



TEXAS A&M

HEALTH SCIENCE CENTER

COLLEGE OF MEDICINE



# ***Ambien<sup>®</sup>, A Molecular Pharmacology of Sleep: Special Considerations for Parkinson's Medications?***

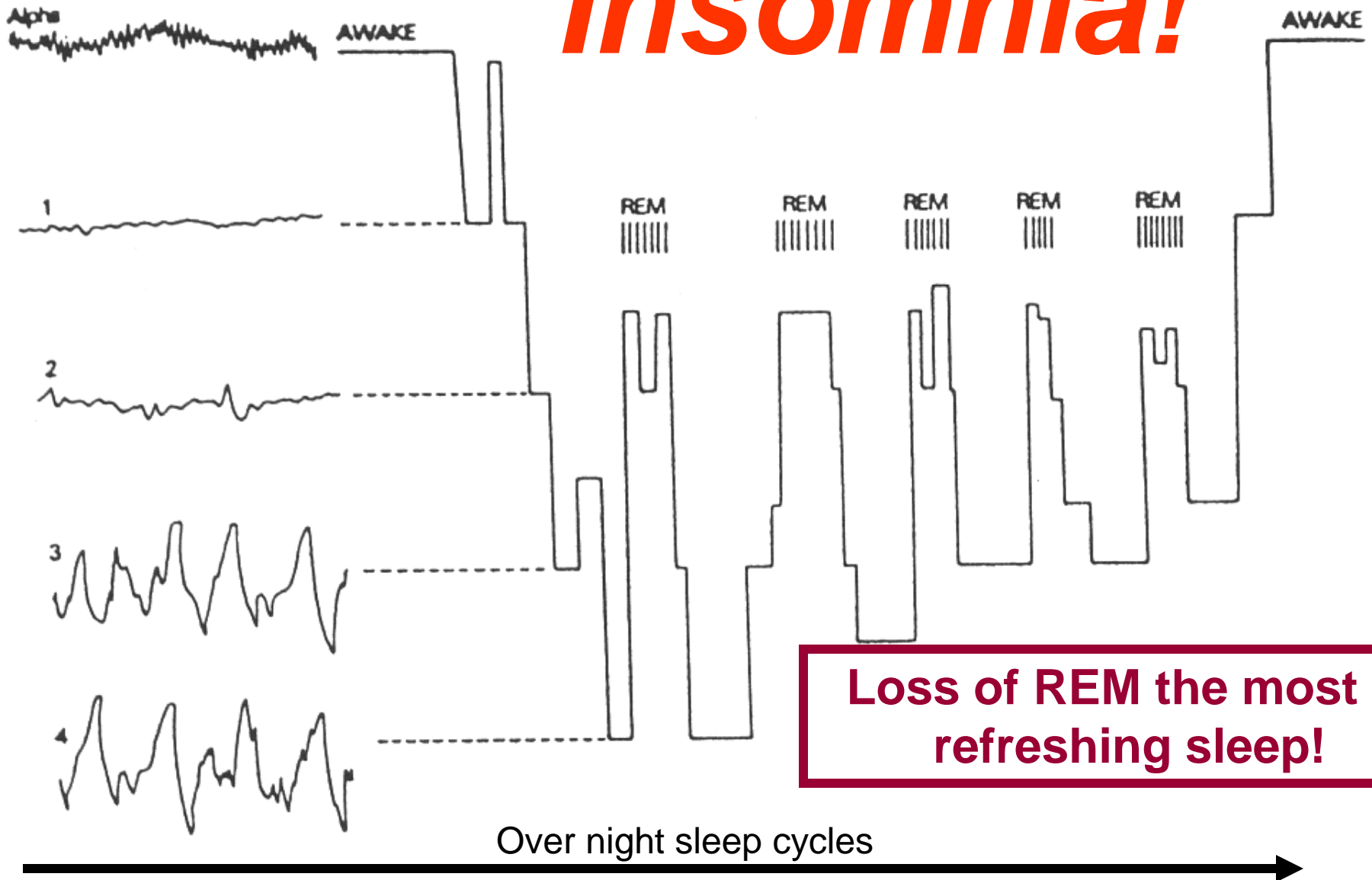
Gerald D. Frye, Ph.D.

