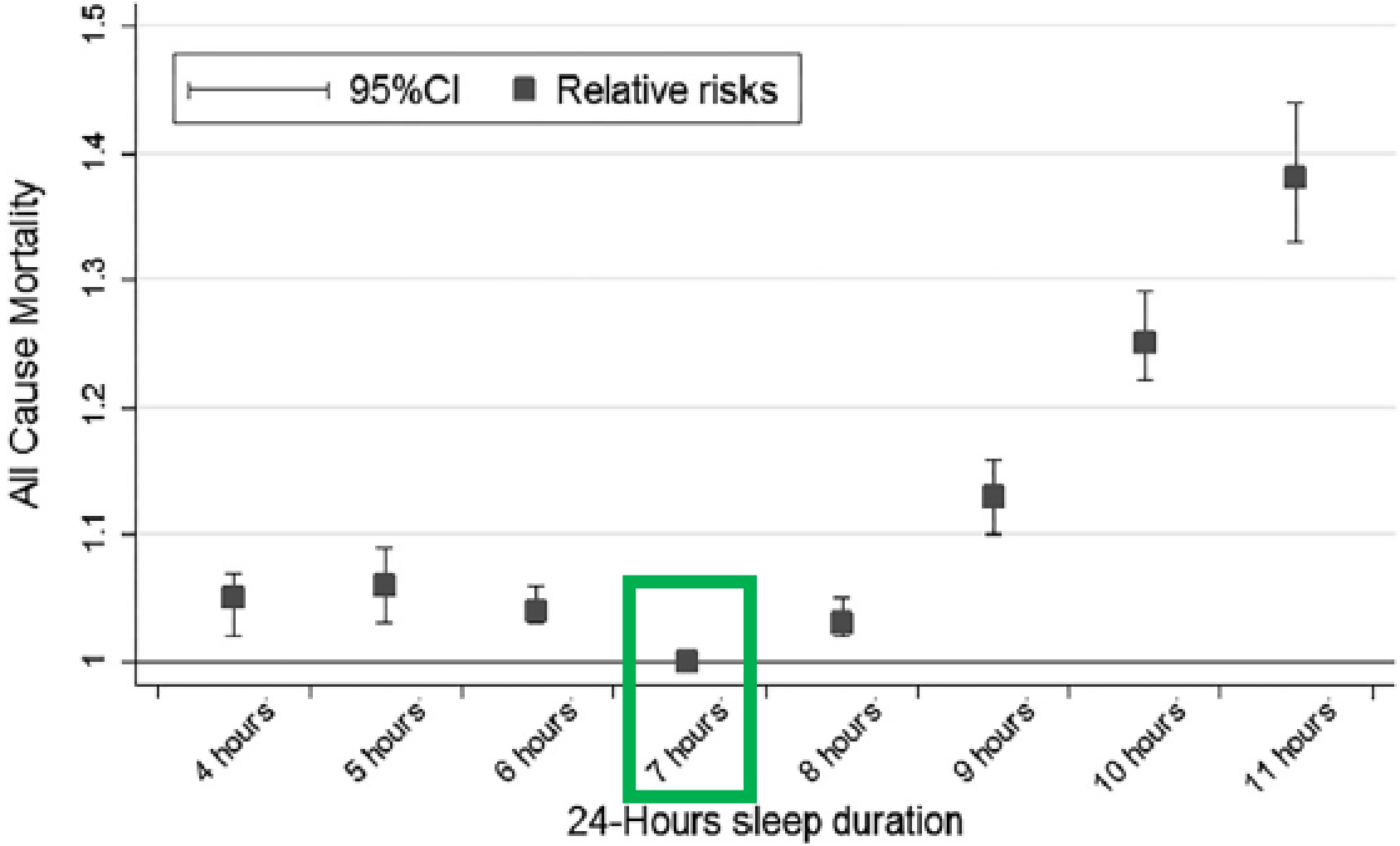
Long sleep duration and health outcomes: A systematic review, meta-analysis and meta-regression

- Long sleep duration is associated with greater mortality and increased incidence of mortality, diabetes mellitus, cardiovascular disease, stroke, coronary heart disease, and obesity.
- Longer duration of sleep is linearly associated with increased mortality risk.
- Currently, whether interventions to reduce long sleep duration also reduce health risk remains an open question.

M. Jike et al. / Sleep Medicine Reviews (2017) 1-12

Non-linearity relationship between 24-h sleep duration and all-cause mortality, with a J-shaped slope.

T.-Z. Liu et al. / Sleep Medicine Reviews 32 (2017) 28–36



Sleep duration may play a role in mortality. Prolonged duration of sleep (>8 h) may increase the risk of all-cause mortality. Long sleep seemed to be a greater risk than short sleep on mortality.