

Sleep and sleep disorders in patients with traumatic brain injury

J. Steven Poceta, MD
Consultant, Scripps Clinic Sleep Center
Head, Division of Neurology

Faculty Disclosure

Company	Nature of Affiliation	Unlabeled Product Usage
<ul style="list-style-type: none">GSKCephalon-Teva	<ul style="list-style-type: none">Speaker's Bureau	<ul style="list-style-type: none">None

Review papers

Sleep Disorders in Patients with Traumatic Brain Injury; A Review

Richard Castriotta and Jayasimha Murthy
University of Texas Health Science Center at Houston
CNS Drugs 2011 25(3): 175–185

Traumatic Brain Injury and Sleep Disturbance: A review of current research

Henry Orff, Liat Ayalon, and Sean Drummund
University of California San Diego
J Head Trauma Rehabil 2009 24(3) 155-165

Problems researching sleep and head injury

- Sleep is adaptable to needs of the organism
- Sleep is affected by multiple environmental factors
- Sleep is affected by psychological and physical maladies
- Sleep is affected by lesions in several brain areas
- Sleep is affected by medications of many types
- Sleep study findings do not always have clinical relevance
- Closed head injuries have multiple mechanisms, degrees of damage, areas of damage, and variable recovery

Problems researching sleep and head injury

Two way effects:

1. Head injury damages neurologic structures directly, affects physical and psychological mechanisms, and thus can produce poor quality sleep, insomnia, daytime sleepiness, or altered timing of sleep.
2. Sleep disorders can increase risk of head injury
3. Co-existent sleep disorders, either independent or secondary, can affect recovery from head injury.

Sleep disorders in TBI

Symptoms of mild TBI:

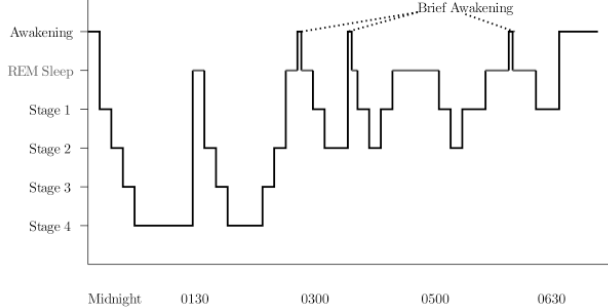
- Headache, confusion, lightheadedness, dizziness, blurred vision, tinnitus, fatigue or lethargy, change in sleep patterns, behavioral or mood changes, trouble with memory, concentration, attention, or thinking.

Moderate to severe TBI:

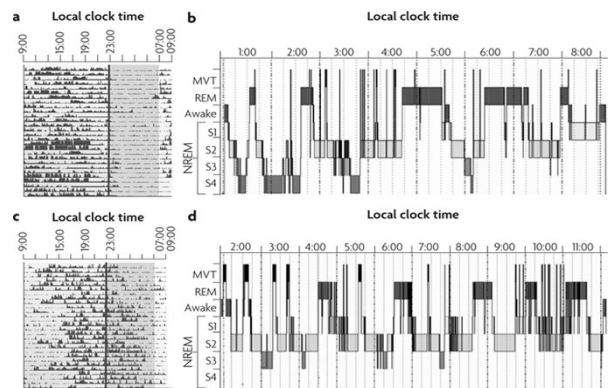
- Worsening headaches, nausea and vomiting, seizures, inability to awaken, dilation of pupils, slurred speech, weakness and numbness of extremities, ataxia, confusion, restlessness, agitation.

