

Medications for Insomnia

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October 2, 2026

Conflict of Interest Disclosures for Speakers

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Learning Objectives

Upon completion of this course, attendees should be able to...

- Discuss dietary supplements, OTC medicine sleep aids, off-label medications, and FDA-approved medications recommended for the treatment of insomnia disorder
- Review key pharmacodynamic and pharmacokinetic features of FDA-approved insomnia medications
- Recommend evidence-based personalized strategies in the pharmacologic treatment of insomnia

Insomnia Treatment Approaches

- Education about sleep and circadian rhythms
- Promote healthy sleep habits
 - Recommend regularity in sleep-wake timing
 - Discuss an environment conducive for sleep
 - Advise caution with caffeine, alcohol, and other drugs
- Optimize management of comorbid conditions
- Cognitive-behavioral therapy for insomnia (CBT-I)
- Circadian strategies with timed light and dark exposure
- Head/body cooling
- Pharmacotherapy



Krafft vnd Wirkung.

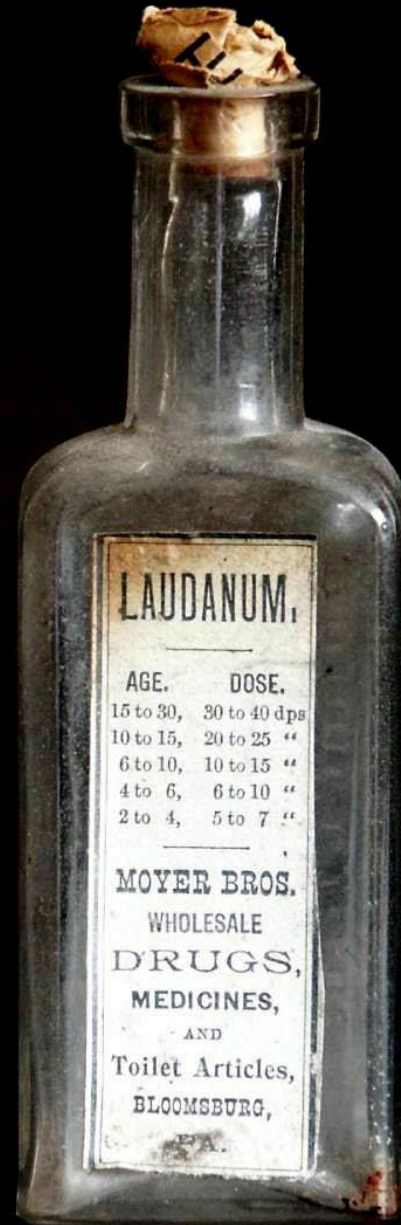
Die Bletter von allen Geschlechtern des Stechdorns/löschen S. Anthonius Feuer/
vnd heilen die vmbfressenden Geschwer/darauff gelegt. Die Zweige dieser Stechdorn
vber die Thüren vnnnd Fenster gehenckt/vertreiben alle
Gespenst vnd Zauberey/schreibt Dioscorides.



Laudanumbaum/ Laudanum.

Cap. xxi.

Laudanumbaum/Ladon oder Ledon, ist ein Ges
schlecht des Cisthi, darvon droben gesagt/nem
lich das dritte/darauff der Safft Ladanum be
reitet wirdt. *Græcis, Λάδον. Italicè, Ladanifero arbuscello. Hispani
cè, Xara.* Es ist dieser Strauch auch dem Cistho
gleich/hat aber länger vnd schwärzere Bletter/welche
ein feuchtigkeit im Lenz an sich ziehen/auff welchen
das Ladanum gemacht wirdt. Solcher Safft oder
feuchtigkeit wirdt also gesamlet: Wann die Beyse
vnnnd Böcke seine Bletter abwendt/so bleibet der
feystte Safft an ihrem Bart vnd Seiten kleben/gleich
wie ein Vogelleim / solcher Safft wirdt dann ab
gekemmet/vnnnd mit den Haren verwickelt vnnnd vers
mendet



LAUDANUM.

AGE.	DOSE.
15 to 30,	30 to 40 dps
10 to 15,	20 to 25 "
6 to 10,	10 to 15 "
4 to 6,	6 to 10 "
2 to 4,	5 to 7 "

MOYER BROS.
WHOLESALE
DRUGS,
MEDICINES,
AND
Toilet Articles,
BLOOMSBURG,
PA.

30 041 (03)

*A monsieur le maître et ami M. Bignon
Faible témoignage de reconnaissance
Bignon*

ÉCOLE NATIONALE VÉTÉRINAIRE DE TOULOUSE

DU
CHLORAL HYDRATÉ

PAR

MICHEL BIGNON

De Bayonne.

THÈSE POUR LE DIPLOME DE MÉDECIN-VÉTÉRINAIRE

Présentée le 24 juillet 1876.

TOULOUSE.

IMPRIMERIE PRADEL, VIGUIER ET BOÉ
RUE DES ORSTES, 6.

1876

Fellows Chloral Hydrate
CAPSULES

NON-BARBITURATE
NON-CUMULATIVE
TASTELESS
ODORLESS



3 3/4 gr.

Daytime sedation -
usually without "hangover"

7 1/2 gr.

Restful sleep - usually without "hangover"

& - specify Fellows for the original, stable, hermetically
sealed soft gelatin capsules Chloral Hydrate.

Available - 3 3/4 gr. (0.25 Gm.), bottles of 24's and 100's
7 1/2 gr. (0.5 Gm.), bottles of 50's

Samples and literature on request

pharmaceuticals since 1866

36 Christopher Street
New York 14, N. Y.

Fellows
Pharmaceuticals



1903



1920s

Historic Hypnotics of the 20th Century

Chloral hydrate

Barbiturates

Paraldehyde

Methaqualone

Ethinamate

Ethchlorvynol

Glutethimide

Methypylon

1. High risk of abuse and dependence
2. Dangerous overdose potential
3. Drug interactions
4. Organ toxicity
5. Daytime impairment
6. Disruption of normal sleep architecture
7. Availability of safer alternatives



Top 300 U.S. Prescription Drugs of 2024 - 1

Rank	Drug	Total Prescriptions	Total Patients
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Top 300 U.S. Prescription Drugs of 2024 - 2

Rank	Drug	Total Prescriptions	Total Patients

What People Take for Insomnia

Formal Sleep Indication?			
		No	Yes
Prescription Required?	No	Dietary Supplements	Over-the-Counter Sleep Aids
	Yes	Assorted Sedating Medications “Off-label”	Regulatory-Approved Insomnia Medications

Dietary Supplement Sleep Aids

- Herbal preparations, homeopathic formulations, vitamins, “natural” products – often combinations of multiple ingredients
- Complementary and Alternative Medicine
- Natural or synthetic compounds
- Two broad types
 - Melatonin
 - Everything else (eg, valerian)
- Limited efficacy data
- Few safety concerns
- Huge number of products marketed as sleep aids
- Melatonin: Use by about 3 million people in the United States during any 30-day period

Dietary Supplement Sleep Aids

Other Assorted Ingredients

- Valerian
- Kava kava
- Passionflower
- Skullcap
- Lavender
- Hops
- Glycine
- Magnesium
- Hyoscyamus
- Stramonium
- L-theanine
- Griffonia
- Wild jujube seeds
- Chamomile
- L-tryptophan



Nature Made
Melatonin Extra...
\$12.99
Target



Life Extension
Melatonin - 3 mg...
\$6.00
Life Extension
★★★★★ (198)



Nature's Bounty
Melatonin 5 mg-9...
\$6.95
Puritan's Pride
★★★★★ (170)



Life Extension
Melatonin IR/XR...
\$9.00
Life Extension
★★★★★ (9)



Source Naturals,
Melatonin...
\$36.05
iHerb
Free shipping



Nature Made
Melatonin 5 mg...
\$9.39
Target
★★★★★ (405)



Melatonin
\$12.99
Best In Nature



Life Extension
Enhanced Sleep...
\$16.50
Life Extension
★★★★★ (35)



Ollly Sleep Vitamin
Gummies - ...
\$12.89
Target
★★★★★ (174)



Nature's Bounty
Melatonin 10 mg...
\$11.50
Walmart
★★★★★ (207)



ZzzQuil Pure Zzzs
Triple Strength...
\$13.49
Target
★★★★★ (6)



ZzzQuil Pure Zzzs
All Night Tablets - ...
\$7.99
Target



Puritan's Pride
Melatonin 3 mg-1...
\$3.19
Puritan's Pride
★★★★★ (341)



Nature Made
Melatonin 3 mg...
\$9.50
Walmart
★★★★★ (70)



REMfresh Sleep
Aids - 36ct
\$18.99
Target
★★★★★ (30)



Amazon.com: Nature ...
amazon.com



Natrol Melatonin Fast ...
amazon.com



Amazon.com: Natrol M...
amazon.com



Fast-Dissolve Melatonin Table...
walmart.com · In stock



Natrol: Natrol Melatonin, Sleep...
natrol.com · In stock



Spring Valley Melatonin Table...
walmart.com · In stock



Natrol: Natrol Melatonin Gumm...
natrol.com · In stock



Nature Made Melatonin 2.5 M...
target.com · In stock



Natrol Melatonin Fast Di...
walmart.com · In stock



Swanson Health Products
swansonvitamins.com · In stock



Nature Made Melatonin 10 mg...
bjs.com · In stock



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target.com · In stock



King Soopers - VitaFusion V...
kingsoopers.com · In stock



Natrol Advanced Sleep Melaton...
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Natrol: Natrol Melatonin Liquid...
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Swanson Health Products
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Melatonin | Optimum
optimumnutrition.com



Triple Action Melatonin Gum...
zzquil.com



Melatonin 10mg Tablets - 120...
target.com · In stock



Kroger - Kroger® Melatonin 5 ...
kroger.com · In stock



Puritan's Pride Melatonin 1 m...
vitamin360.com · In stock



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costco.com · In stock



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Melatonin, 10 mg,
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NOW - Melatonin 5
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Adult Melatonin Gummies - ...
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Supplement Facts

Serving size 1 capsule
Servings per container 180

	Amount Per Serving	%DV
Melatonin	0.5 mg	*

* Daily value (DV) not established

Other ingredients: hypoallergenic plant fiber (cellulose),
vegetarian capsule (cellulose, water)

WARNING: Consult a healthcare professional if you are experiencing long-term sleep difficulties, before use in children, before use in pregnant or lactating women, those with a medical condition, and those taking medication. Do not drive or operate machinery when taking melatonin. This product may be contraindicated with autoimmune disease or for individuals taking corticosteroids.