Joseph H. Shelton Professor  
Neuroscience & Experimental Therapeutics (NExT)

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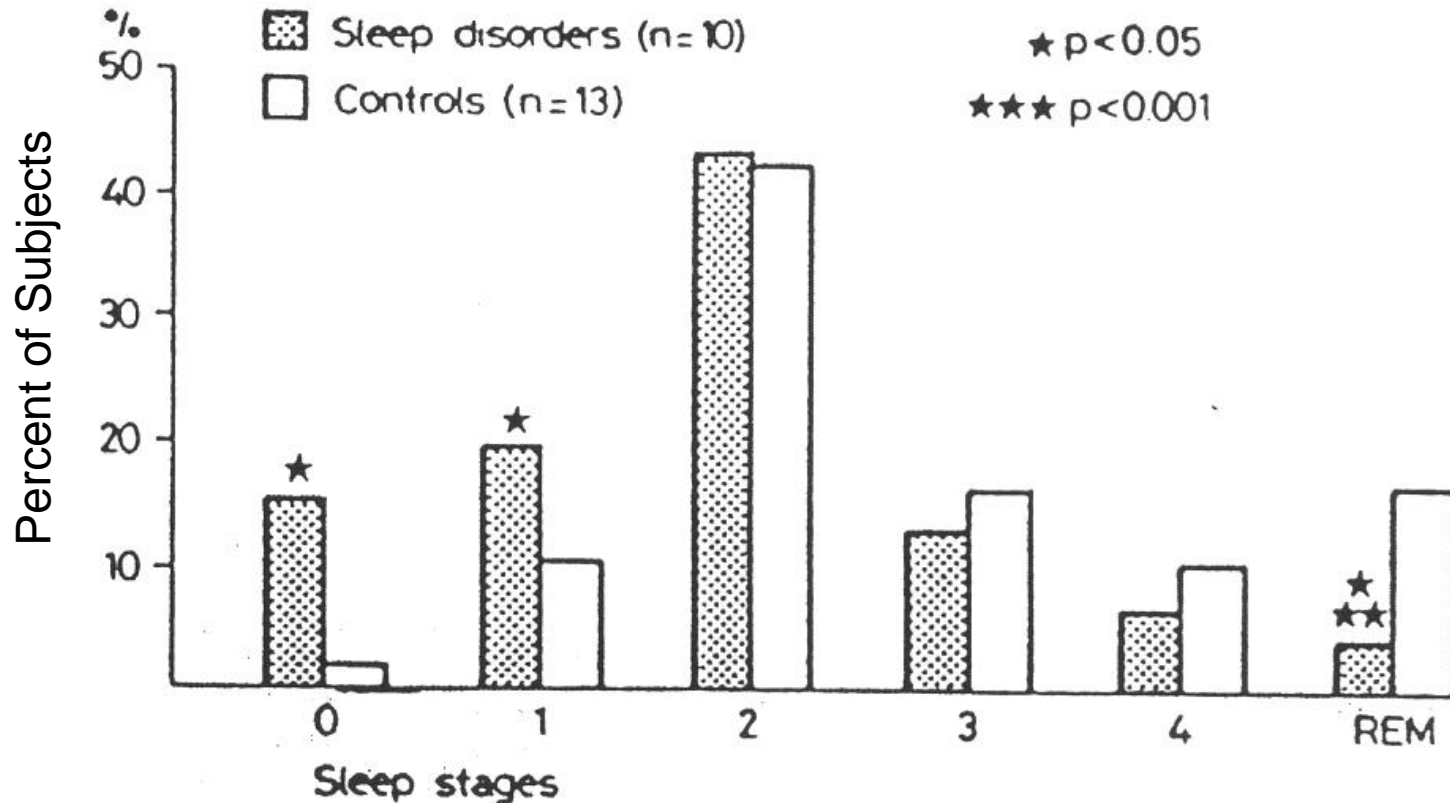
# Insomnia!



- Insomnia - - often secondary to other problems

# Sedative-Hypnotic Drugs

Intended to relax / induce drowsiness / sleep



Ideally without depressing brain function

# MAIN DRUGS USED TODAY

## Benzodiazepines (BZs)

**flurazepam** (Dalmane)  
**quazepam** (Doral)  
**temazepam** (Restoril)  
**triazolam** (Halcion)  
**estazolam** (ProSom)

## Barbiturates

**amobarbital** (Amytal)  
**phenobarbital** (Luminol)  
**pentobarbital** (Nembutal)  
**secobarbital** (Seconal)

**GABA<sub>A</sub>R  
activators**

## Non-benzodiazepine BZ agonists

**zolpidem** (Ambien +  
Ambien CR)  
**eszopiclone** (Lunesta)  
**zaleplon** (Sonata)

**Sleep  
Aids**

**\*\* FDA approved 2005 \*\***

**ramelteon** (Rozerem)  
melatonin MT<sub>1/2</sub> receptors

# Miscellaneous Sedative Drugs

## **Classic H1 Antihistamines & OTC sleeping aids**

diphenhydramine (Benadryl)

hydroxyzine (Atarax).

## **Older Antidepressants – H<sub>1</sub> blocker sedative side-effects**

trazadone (Desyrel) used in those suffering depression and insomnia.