Normal sleep architecture

Hypnogram

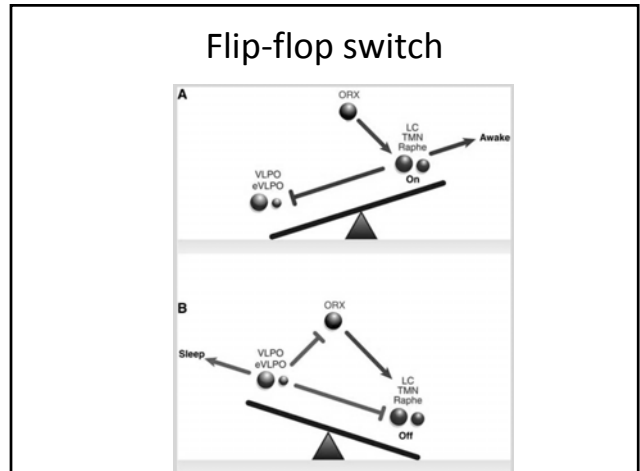
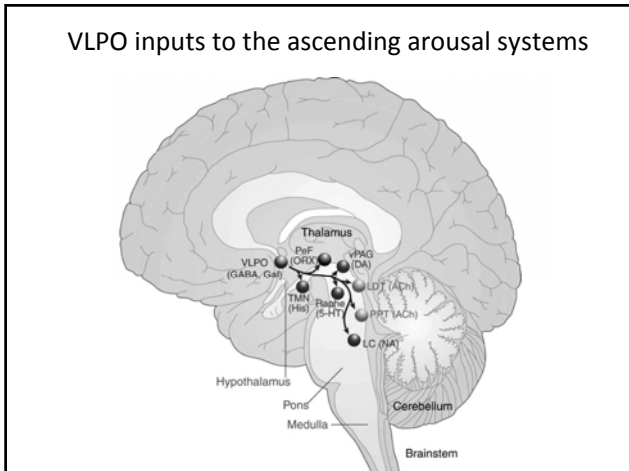
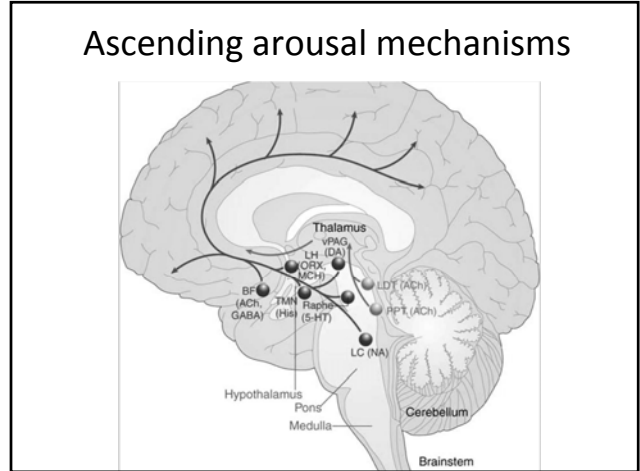
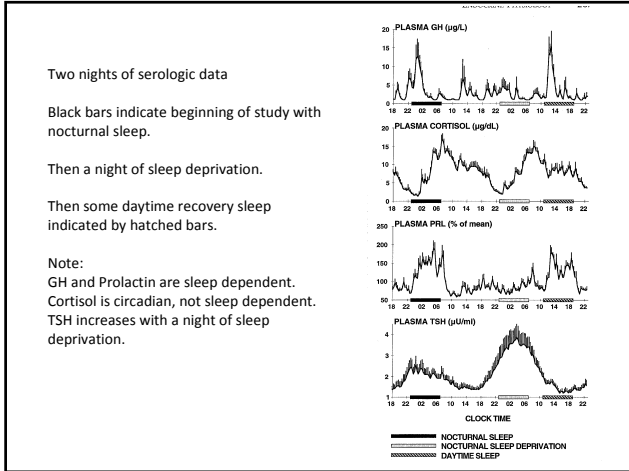


Actigraphy and Sleep stages



Traumatic Brain Injury and Sleep Disturbances

J. Steven Poceta, MD



Traumatic Brain Injury and Sleep Disturbances

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Sleep-Wake Cycle and the Suprachiasmatic Nucleus (SCN)

Wake¹⁻³

- During the day, SCN activity promotes arousal
- Maintains state of wakefulness

Sleep^{1,2}

- At night, SCN arousal is attenuated
- Allows normal sleep to occur

1. Lavie P. Annu Rev Psychol. 2001;52:277-303. 2. Monk TH, Welsh DK. Sleep Med Rev. 2003;7:455-473.
3. Edgar DM et al. J Neuroscience. 1993;13:1065-1079.

Circadian Rhythms and the Suprachiasmatic Nucleus (SCN)

Melatonin (N-acetyl-5-methoxytryptamine)

CC(=O)Nc1ccc(OC)cc1

Adapted from Brzezinski A. N Engl J Med. 1997;336:186-195.