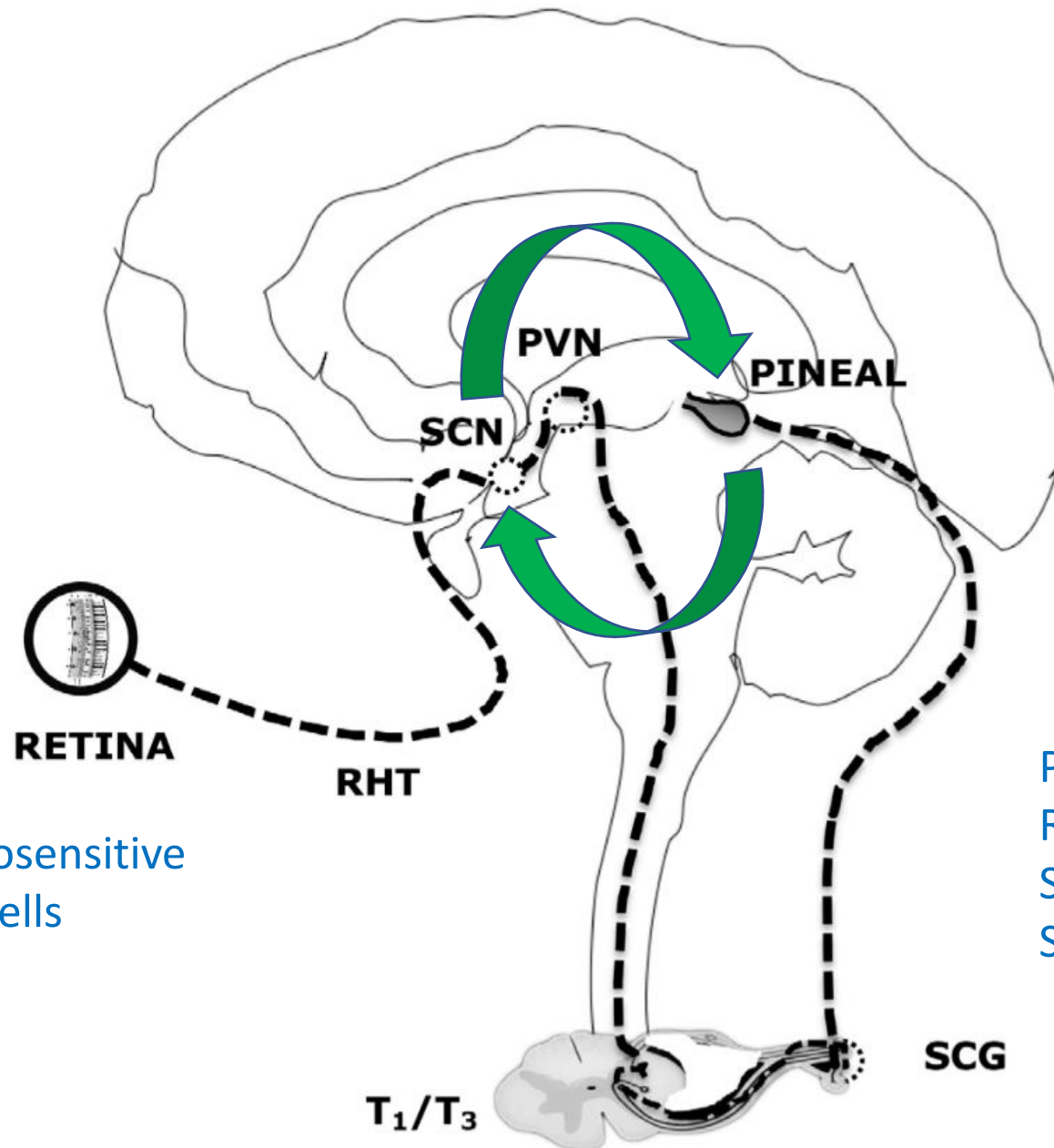
***This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

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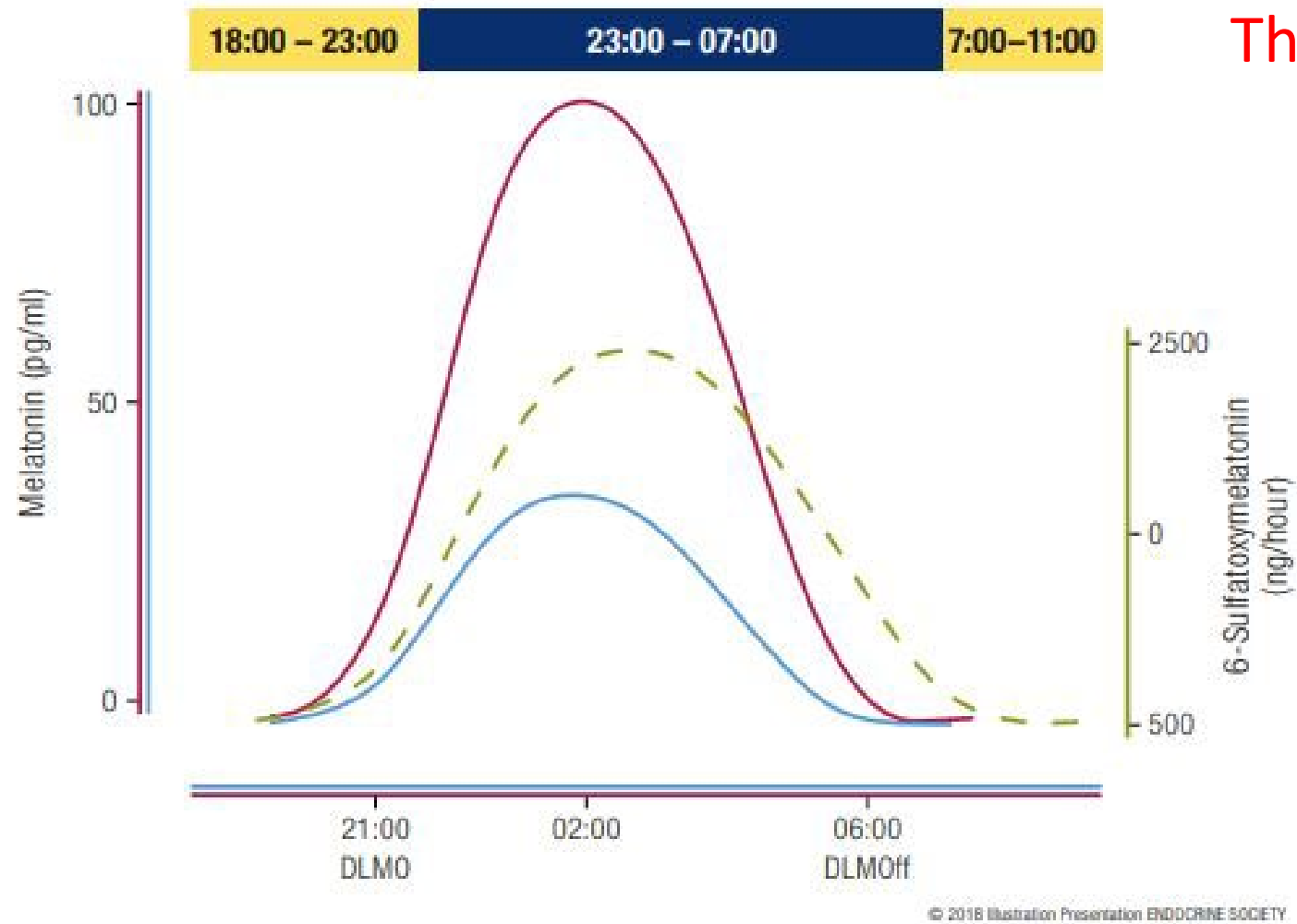
Melatonin: Possible Side Effects

- Daytime drowsiness, dizziness, weakness, or confusion
- Vivid dreams, nightmares
- Feeling depressed, anxious, irritable
- Headache
- Loss of appetite, diarrhea, nausea, stomach pain
- Blood pressure changes
- Joint or back pain
- Elevated risk for seizures



PVN – Paraventricular nucleus
RHT – Retinohypothalamic tract
SCG – Superior cervical ganglion
SCN – Suprachiasmatic nucleus