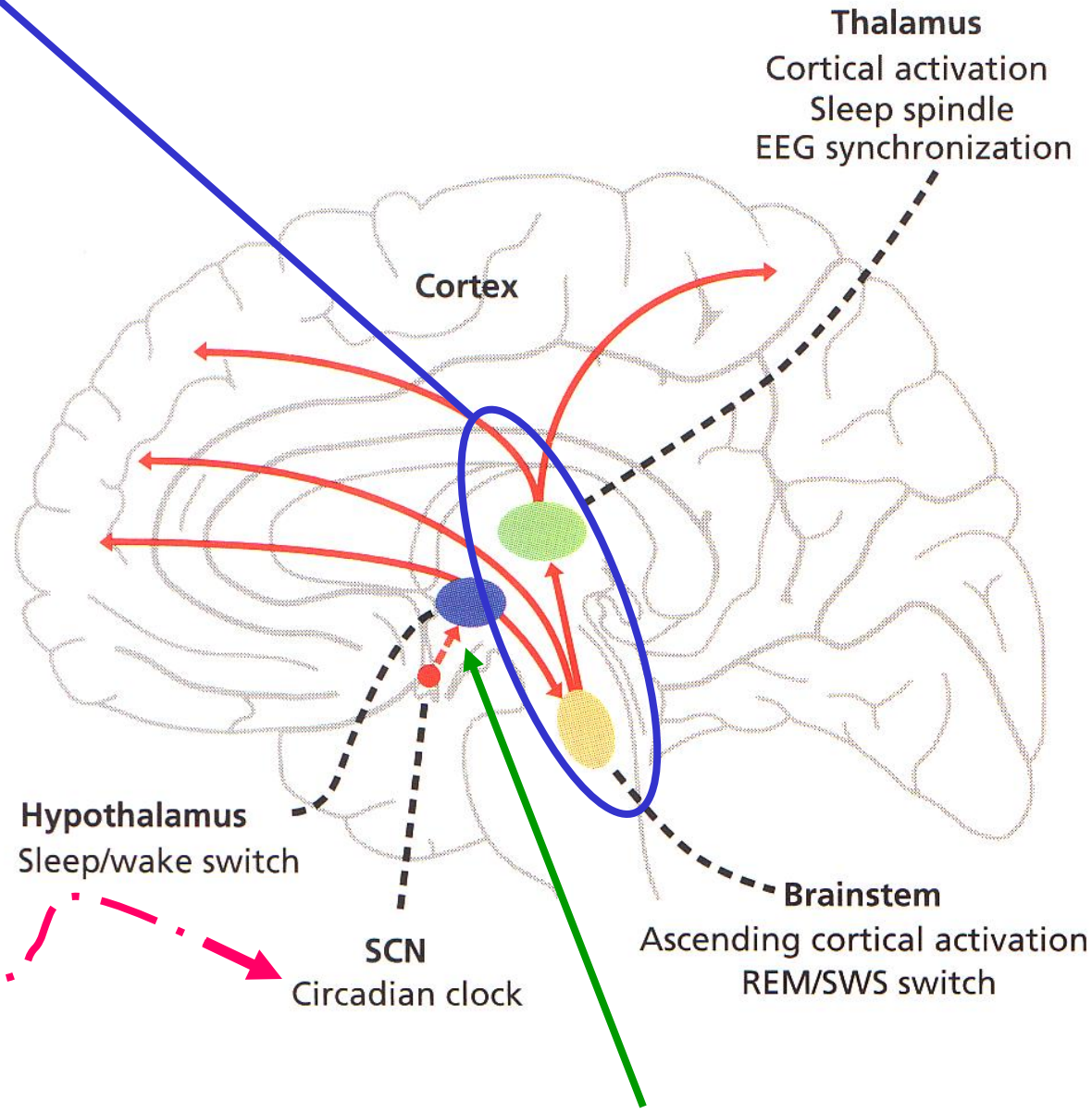
## **Dietary supplements (not FDA approved)**

Valerian root enhance sleep (few side-effects) but at what dose?

Kava root has sedative effects / liver toxicity concerns.

GABA<sub>A</sub>R activators

dampen  
ascending  
arousal  
system



Ramelteon  
activates SCN  
and resets  
circadian rhythm?

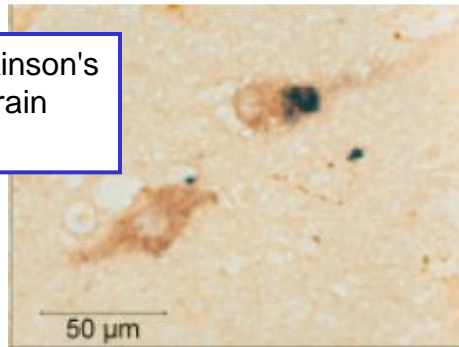
Diphenhydramine blocks H1 histamine receptors in hypothalamus?