Transition From Wake to Sleep: An Integrated View

DAYLIGHT

SCN ⊕ → Sleep Pathways ⊖

SCN ⊕ → Wake Pathways ⊕

NIGHT

Melatonin ⊕ → Sleep Pathways ⊕

Melatonin ⊖ → Wake Pathways ⊖

Sleep disorders in TBI

- Sleep disturbance: 30 to 70 % of all TBI cases.
- Possibly impedes rehabilitation process and ability to return to work.
- Mild TBI more frequently associated with sleep disturbance than severe TBI.

Sleep disturbance and TBI

TBI can cause:

1. Insomnia (less sleep)
2. Excessive daytime sleepiness (more sleep)
3. Specific sleep disorder (OSA, RLS)
4. Circadian rhythm disturbance

Sleep disturbance and TBI

- TBI and subjectively reported sleep disturbance: 12 studies
- TBI and objectively measured sleep disturbance: 11 studies
- TBI and circadian rhythm changes: 4 studies
- 36 % of TBI patients referred for insomnia had delayed sleep phase disorder (DSPD)

Subjective insomnia and TBI

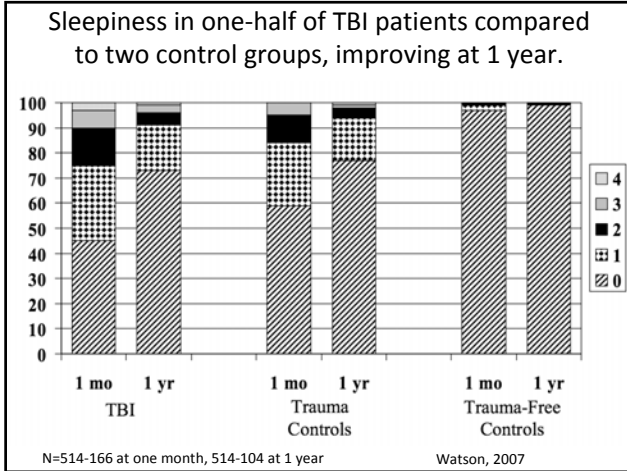
Ouellet, 2006:

- Survey of 452 TBI patients on average 8 years after injury
- Insomnia in 50 %
- Met insomnia diagnostic criteria: 29 %
- Severe, chronic, and untreated in 60 %
- Insomnia associated with milder TBI's, higher levels of fatigue, depression, and pain. Assault victims worse than other CHI patients

Sleepiness and TBI

Fatigue or EDS:

- 25 to 47 % of TBI patients have elevated ESS indicating significant daytime sleepiness, compared with 5 to 15 % in general population.
- Post-traumatic narcolepsy (based on sleep testing) in 6 to 32 %.
- Objective sleep data less convincing, consistent with literature in non-TBI insomnia and sleepiness.



Sleep and sustained attention in TBI

Table 1. Characteristics of whole sample, and good and poor sleep groups

Variable	Whole sample (n = 44)	Good sleep group (n = 15)	Poor sleep group (n = 11)
Age	46 (55)	51 (51)	44 (41)
Gender	38 males, 6 females	13 males, 2 females	10 males, 1 females
WTAR	97 (72)	97 (57)	96 (51)
WASI	98 (62)	107 (38)	90 (53)
Time since TBI	71.5 (482)	48 (482)	124.5 (269)
TBI Mechanism	Fall = 10 RTA = 25 Assault = 5 Other = 4	Fall = 6 RTA = 9	Fall = 1 RTA = 5 Assault = 3 Other = 2
TBI - severity	Mild = 5 Moderate = 9 Severe = 30	Moderate = 3 Severe = 12	Mild = 2 Moderate = 3 Severe = 6

Note. Median and range are reported where appropriate.
n = number; WTAR = The Wechsler Test of Adult Reading; WASI = The Wechsler Abbreviated Scale of Intelligence; RTA = Road Traffic Accident; TBI = traumatic brain injury.