Melatonin: The hormone of darkness? Yes and No



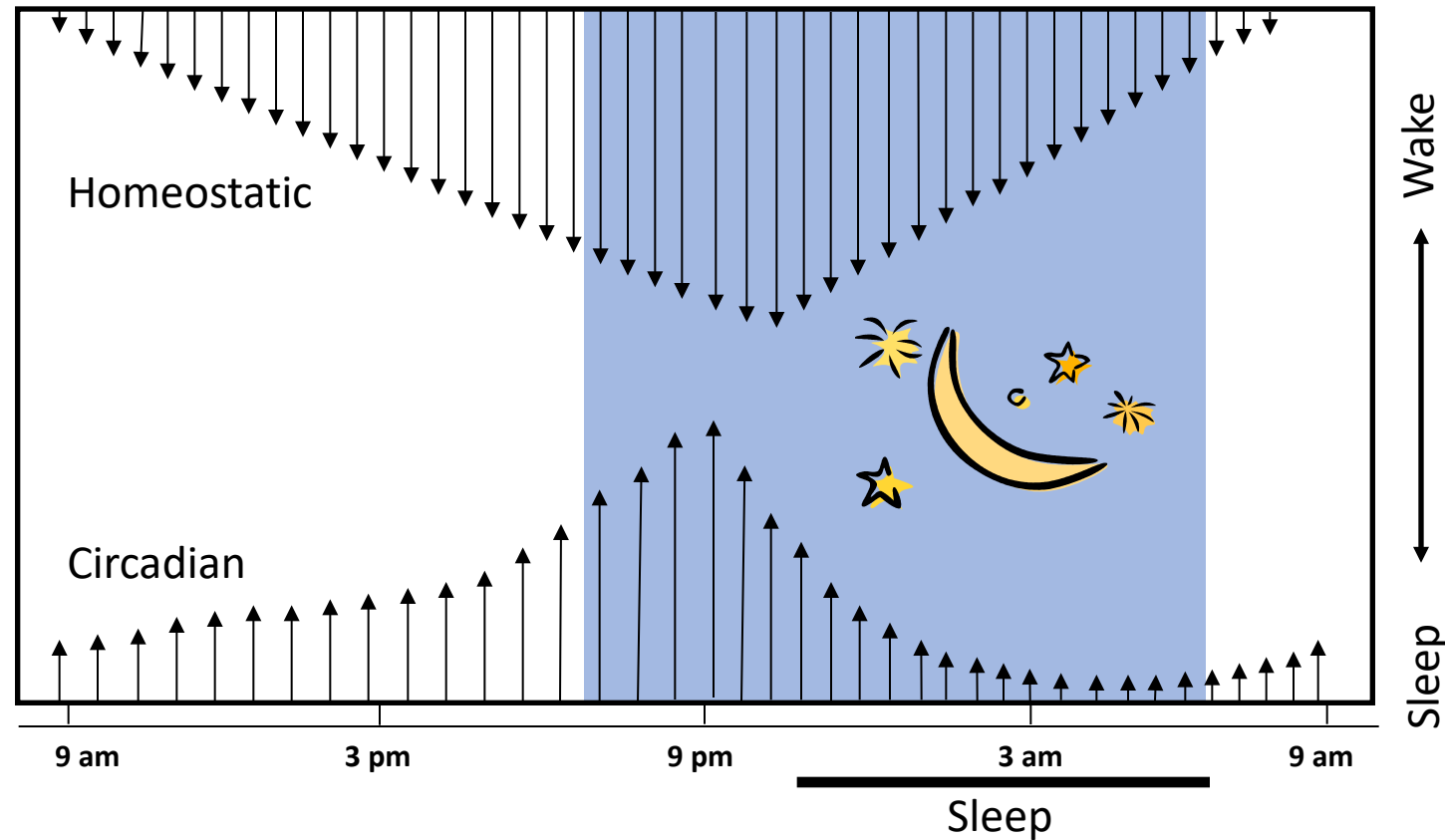
Plasma melatonin

Saliva melatonin

6-Sulfatoxymelatonin

DLMO: Dim Light Melatonin Onset
DLMOFF: Dim Light Melatonin Offset

Homeostatic and Circadian Sleep Regulation



The Efficacy and Safety of Exogenous Melatonin for Primary Sleep Disorders

A Meta-Analysis

Nina Buscemi, PhD,¹ Ben Vandermeer, MSc,¹ Nicola Hooton, BSc,¹ Rena Pandya, MPH,¹ Lisa Tjosvold, MLIS,¹ Lisa Hartling, MSc,¹ Glen Baker, PhD, DSc,² Terry P. Klassen, MD, MSc,¹ Sunita Vohra, MD, MSc³

¹University of Alberta Capital Health Evidence-based Practice Centre, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada; ²Department of Psychiatry, University of Alberta, Edmonton, AB, Canada; ³Complementary and Alternative Research and Education Program, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada.

- Melatonin efficacy relative to placebo
 - Decreased sleep onset latency: 11.7 minutes (WMD)
 - Improved sleep efficiency: 2.5% (WMD) – NS
 - Sleep quality – NS
 - Wakefulness after sleep onset – NS
 - Total sleep time – NS
 - REM sleep % – NS
- Melatonin safety: “evidence to suggest safe with short-term use”



Insomnia: 7.5 minutes
Delayed sleep phase: 38.8 minutes

“There is evidence to suggest that melatonin is not effective in treating most primary sleep disorders with short-term use; however, additional large-scale RCTs are needed before firm conclusions can be drawn.”

WMD = weighted mean difference; NS = nonsignificant; RCT = randomized controlled trial.

Buscemi N, et al. *J Gen Intern Med.* 2005;20(12):1151-1158.

Efficacy of Melatonin: An Umbrella Review

- Analysis of 14 meta-analyses and systematic reviews (4266 participants)
- Methodologic quality: moderate to critically low
- Statistically significant improvement
 - Sleep onset latency (positive in 9 out of 12 analyses)
 - Total sleep time (positive in 3 out of 7 analyses)
 - Sleep quality (positive in 5 out of 6 analyses)
- Clinical significance questionable

“...it appears that there is inadequate evidence to confirm the efficacy of MLT in primary insomnia.”

Acute Melatonin Administration in Humans Impairs Glucose Tolerance in Both the Morning and Evening

Patricia Rubio-Sastre, PhD¹; Frank A.J.L. Scheer, PhD²; Purificación Gómez-Abellán, PhD¹; Juan A. Madrid, PhD¹; Marta Garaulet, PhD¹

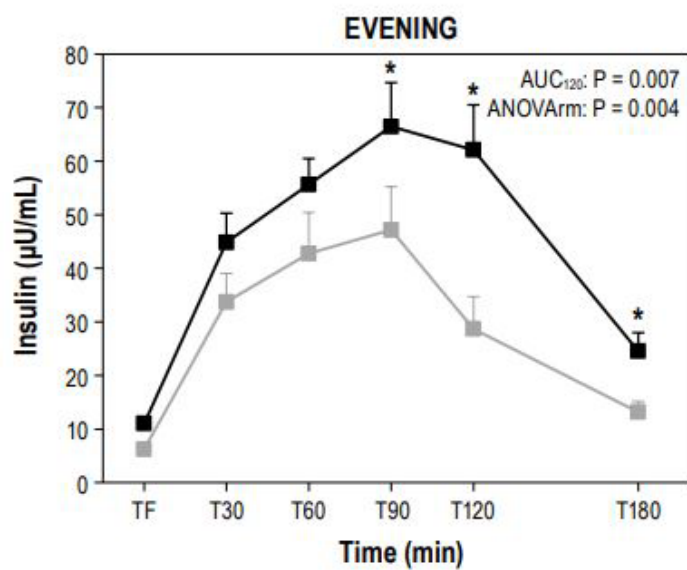
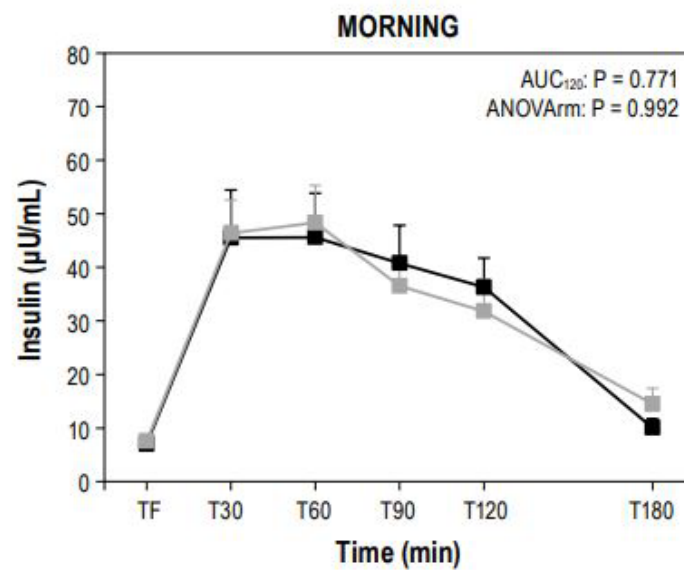
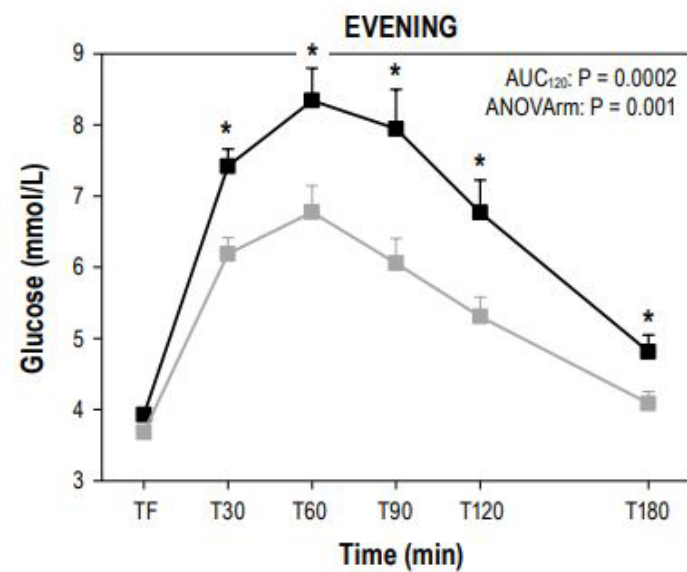
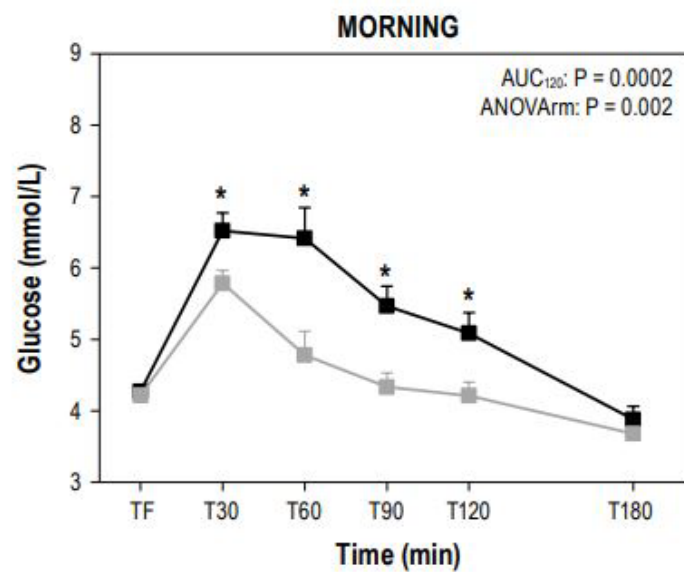
¹Department of Physiology, University of Murcia, IMIB-Arrixaca, Murcia, Spain; ²Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, and Division of Sleep Medicine, Harvard Medical School, Boston, MA