**Narcolepsy** - rapid onset day-time sleep disorder - also poor night-time sleep patterns. Neurons using the transmitter **hypocretin (orexin)** are lost from the lateral hypothalamus - - none in cerebrospinal fluid (CSF)

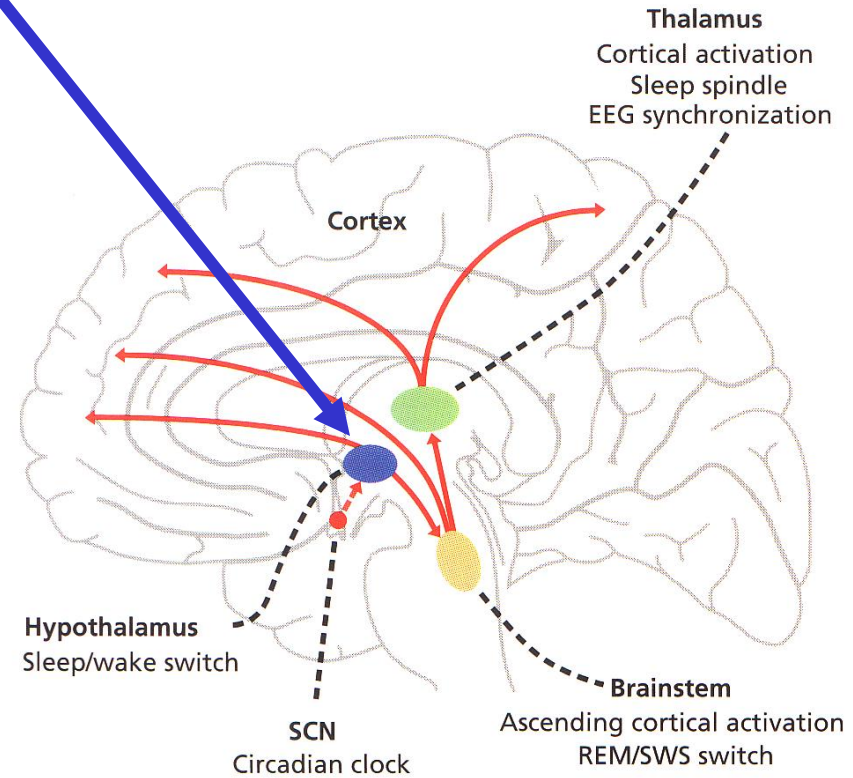
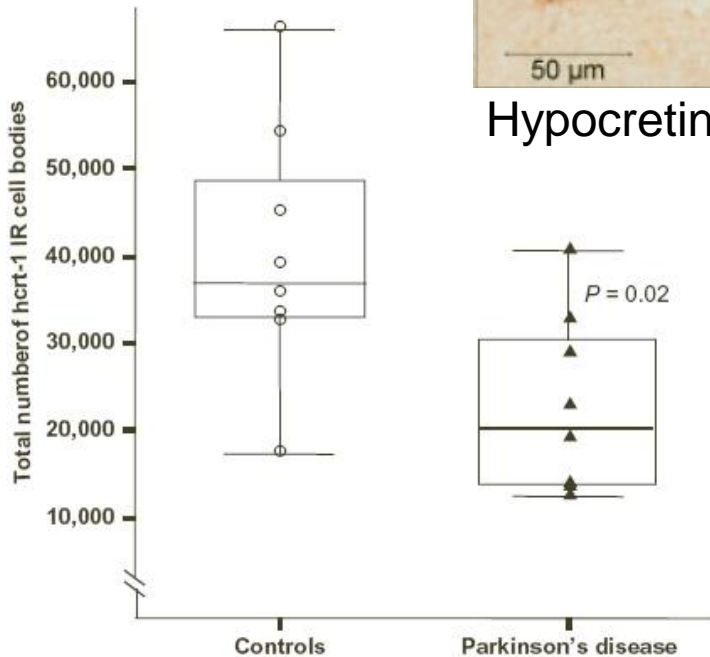
Many Parkinson's suffers experience excessive day-time sleepiness / sleep attacks - □ also insomnia at night.

Some Parkinson's suffers may loose hypocretin (orexin) neurons?

"Hypocretin (orexin) loss in Parkinson's disease", Fronczek et al., Brain 130:1577-1585, 2007



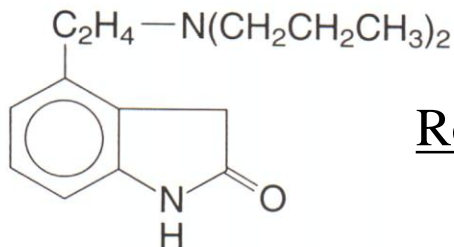
Hypocretin neurons



gamma-hydroxybutyrate (GHB) Xyrem<sup>®</sup> is FDA approved for Narcolepsy - but controversial - known as a 'date-rape' drug