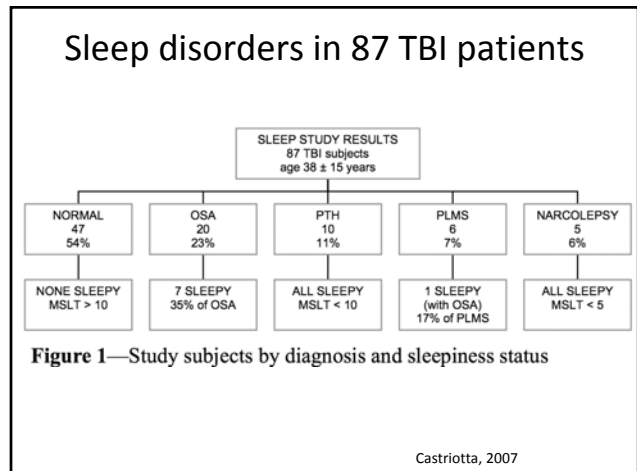
Bloomfield, 2010

Sleep and sustained attention in TBI

Table 4. Scores on cognitive measures for the good and poor sleep groups

Variable	Good sleep group		Poor sleep group		p	r
	Median (R)	Mean (SD)	Median (R)	Mean (SD)		
Primary hypotheses						
SART random commission	9 (16)	10.13 (5.19)	17(20)	15.18 (5.76)	.032	-0.42
SART random mean reaction time	416.2 (205.1)	400.17 (61.2)	315.2 (164.6)	330.02 (53.63)	.009	0.52
Secondary hypotheses						
PASAT total score	61(48)	60.92 (13.15)	47 (65)	54.36 (18.65)	.659	0.2
CFQ	38 (27)	37.73 (7.96)	50 (69)	52.00 (21.23)	.086	-0.41
LNS	9 (13)	8.00 (3.68)	7 (7)	8.45 (2.58)	.734	-0.07
DSS	5(7)	6.5 (2.71)	7 (5)	7.55 (1.75)	.171	-0.224

Note. Median and range (R), mean, standard deviation (SD), Mann-Whitney two-tailed (p), and effect size (r) are reported.
p = p value; SART = Sustained Attention to Response Test; PASAT = Paced Auditory Serial Attention Test; CFQ = Cognitive Failures Questionnaire; LNS = letter number sequencing; DSS = digit symbol substitution.



Treatment of sleep disorders in TBI

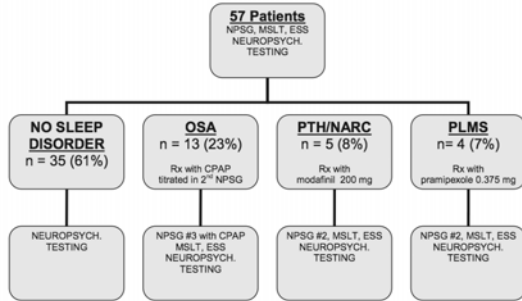


Figure 1—Flow of study participants. OSA = obstructive sleep apnea; PTH = post-traumatic hypersomnia; NARC = narcolepsy; PLMS = periodic limb movements in sleep; NPSG = nocturnal polysomnography; MSLT = multiple sleep latency test; CPAP = continuous positive airway pressure.

Castriotta, 2009

Table 2—Demographic Data for the TBI Patients with and without Sleep Disorders

	NO SLEEP DISORDER N (%)	SLEEP DISORDER N (%)
N	35	22
Sex		
Male	25 (44)	16 (11)
Female	10 (17)	6 (28)
Race		
Caucasian	27 (47)	17 (30)
African American	5 (9)	3 (5)
Hispanic	3 (5)	2 (4)
Cause of Injury		
Assault	2 (4)	2 (4)
Auto/Vehicle	29 (51)	15 (26)
Fall	3 (5)	2 (4)
Hit by Falling Object	1 (6)	3 (5)
CT Scan Findings		
Unknown	12 (21)	11 (19)
Negative	6 (11)	0 (0)
Positive	17 (30)	11 (19)
Brain Injury Severity		
Unknown	11 (50)	11 (53)
Mild	5	
Moderate	2 (12)	1 (6)
Moderate/Severe	9 (19)	1 (5)
Severe	8 (19)	9 (26)

Treatment of sleep disorders did little to improve quality of life, cognitive, or vigilance measures