Participants: 21 healthy women (24 ± 6 y; body mass index: 23.0 ± 3.3 kg/m²).

Interventions: Glucose tolerance was assessed by oral glucose tolerance tests (OGTT; 75 g glucose) on 4 occasions: in the morning (9 AM), and evening (9 PM); each occurring 15 minutes after melatonin (5 mg) and placebo administration on 4 non-consecutive days.

Conclusions: Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. When administering melatonin, the proximity to meal timing may need to be considered, particularly in those at risk for glucose intolerance.

■ Placebo ■ Melatonin



Opinion

Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy

Marta Garaulet,^{1,2,8} Jingyi Qian,^{2,3,8} Jose C. Florez,^{3,4,5} Josephine Arendt,⁶ Richa Saxena,^{3,4,5,7,*} and Frank A.J.L. Scheer^{2,3,5,7,*}

The concurrence of elevated melatonin concentrations with food intake decreases glucose tolerance, while high melatonin during fasting may facilitate β -cell recovery.

Shift workers, night eaters, and melatonin users are susceptible to the adverse effect brought by the concurrence of food intake and high melatonin levels.

Take-Away Points

Therapeutic use of dietary supplement melatonin products

- Might help with sleep onset, unlikely for sleep maintenance
- Most likely helpful for people with circadian rhythm phase delay (night owls) and non-24-hour disorder
- Limited support for jet lag and shift work
- Try 0.5 to 3 mg – more is not better with melatonin
- Take prior to bedtime (1 to 2 hours)
- But not too early – at least 2 hours after last meal
- Avoid eating late in the evening, even if you're not taking melatonin

What People Take for Insomnia

Formal Sleep Indication?			
		No	Yes
Prescription Required?	No	Dietary Supplements	Over-the-Counter Sleep Aids
	Yes	Assorted Sedating Medications "Off-label"	Regulatory-Approved Insomnia Medications

Over-the-Counter Medicine Sleep Aids

- Non-prescription but regulated (U.S. – FDA)
 - Composition
 - Dosing
 - Manufacturing
 - Labeling
 - Marketing (FTC)
- Antihistamines (brand or generic)
- Sedating effect (tolerance possible)
- Available alone or combined with analgesics
- May be prescribed at doses higher than OTC instructions

Over-the-Counter Medicine Sleep Aids

- All are antihistamines
 - Diphenhydramine (most products)
 - Peak concentration: 2 to 3 hours
 - Elimination half-life: 8.5 ± 3.2 hours (short in children; longer in elderly)
 - Doxylamine
 - Peak concentration: 2 to 4 hours
 - Elimination half-life: 10 to 12 hours (longer in elderly)
 - Pharmacodynamics
 - Histamine H₁ receptor antagonist
 - Muscarinic acetylcholine receptor antagonist
 - Tolerance to sedating effects may develop with daily use
 - Adverse effects: Sedation, anticholinergic symptoms
 - (Non-OTC hydroxyzine similar to above medications)

Antihistamines: Potential Adverse Effects

- Next day residual sedation - common
- Anticholinergic effects
 - Confusion and delirium
 - Urinary retention
 - Dry mouth
 - Blurred vision
 - Narrow angle glaucoma exacerbation
 - Greater risk:
 - Elderly individuals
 - Patients concomitantly taking other anticholinergic medications (e.g., antidepressants, antipsychotics)

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“Off-Label” Prescriptions for Insomnia

- Antidepressants
- Antipsychotics
- Anxiolytics
- Antihistamines
- Anticonvulsants/mood stabilizers
- Antihypertensives
- Anesthetics
- Lacking
 - Efficacy for insomnia
 - Safety in insomnia patients
 - Prescribing guidelines
 - Knowledge of sleep effects
- Is there comorbidity with an indicated condition?

Trazodone: *Highlights of Prescribing Information*

- **Indications and Usage:** “a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder (MDD)”
- **Dosage and Administration**
 - Maximum dose: 400 mg/day in divided doses
 - Should be taken shortly after a meal
 - When discontinued, gradual doses reduction is recommended

Trazodone: *Pharmacology*

- **Pharmacodynamics**

- 5-HT_{2A} antagonist (K_i = 35.6 nM)
- 5-HT_{2B} antagonist (K_i = 78.4 nM)
- 5-HT_{2C} antagonist (K_i = 224 nM)
- Serotonin reuptake inhibition (K_i = 367 nM)
- α_{1A} antagonist (K_i = 153 nM)
- α_{2C} antagonist (K_i = 155 nM)
- 5-HT_{1A} partial agonist (K_i = 118 nM)

- **Pharmacokinetics**

- Peak plasma level (empty stomach) approximately 1 hour
- Elimination half-life: Biphasic 10–12 hours
- Active metabolite (CYP3A4): *m*-chlorophenylpiperazine (mCPP)

What People Take for Insomnia

Formal Sleep Indication?			
		No	Yes
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	Yes	Assorted Sedating Medications "Off-label"	Regulatory-Approved Insomnia Medications

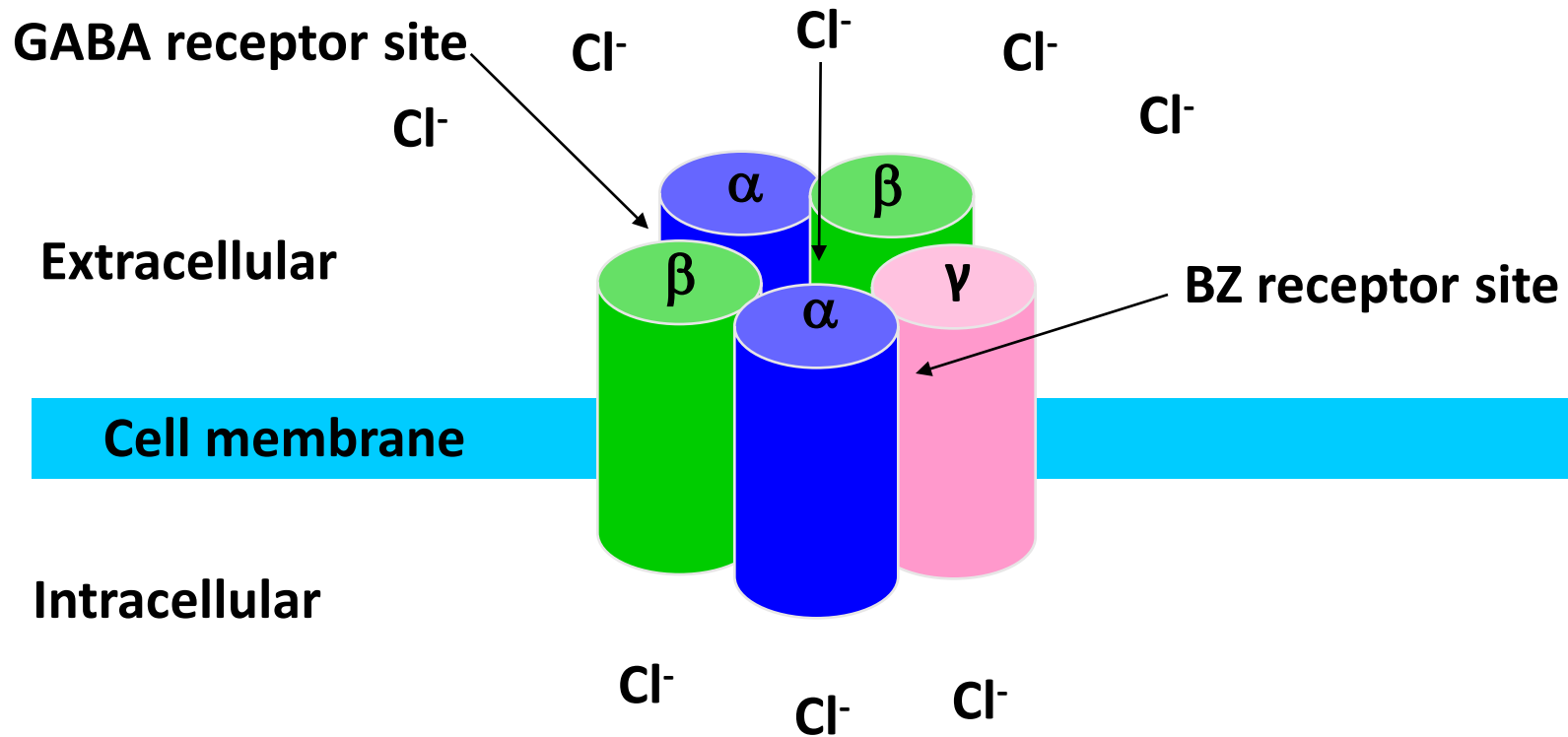
Current Regulatory-Approved Insomnia Treatment Medications