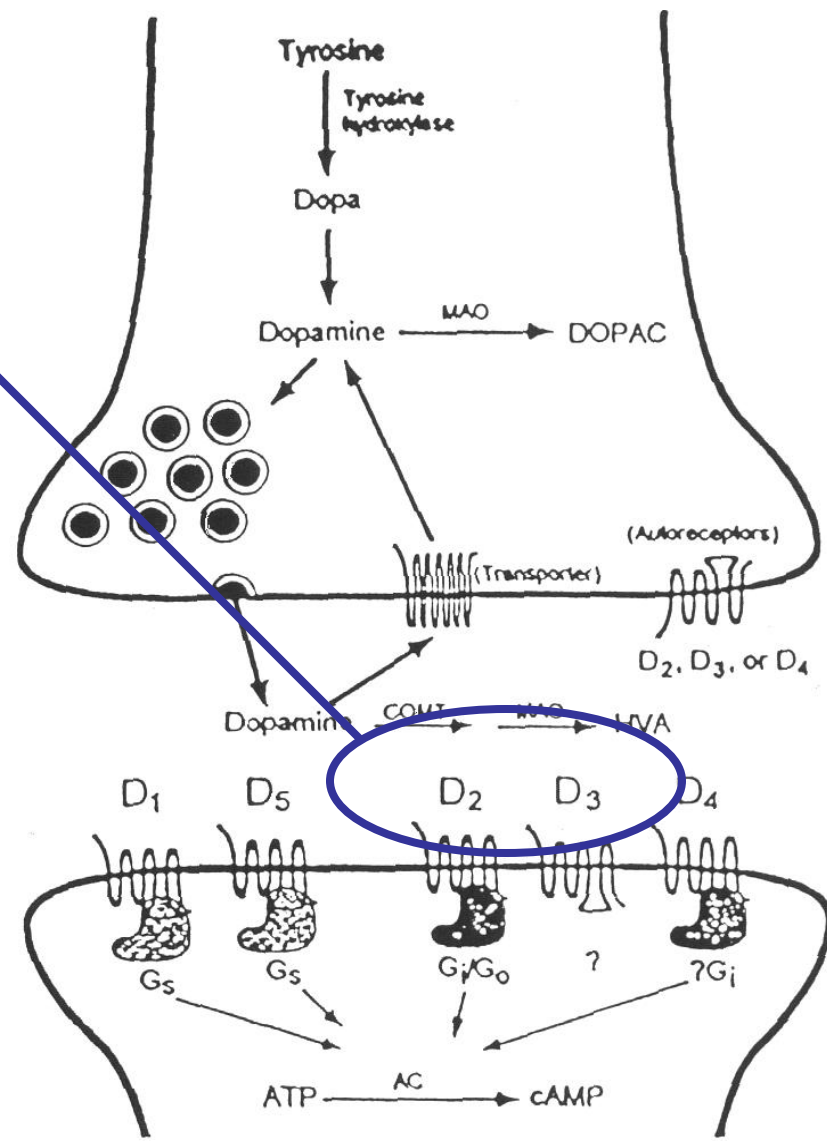
# NEW FDA APPROVAL – sleep aid?

## Dopamine D<sub>2</sub> / D<sub>3</sub> Agonist



Ropinirole (Requip;  
ReQuip CR -  
controlled-release) is  
largely metabolized  
with 1/2 life ~ 6 hrs

**Parkinson's drug** now FDA approved *for use in moderate to severe "Restless Legs Syndrome"* is characterized by an urge to move the legs to relieve discomfort or pain. Disturbs sleep and occurs more frequently in women, increasing with age.



# Another NEW FDA APPROVAL – sleep aid?

## Dopamine D<sub>2</sub> / D<sub>3</sub> Agonist

Neupro® Approved May 2007 from Europe

(Rotigotine Transdermal System)

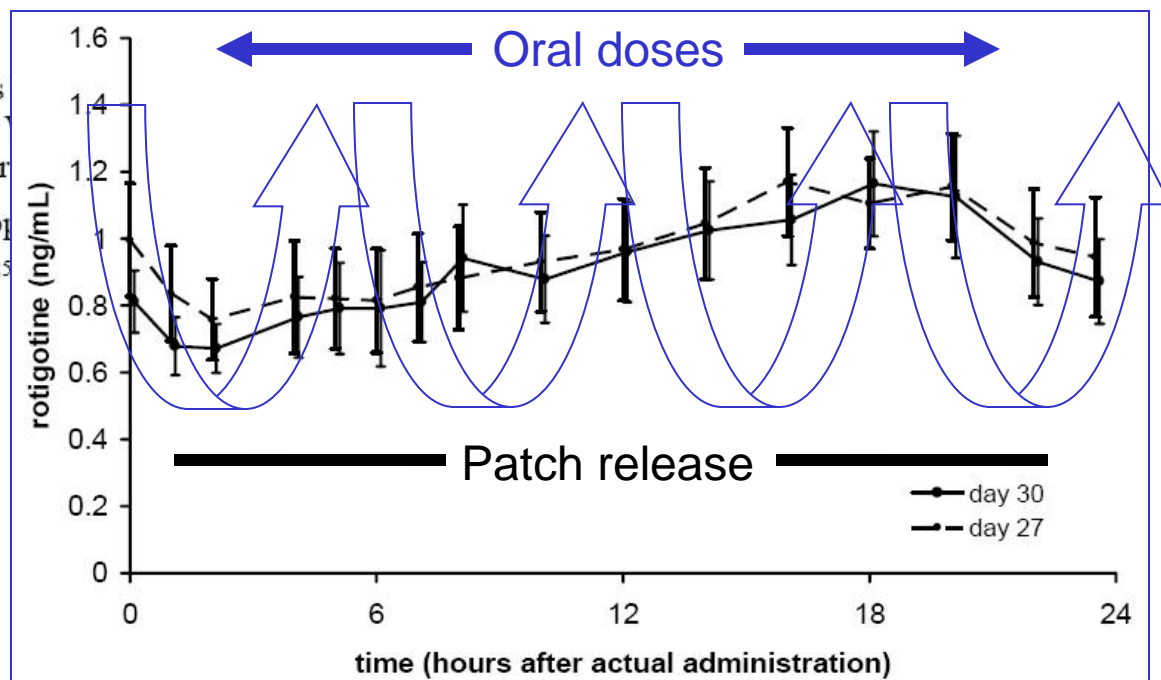
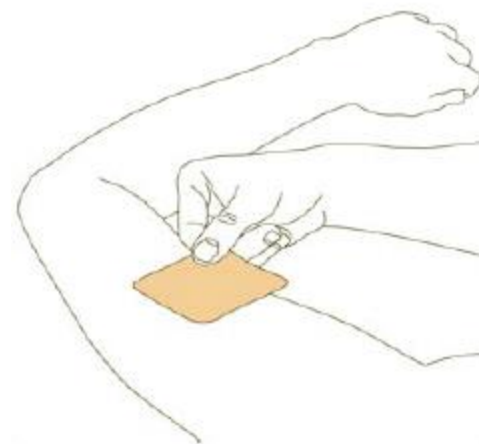
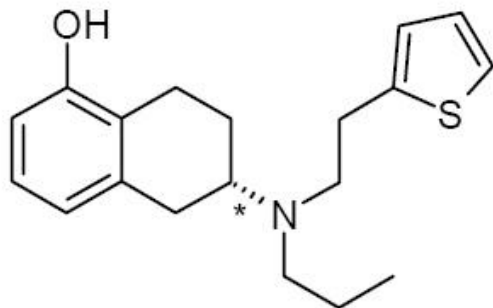
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx Only

### DESCRIPTION

Neupro® (Rotigotine Transdermal System) is rotigotine, a non-ergolinic dopamine agonist, continuously deliver rotigotine over a 24-hour

The chemical name of rotigotine is (6S)-6-{prop naphthalenol. The empirical formula is C<sub>19</sub>H<sub>25</sub> structural formula for rotigotine is:



Transdermal Systems - a more steady release of drug – may reduce side-effects from fluctuating blood levels

**Table 5 Treatment-Emergent Adverse Event (Regardless of Causal Relationship) Incidence in Double-Blind, Placebo-Controlled Early-Stage Parkinson's Disease Studies (Events  $\geq 2\%$  of Subjects Treated with Neupro and Numerically More Frequent Than in the Placebo Group)**

<b>Body system/preferred term</b>	<b>Placebo N=289 (%)</b>	<b>Neupro N=649 (%)</b>
Application site reactions	14	37
Psychiatric		
Somnolence	16	25
Insomnia	5	10

**Tell your doctor if you drink alcohol**

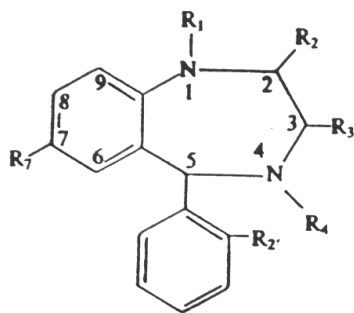
Alcohol should be avoided while using NEUPRO. ALCOHOL and NEUPRO can interact and increase your chance of being sleepy or falling asleep suddenly while doing normal activities.

**Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** Some medicines may affect how NEUPRO works. NEUPRO may also affect how your other medicines work. **Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.**

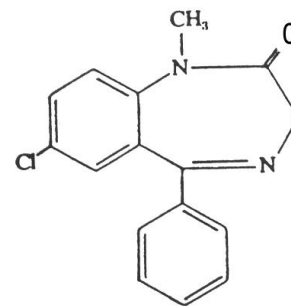
Rotigotine alone increases sleepiness and insomnia – we do not know how Dopamine agonists do this? But can interact with sleep aids!

# Ambien<sup>®</sup>, A Molecular Pharmacology of Sleeping -- or -- Forgetting?

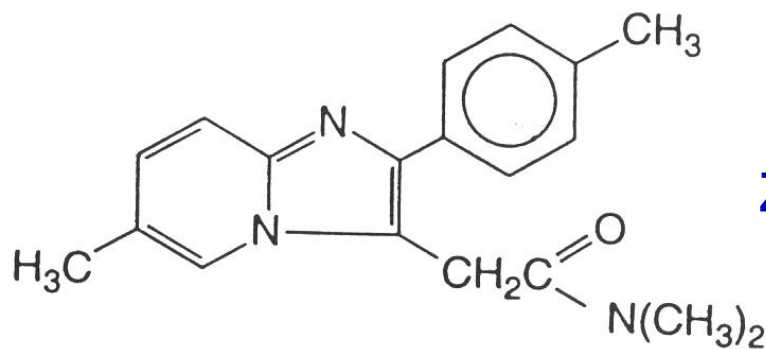
Ambien<sup>®</sup> = zolpidem = non-benzodiazepine BZ agonist



1,4-benzodiazepine nucleus



diazepam = Valium<sup>®</sup>



zolpidem = Ambien<sup>®</sup>

non-benzodiazepine benzodiazepine agonists

Learn more about the card.