- Benzodiazepine receptor agonists
 - Benzodiazepine hypnotics
 - Nonbenzodiazepine hypnotics
- Melatonin receptor agonist
 - Ramelteon
 - Controlled-release melatonin
- Selective histamine receptor antagonist
 - Low dose doxepin
- Dual orexin/hypocretin receptor antagonist
 - Suvorexant
 - Lemborexant
 - Daridorexant

FDA-Approved Insomnia Medications, Part 1

Generic name	Brand name	Available doses (mg)	Elimination half-life (hours)
Benzodiazepine Receptor Agonists			
Benzodiazepines Immediate Release			
Estazolam	ProSom	1, 2	10 to 24
Flurazepam	Dalmane	15, 30	2.3 (active metabolite: 48 - 160)
Quazepam	Doral	7.5, 15	39 (active metabolite 73)
Temazepam	Restoril	7.5, 15, 22.5, 30	3.5 to 18.4
Triazolam	Halcion	0.125, 0.25	1.5 to 5.5
Nonbenzodiazepines Immediate Release			
Eszopiclone	Lunesta	1, 2, 3	~6 (~9 in elderly)
Zaleplon	Sonata	5, 10	1
Zolpidem	Ambien	5, 7.5, 10	~2.5
Nonbenzodiazepines Extended Release			
Zolpidem ER	Ambien CR	6.25, 12.5	2.8 in males (longer in females)
Nonbenzodiazepines Alternate Delivery			
Zolpidem oral spray	Zolpimist	5, 10	2.7 – 3.0
Zolpidem sublingual	Edluar	5, 10	~2.5
Zolpidem sublingual	Intermezzo	1.75, 3.5	~2.5

GABA_A Receptor Complex



Benzodiazepine Receptor Agonists

Benzodiazepines

- Pharmacodynamics
 - Positive allosteric modulators of GABA responses at the GABAA receptor complex
 - Multiple GABAA receptor α subunit subtypes
 - Targeted action in the hypothalamic sleep nuclei
 - Global CNS effects
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Very wide range of elimination half-lives: hours to days
 - Expect prolonged half-life in older adults
 - Most efficacious for sleep onset and maintenance
 - Potential for residual daytime sedation

Benzodiazepine Receptor Agonists

Non-Benzodiazepines (Z-Drugs)

- Pharmacodynamics
 - Positive allosteric modulators of GABA responses at the GABAA receptor complex
 - Selected GABAA receptor α subunit subtypes
 - Targeted action in the hypothalamic sleep nuclei
 - Global CNS effects
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Relatively shorter elimination half-lives: About 1 to 6 hours
 - Expect prolonged half-life in older adults and for zolpidem in women
 - Indications vary for sleep onset and maintenance
 - Limited potential for residual daytime sedation

Benzodiazepine Receptor Agonists

Possible Adverse Effects

- Residual effects
- Dizziness
- Headache
- Somnolence
- Blurred vision
- Nausea/diarrhea
- Fatigue
- Ataxia
- Anterograde amnesia
- Somnambulism/complex sleep behaviors

2019 FDA Update: Eszopiclone, zolpidem, and zaleplon

- U.S. FDA Safety Announcement
 - Boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines
 - Contraindication: avoid use in patients who have previously experienced an episode of complex sleep behavior with these medications
 - Serious injuries and death from complex sleep behaviors
 - Even at the lowest recommended doses
 - Can occur after just one dose
 - Can occur with or without alcohol or other CNS depressants

Melatonin Receptor Agonist: Ramelteon - 1

- Pharmacodynamics
 - Melatonin MT₁ and MT₂ receptor agonist
 - Targeted action in the hypothalamic suprachiasmatic nucleus (SCN)
 - Reduces evening circadian driven arousal
 - Reinforces circadian periodicity
 - Enhances sleep onset
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Relatively short elimination half-life: 1 to 2.6 hours
 - Limited potential for residual daytime sedation

Melatonin Receptor Agonist: Ramelteon - 2

- Indicated for insomnia with sleep onset difficulty
- Adverse events
 - Somnolence (5%)
 - Dizziness (5%)
 - Fatigue (4%)
- No abuse liability
- Avoid with
 - Hepatic impairment (moderate to severe)
 - Fluvoxamine (Luvox) coadministration

Histamine Receptor Antagonist

Low-Dose Doxepin - 1

- Pharmacodynamics
 - At very low doses primarily histamine receptor antagonist (avoiding receptor effects associated with higher doses)
 - Histamine is a potent wake-promoting neurotransmitter
 - Enhances sleep by reducing nighttime histamine arousal
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Elimination half-life: About 15.3 hours
 - Limited potential for residual daytime sedation

Histamine Receptor Antagonist

Low-Dose Doxepin - 2

- Indicated for the treatment of insomnia characterized by difficulties with sleep maintenance
- Approved by the FDA (2010)
- Ultra-low dose (3 mg, 6 mg)
- No abuse liability
- Most common adverse effects
 - Somnolence/sedation
 - Nausea
 - Upper respiratory tract infection

FDA-Approved Insomnia Medications, Part 2

Generic name	Brand name	Available doses (mg)	Elimination half-life (hr)
Selective melatonin receptor agonist			
Ramelteon	Rozerem	8	1 – 2.6
CR Melatonin	Circadin	2	3.5 – 4.0
Selective histamine H₁ receptor antagonist			
Doxepin	Silenor	3, 6	15.3
Dual orexin receptor antagonist			
Daridorexant	Quviviq	25, 50	8
Lemborexant	Dayvigo	5, 10	17 - 19
Suvorexant	Belsomra	5, 10, 15, 20	12

Orexin/Hypocretin and Insomnia

Dual Orexin Receptor Antagonists

1998

Orexins and Orexin Receptors: A Family of Hypothalamic Neuropeptides and G Protein-Coupled Receptors that Regulate Feeding Behavior

Takeshi Sakurai,^{1,4} Akira Amemiya,^{1,8} Makoto Ishii,¹ Ichiyo Matsuzaki,^{1,10} Richard M. Chemelli,^{1,2} Hirokazu Tanaka,¹ S. Clay Williams,¹ James A. Richardson,¹ Gerald P. Kozlowski,¹ Shelagh Wilson,¹ Jonathan R. S. Arch,¹ Robin E. Buckingham,⁵ Andrea C. Haynes,¹ Steven A. Carr,¹ Roland S. Annan,¹ Dean E. McNulty,¹ Wu-Schyong Liu,¹ Jonathan A. Terrett,¹ Nabil A. Elshourbagy,⁴ Derk J. Bergsma,⁴ and Masashi Yanagisawa^{1,7}

¹Howard Hughes Medical Institute Department of Molecular Genetics
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Summary

The hypothalamus plays a central role in the integrated control of feeding and energy homeostasis. We have identified two novel neuropeptides, both derived from the same precursor by proteolytic processing, that bind and activate two closely related (previously) orphan G protein-coupled receptors. These peptides, termed orexin-A and -B, have no significant structural similarities to known families of regulatory peptides. *prepro-orexin* mRNA and immunoreactive orexin-A are localized in neurons within and around the lateral and posterior hypothalamus in the adult rat brain. When administered centrally to rats, these peptides stimulate food consumption. *prepro-orexin* mRNA level is up-regulated upon fasting, suggesting a physiological role for the peptides as mediators in the central feedback mechanism that regulates feeding behavior.

lipids, peptides, and proteases. Ligand binding initiates intracellular signal transduction through the activation of heterotrimeric G proteins. All of the known small regulatory peptides (small peptide hormones and neuropeptides) exert their biological actions by acting on GPCRs. Recent efforts in genomics research have identified a large number of cDNA sequences that encode "orphan" GPCRs, i.e., putative GPCRs without known cognate ligands. Many of these orphan GPCRs are likely to be receptors for heretofore unidentified signaling molecules, including new peptide hormones and neuropeptides. GPCRs already represent the largest class of target molecules for drugs available in the clinic (Hardman et al., 1996). The orphan GPCRs therefore represent a fruitful resource for drug discovery (Stadel et al., 1997).

To approach these possibilities, we undertook a systematic biochemical search for endogenous peptide ligands for multiple orphan GPCRs, using a cell-based reporter system. These screening experiments led to the identification of a novel family of neuropeptides that bind to two closely related orphan GPCRs. We call these peptide ligands "orexins," after the Greek word orexis, which means appetite. The mRNA for the precursor of these peptides is abundantly and specifically expressed in the lateral hypothalamus and adjacent areas, a region classically implicated in the central regulation of feeding behavior and energy homeostasis (Oomura, 1980; Bernardis and Bellinger, 1993, 1996). These peptides stimulate food consumption when administered centrally, and their production is influenced by nutritional state of the animal. Here we report the identification and initial biological characterization of two orexins as well as their two receptors.