# Alcohol, Ambien® & Amnesia: Windows Home Server A Molecular Pharmacology of Forgetting?



Welcome to the Center for  
Digital Amnesia Awareness Web Site

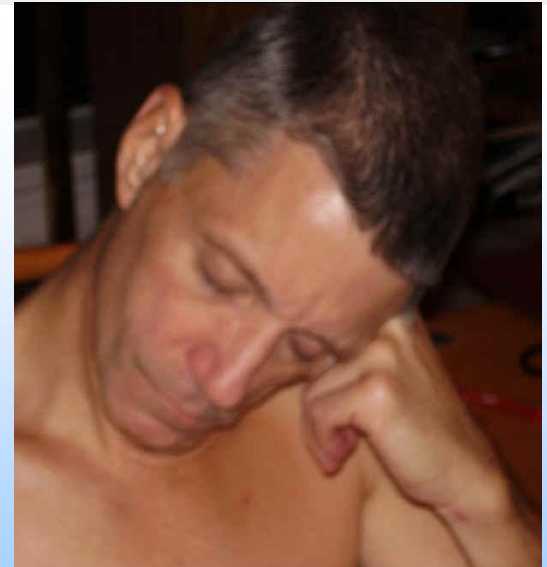
> HOW TO TELL IF YOU HAVE DIGITAL AMNESIA.

***THINK Macaroon!***

Mun ching ma ca roons

Un der spell of Am bi en®

Am bi en® bed yet?



GET THE FACTS  
Click here ▶

FOR U.S. RESIDENTS ONLY

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**AMBIENCR**<sup>™</sup>  
[ZOLPIDEM TARTRATE EXTENDED RELEASE] <sup>Ⓒ</sup>  
6.25-MG • 12.5-MG EXTENDED RELEASE TABLETS