Results and Discussion

Purification and Structure of Orexins

Our general strategy was to screen high-resolution HPLC fractions of various tissue extracts for GPCR-agonist activity, using multiple orphan GPCR-expressing cell lines tested in parallel. For this purpose, we generated over 50 stable transfectant cell lines, each expressing a distinct orphan GPCR cDNA, which can be used as reporter cell lines in order to identify endogenous ligands for these receptors. We challenged the cells with HPLC fractions derived from tissue extracts and we monitored

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 322–327, January 1998
Neurobiology

The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity

L. DE LECEA*†, T. S. KILDUFF*†‡, C. PEYRON‡, X.-B. GAO§, P. E. FOYE*, P. E. DANIELSON*, C. FUKUHARA*‡, E. L. F. BATTENBERG¶, V. T. GAUTVIK*||, F. S. BARTLETT II**, W. N. FRANKEL**, A. N. VAN DEN POL‡§, F. E. BLOOM¶, K. M. GAUTVIK*||, AND J. G. SUTCLIFFE*

Departments of *Molecular Biology and †Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037; ‡Center for Sleep and Circadian Neurobiology, Stanford University, Stanford, CA 94305; §Department of Neurosurgery, Yale University, New Haven, CT 06520; ||Institute of Basic Medical Sciences, Department of Biochemistry, University of Oslo, P.O. Box 1112, Blindern, N-0317 Oslo, Norway; and **The Jackson Laboratory, Bar Harbor, ME 04609

Contributed by F. E. Bloom, November 17, 1997

ABSTRACT We describe a hypothalamus-specific mRNA that encodes preprohypocretin, the putative precursor of a pair of peptides that share substantial amino acid identities with the gut hormone secretin. The hypocretin (Hcrt) protein products are restricted to neuronal cell bodies of the dorsal and lateral hypothalamic areas. The fibers of these neurons are widespread throughout the posterior hypothalamus and project to multiple targets in other areas, including brainstem and thalamus. Hcrt immunoreactivity is associated with large granular vesicles at synapses. One of the Hcrt peptides was excitatory when applied to cultured, synaptically coupled hypothalamic neurons, but not hippocampal neurons. These observations suggest that the hypocretins function within the CNS as neurotransmitters.

MATERIALS AND METHODS

Production of Antisera. Antiserum 2050 was generated by coupling the synthetic 17-mer CPTATATALAPRGGSRV to the carrier keyhole limpet hemocyanin with glutaraldehyde and immunizing rabbits as described (3). In Western transfer blots using as target electrophoretically separated proteins from bacteria transformed with the plasmid pRSET B engineered to express preprohcr, we observed a single prominent immunoreactive band with a migration of ~19 kDa with the hyperimmune serum, but not with the preimmune serum (not shown). No immunoreaction was detected with an extract from bacteria transformed with a preprocrortistatin/pRSET B expression plasmid, indicating that detection of the 19-kDa target requires Hcrt expression. Analogous results were obtained with an additional antiserum to the 17 mer and two

The Hypocretin Discovery

- Sutcliffe lab at The Scripps Research Institute, La Jolla, CA
- Directional tag PCR subtractive hybridization
- Searched for mRNA species selectively expressed in the hypothalamus
- “We describe a hypothalamus-specific mRNA that encodes preprohypocretin, the putative precursor of a pair of peptides that share substantial amino acid identities with the gut hormone secretin.”
- “Our name, hypocretin, is intended to indicate a hypothalamic member of the incretin family.”
- “The circuitry revealed by the immunohistochemistry suggests a role in nutritional homeostasis.”



JG Sutcliffe, PhD

The Orexin Discovery

- Yanagisawa lab at the University of Texas Southwestern Medical Center at Dallas
- Cell-based reporter system
- Searched for ligands for 2 orphan G-protein coupled receptors
- “We have identified two novel neuropeptides, both derived from the same precursor by proteolytic processing, that bind and activate two closely related (previously) orphan G protein-coupled receptors.”
- “....suggesting a physiological role for the peptides as mediators in the central feedback mechanism that regulates feeding behavior.”