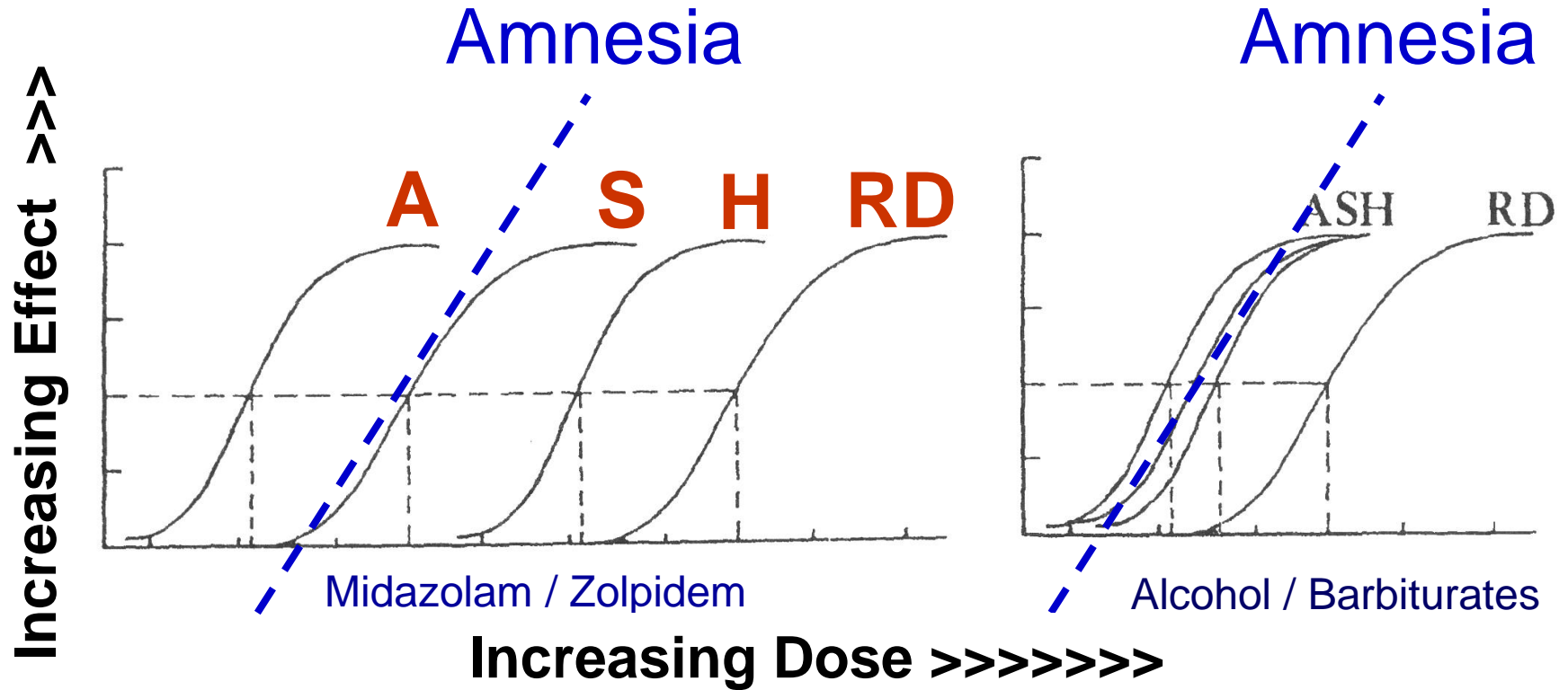
## 6 ADVERSE REACTIONS

Serious adverse reactions including severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavior, complex behaviors, withdrawal effects, amnesia, anxiety, other neuro-psychiatric symptoms, and CNS depression effects have been reported with zolpidem. For

“ [“sleep-driving” (ie., driving while not fully awake . . . . . Due to the risk to the patient and the community, discontinuation of Ambien should be strongly considered for patients who report a “sleep-driving” episode.] ”

*Sanofi Aventis* package insert

# Dose-Dependent CNS Depression



**A**nti-anxiety

**S**edation

**H**ypnosis

**R**espiratory **D**epression

# Ambien® and alcohol unplug – unbind the wandering mind?

## Wandering Minds: The Default Network and Stimulus-Independent Thought

Malia F. Mason,<sup>1\*§</sup> Michael I. Norton,<sup>2</sup> John D. Van Horn,<sup>1†</sup> Daniel M. Wegner,<sup>3</sup>  
Scott T. Grafton,<sup>1‡</sup> C. Neil Macrae<sup>4</sup>

Despite evidence pointing to a ubiquitous tendency of human minds to wander, little is known about the neural operations that support this core component of human cognition. Using both thought sampling and brain imaging, the current investigation demonstrated that mind-wandering is associated with activity in a default network of cortical regions that are active when the brain is “at rest.” In addition, individuals’ reports of the tendency of their minds to wander were correlated with activity in this network.

[Science. 2007 Jul 6;317\(5834\):43](#)

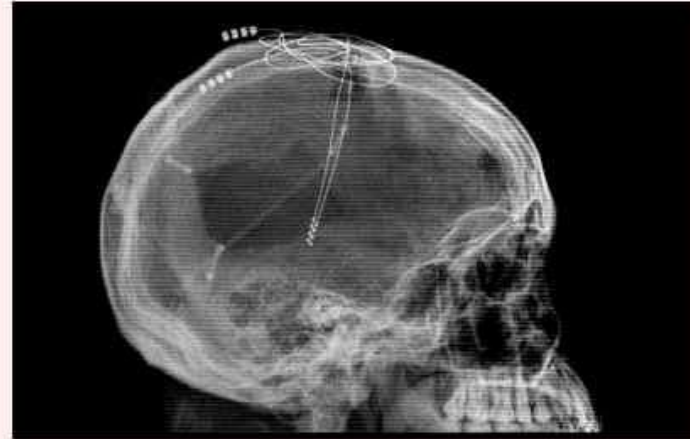
*Nature* 448, 522 (2 August 2007) | doi:10.1038/448522a; Published online 1 August 2007

### Implant boosts activity in injured brain

Michael Hopkin

Deep-brain stimulation offers hope for minimally conscious patients.

▲ Top



CLEVELAND CLINIC

Deep-brain stimulation might help trauma patients regain consciousness.

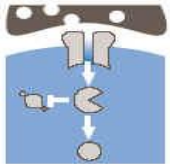
[Nature 448:522 \(8-2-07\)](#)

# Collective Consciousness / Contextual Memory – Is Unbound by Alcohol and Ambien®



Unifying processes are the culmination of the interweaving of multiple brain / mind neurocircuits that are the fabric of our focus, intelligence and understanding.

Molecules



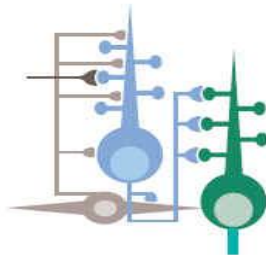
Synapse



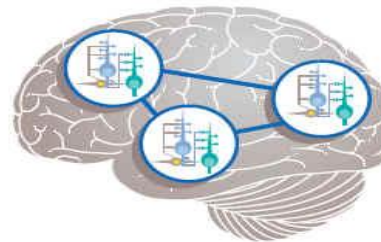
Neuron



Circuit



Networks



“Amnesia” from alcohol or zolpidem is the pulling a single molecular thread that unravels the tapestry of collective consciousness.