Masashi Yanagisawa, MD, PhD



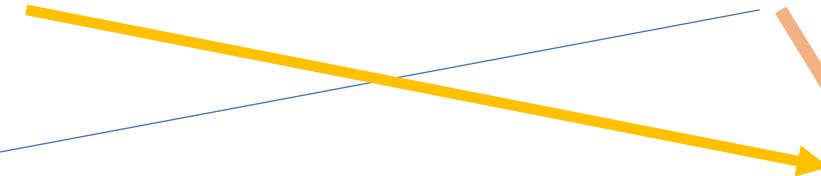
Hypocretin Neuropeptide Precursor



Orexin-A



Orexin-B

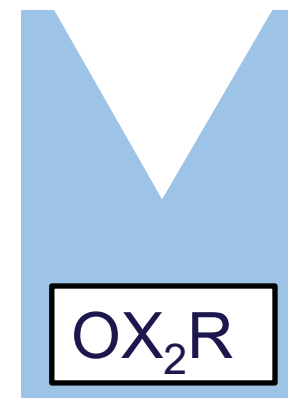


425
amino acids

OX₁R

64%

amino acid identity



444
amino acids

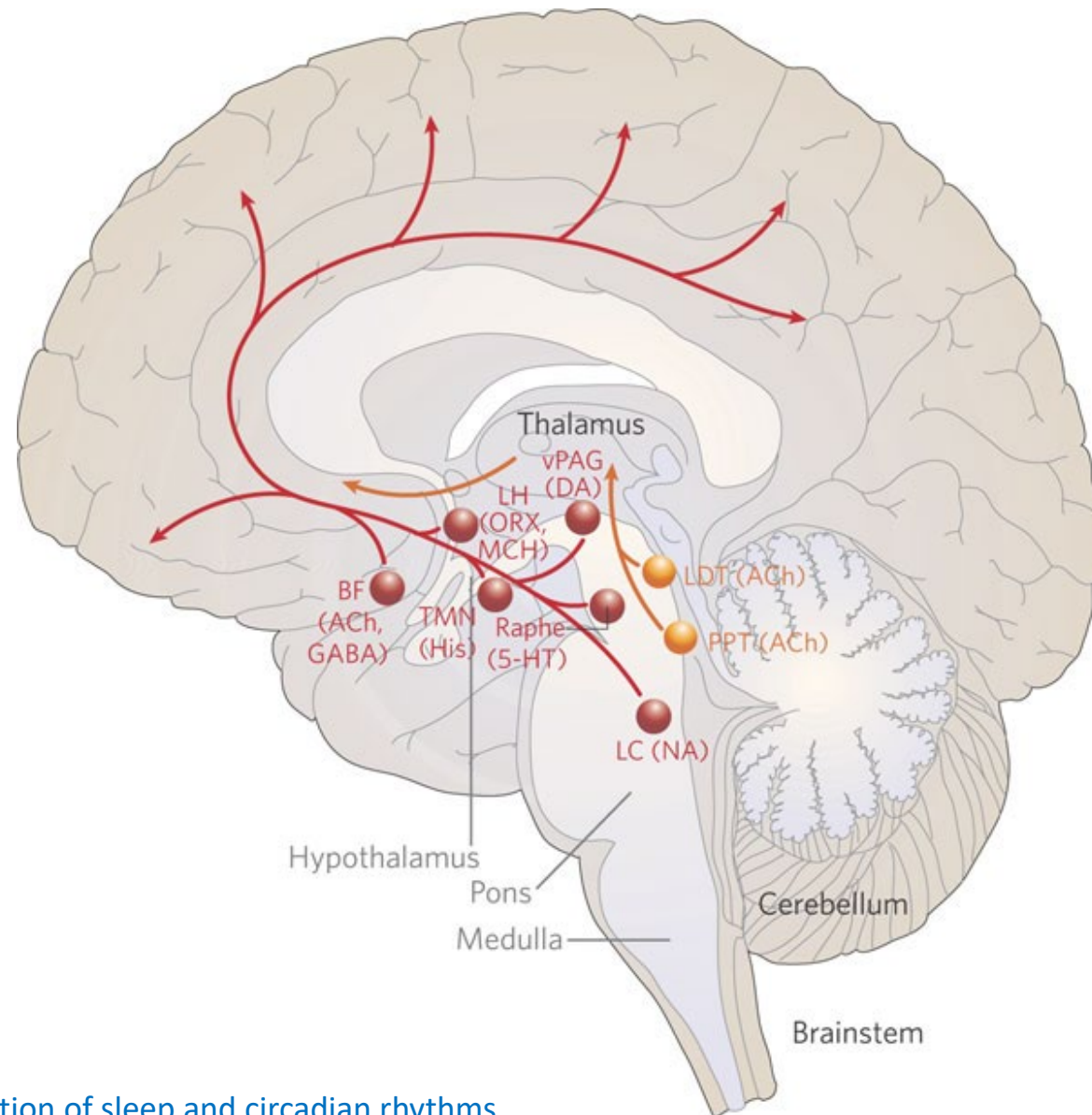
OX₂R

1999

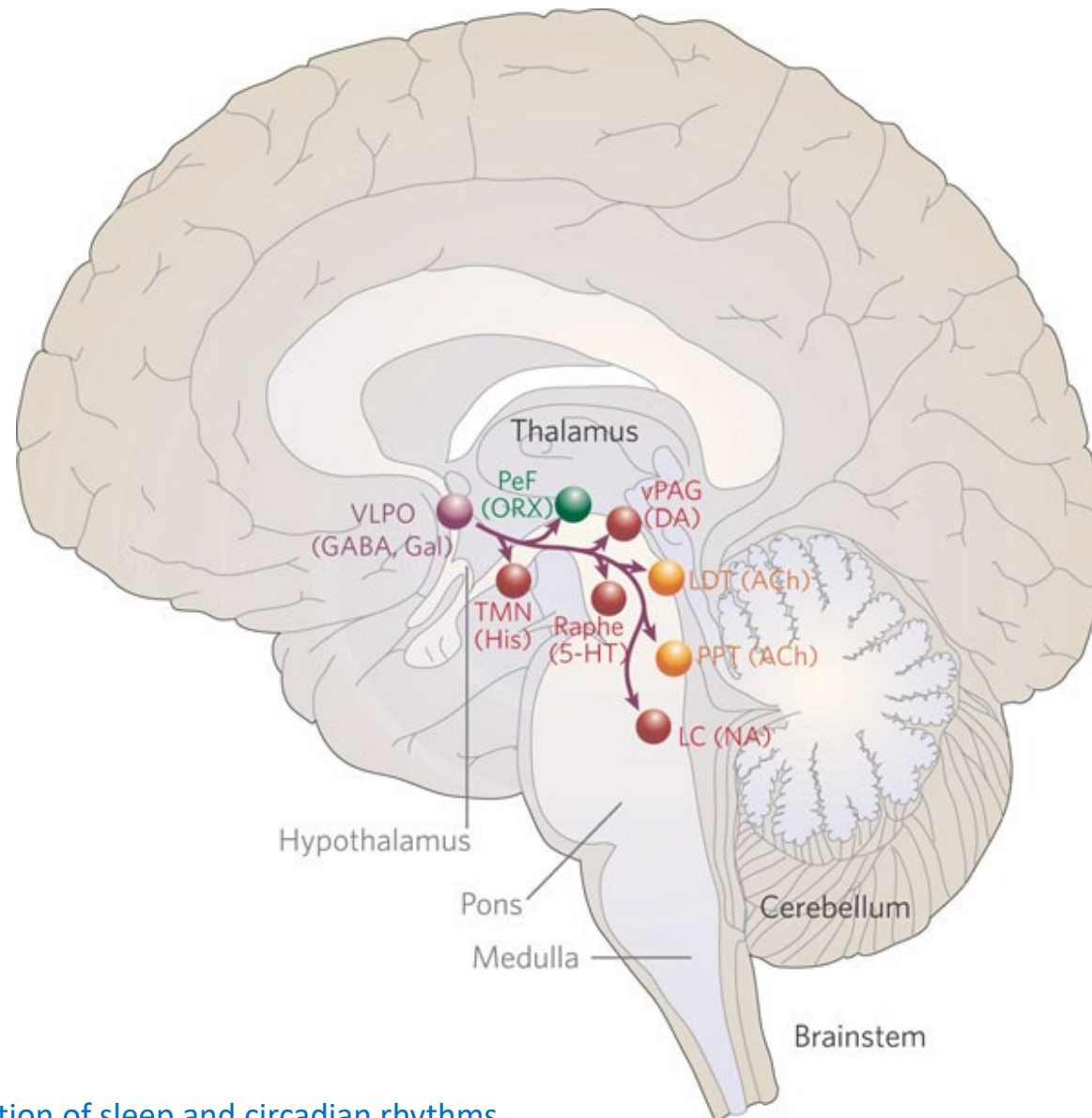
Narcolepsy: Orexin/Hypocretin Abnormality

Chemelli RM, Willie JT, Sinton CM, Elmquist J, Scammell T, Lee C, Richardson J, Williams S, Xiong Y, Kisanuki Y, Fitch T, Nakazato M, Hammer R, Saper C, Yanagisawa M. Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell*. 1999;98(4):437-451

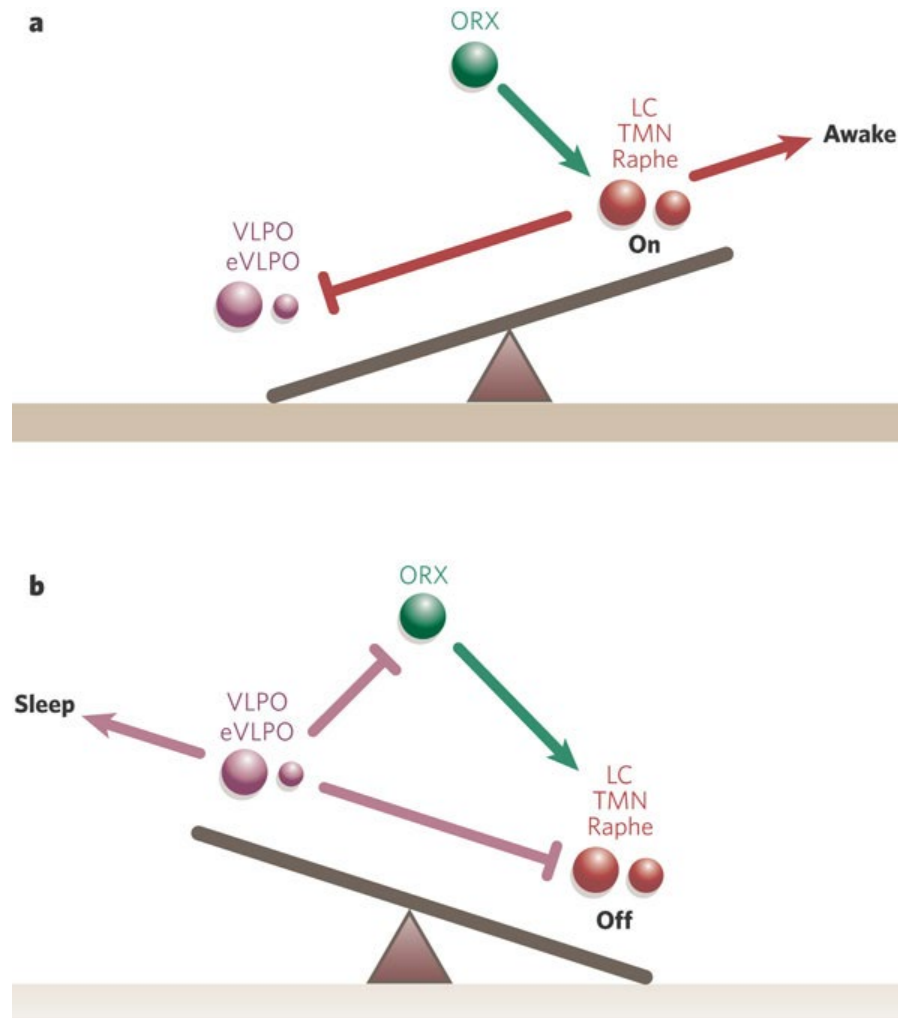
Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*. 1999;98(3):365-376.



Hypothalamic regulation of sleep and circadian rhythms
 Clifford B. Saper, Thomas E. Scammell and Jun Lu
Nature 437, 1257-1263 (27 October 2005)



Hypothalamic regulation of sleep and circadian rhythms
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Hypothalamic regulation of sleep and circadian rhythms
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Orexin/Hypocretin and Insomnia

- Discovered in 1998
- Two orexin peptides: Orexin A and Orexin B
- Neurons in the perifornical lateral hypothalamic regions with projections widely distributed in the brain and spinal cord
- Two orexin G-protein-coupled-receptors: OX1R and OX2R – partially overlapping distribution
- Promotes arousal and stabilizes wakefulness; deficient in narcolepsy
- Will decreasing orexin tone enhance sleep?

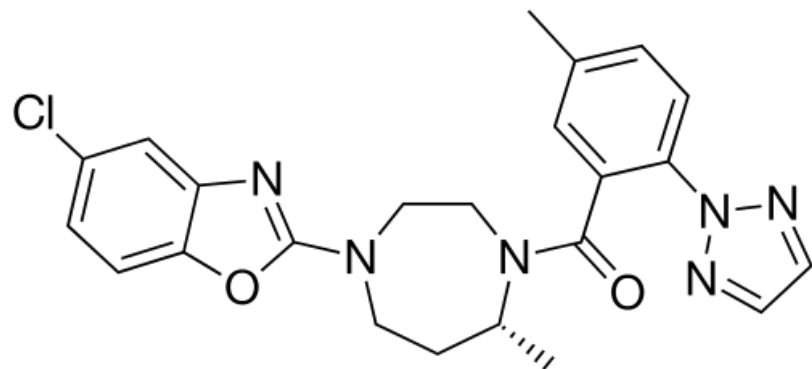
Promotion of sleep by targeting the orexin system in rats, dogs and humans

Catherine Brisbare-Roch¹, Jasper Dingemanse¹, Ralf Koberstein¹, Petra Hoeber¹, Hamed Aissaoui¹, Susan Flores¹, Celia Mueller¹, Oliver Nayler¹, Joop van Gerven², Sanne L de Haas², Patrick Hess¹, Changbin Qiu³, Stephan Buchmann¹, Michael Scherz¹, Thomas Weller¹, Walter Fischli¹, Martine Clozel¹ & François Jenck¹

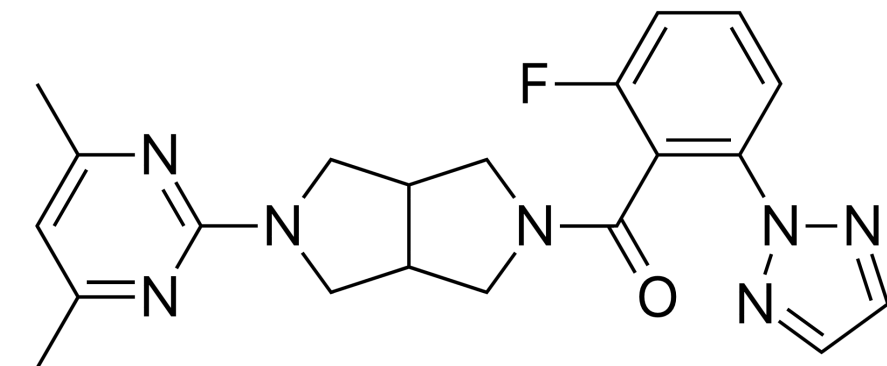
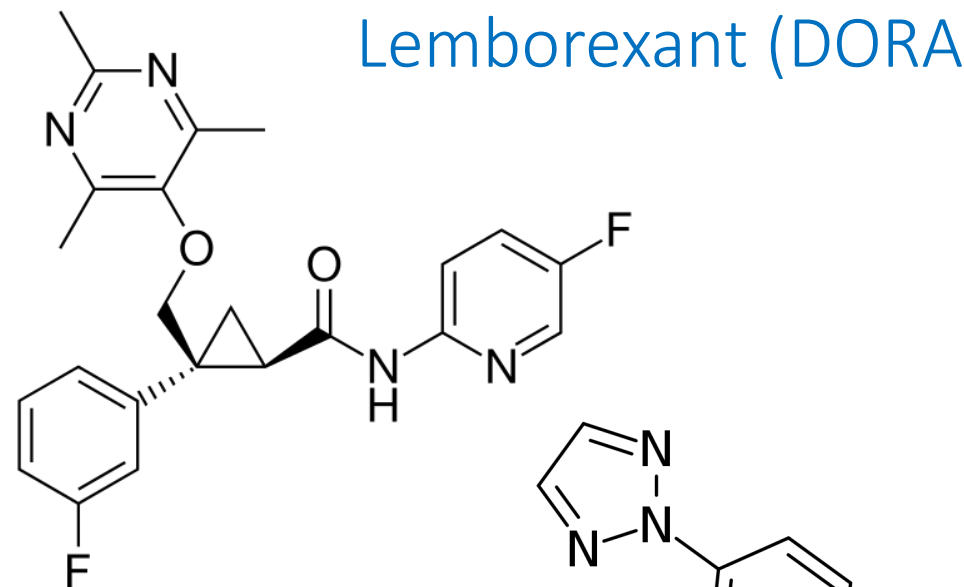
Orexins are hypothalamic peptides that play an important role in maintaining wakefulness in mammals. Permanent deficit in orexinergic function is a pathophysiological hallmark of rodent, canine and human narcolepsy. Here we report that in rats, dogs and humans, somnolence is induced by pharmacological blockade of both orexin OX₁ and OX₂ receptors. When administered orally during the active period of the circadian cycle, a dual antagonist increased, in rats, electrophysiological indices of both non-REM and, particularly, REM sleep, in contrast to GABA_A receptor modulators; in dogs, it caused somnolence and increased surrogate markers of REM sleep; and in humans, it caused subjective and objective electrophysiological signs of sleep. No signs of cataplexy were observed, in contrast to the rodent, dog or human narcolepsy syndromes. These results open new perspectives for investigating the role of endogenous orexins in sleep-wake regulation.

Orexin Receptor Antagonists

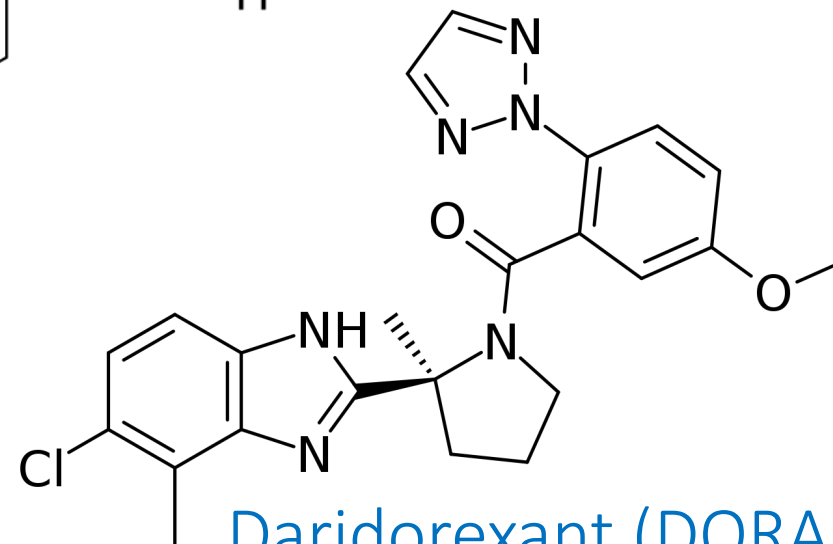
Suvorexant (DORA)



Lemborexant (DORA)



Seltorexant (2-SORA)*



Daridorexant (DORA)

* Investigational, DORA: Dual orexin receptor antagonist, SORA: Single orexin receptor antagonist OX2R

Orexin/Hypocretin Receptor Antagonist

Suvorexant - 1

- Pharmacodynamics
 - Dual orexin receptor (OX1 and OX2) antagonist
 - Hypothalamic neurons with peptides orexin-A and orexin-B project to cortex and wake-promoting nuclei to reinforce and stabilize wakefulness
 - Suvorexant promotes sleep by decreasing orexin-associated CNS arousal
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Elimination half-life: About 12 hours
 - Dose-dependent potential for residual daytime sedation

Orexin/Hypocretin Receptor Antagonist

Suvorexant - 2

- Indication: For the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- FDA approved in 2014
- Contraindication: narcolepsy
- Adverse reactions: somnolence
- Schedule IV controlled substance

Orexin/Hypocretin Receptor Antagonist

Lemborexant- 1

- Pharmacodynamics
 - Dual orexin receptor (OX1 and OX2) antagonist
 - Hypothalamic neurons with peptides orexin-A and orexin-B project to cortex and wake-promoting nuclei to reinforce and stabilize wakefulness
 - Lemborexant promotes sleep by decreasing orexin-associated CNS arousal
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Elimination half-life: About 17 - 19 hours
 - Dose-dependent potential for residual daytime sedation

Orexin/Hypocretin Receptor Antagonist

Lemborexant- 2

- Indication: For the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- FDA approved in 2019
- Contraindication: narcolepsy
- Adverse reactions: somnolence
- Schedule IV controlled substance

Orexin/Hypocretin Receptor Antagonist

Daridorexant- 1

- Pharmacodynamics
 - Dual orexin receptor (OX1 and OX2) antagonist
 - Hypothalamic neurons with peptides orexin-A and orexin-B project to cortex and wake-promoting nuclei to reinforce and stabilize wakefulness
 - Daridorexant promotes sleep by decreasing orexin-associated CNS arousal
- Pharmacokinetics
 - Relatively rapidly absorbed
 - Elimination half-life: About 8 hours
 - Dose-dependent potential for residual daytime sedation

Orexin/Hypocretin Receptor Antagonist

Daridorexant- 2

- Indication: For the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- FDA approved in 2022
- Contraindication: narcolepsy
- Adverse reactions: somnolence or fatigue, headache
- Schedule IV controlled substance

	LEMBOREXANT	SUVOREXANT	DARIDOREXANT
Approval	2019	2014	2022
Indication	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance	Difficulty with sleep onset and/or sleep maintenance
Available doses	5, 10	5, 10, 15, 20	25, 50
Contraindications	Narcolepsy	Narcolepsy	Narcolepsy
Most common adverse reaction	Somnolence	Somnolence	Headache, fatigue, somnolence
Pharmacokinetics Half-life (hours)	17, 19	12	8
DEA Schedule	IV	IV	IV

Available DORAs: Warnings and Precautions

Suvorexant

- CNS depressant effects and daytime impairment
- Worsening of depression/suicidal ideation
- Complex sleep behaviors
- Sleep paralysis, hypnagogic hallucinations, and cataplexy-like symptoms
- Compromised respiratory function
- Need to evaluate for comorbid diagnoses

Lemborexant

Daridorexant

Same

Suvorexant: Adverse Reactions*

	Placebo (n=767) %	Suvorexant 15 mg in elderly 20 mg in non-elderly (n=493) %
Diarrhea	1	2
Dry mouth	1	2
Upper respiratory infection	1	2
Headache	6	7
Somnolence	3	7
Dizziness	2	3
Abnormal dreams	1	2
Cough	1	2

*Reported in $\geq 2\%$ of suvorexant-treated patients + at a frequency > than placebo-treated patients – clinical trials: [90 days](#)
Belsomra Prescribing Information, 2023.

Lemborexant: Adverse Reactions*

	Placebo (n=528) %	Lemborexant 5 mg (n=580) %	Lemborexant 10 mg (n=582) %
Somnolence, lethargy, fatigue, or sluggishness	1.3	6.9	9.6
Headache	3.4	5.9	4.5
Nightmare or abnormal dreams	0.9	0.9	2.2

*Reported in $\geq 2\%$ of lemborexant-treated patients + at a frequency > than placebo-treated patients – clinical trials: [1st 30 days](#)
Dayvigo Prescribing Information, 2023.

Daridorexant: Adverse Reactions*

	Placebo (n=309) %	Daridorexant 25 mg (n=310) %	Dardiorexant 50 mg (n=308) %
Headache, migraine	5	6	7
Somnolence, fatigue, sedation, lethargy, hypersomnia	4	6	5
Dizziness	2	2	3
Nausea, vomiting	2	0	3

*Reported in $\geq 2\%$ of daridorexant-treated patients + at a frequency > than placebo-treated patients (3-month clinical trial)
Quviviq Prescribing Information, 2023.

Why are DORAs Controlled Substances?

- Abuse liability determined by “drug liking” studies with daytime doses given to recreational sedative drug users
- No physical dependence or withdrawal effects
- Orexins have a central role in neural reward circuitry
- Research supports potential therapeutic benefits of DORA in the treatment of substance use disorders
 - Cocaine
 - Opioids
 - Alcohol
 - Nicotine
 - Cannabinoids