RJ Castriotta, S Atanasov, MC Wilde et al

Table 1—Sleep Study Data for TBI Patients with Sleep Disorders

	OSA				NAR PTH				PLM			
	aRx		pRx		aRx		pRx		aRx		pRx	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
TST	5.9	1.5	6.1	1.1	7.0	0.7	6.6	0.6	5.7	1.8	6.3	0.5
ESS	12.2	6.2	13.0	6.4	7.8	3.6	6.4	5.0	17.0	2.0	8.5	2.1
%N1	15.8	12.3	12.3	8.3	11.6	3.5	11.0	6.6	8.7	2.6	8.6	4.4
%N2	61.4	11.7	63.7	13.6	62.2	21.6	58.4	17.7	69.8	13.0	74.8	7.6
%N3	3.8	8.8	4.7	8.4	9.2	8.1	10.6	13.2	7.8	7.5	5.7	6.0
%REM	20.3	9.8	19.2	9.8	18.4	1.8	19.6	6.8	13.5	10.1	10.9	8.5
SL	50.9	127	25.7	37.1	10.3	10.4	27.6	39.6	38.9	50.3	9.0	6.9
SOREM	1.42	3.1	0.8	2.6	2.4	3.1	0.6	0.9	3.0	6.0	2.6	5.3
AHI	31.4*	21.5	3.8*	3.7	0.8	1.3	1.6	1.3	1.2	1.7	2.9	3.2
PLMI	9.9	17.1	19.8	28.8	1.8	3.5	1.8	4.0	17.7#	7.2	1.3#	2.5
MSLT	10.3	6.2	12.1	5.1	5.7	1.7	9.3	6.9	13.1	3.6	13.2	7.7

BUT:

N was small, unselected group, fixed regimens of treatments, improper outcome measures

How does TBI cause sleep disturbance?

Pathophysiology:

- Hypothalamic injury and decreased CSF hypocretin-1 and histamine levels
- Psychological trauma, depression, pain
- Injury to SCN or thalamus; hospitalization; loss of environmental cues
- Melatonin

TBI, sleep, melatonin

Table 1 Participant characteristics

Parameter	TBI group	Control group
No.	23	23
Gender, M/F	17/6	17/6
Age, y, mean \pm SD (range)	32.5 \pm 12.0 (19-63)	31.6 \pm 11.6 (19-63)
Days postinjury, mean \pm SD (range)	429.7 \pm 287.6 (74-1,194)	—
Duration of PTA, d, mean \pm SD (range)	29.7 \pm 29.9 (1-119)	—
Glasgow Coma Scale, mean \pm SD (range)	8.8 \pm 3.7 (3-14)	—

Shekleton, 2010

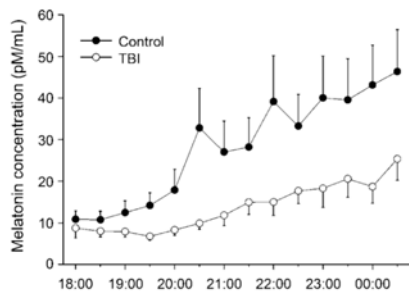
TBI, sleep, melatonin

Table 2 Self-reported sleep quality, sleep timing, and psychopathology measures

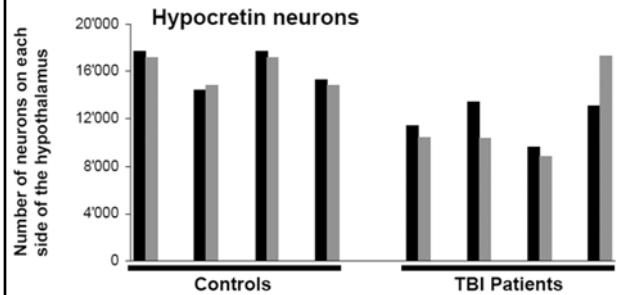
Measure	TBI group, mean \pm SD	Control group, mean \pm SD
PSQI	9.2 \pm 5.0 ^a	4.3 \pm 2.0
MEQ	52.0 \pm 13.0	54.3 \pm 10.2
ESS	7.1 \pm 4.1	5.1 \pm 2.8
HADS anxiety	10.1 \pm 6.2 ^a	4.5 \pm 3.2
HADS depression	7.0 \pm 4.4 ^a	2.3 \pm 1.8

TBI, sleep, melatonin

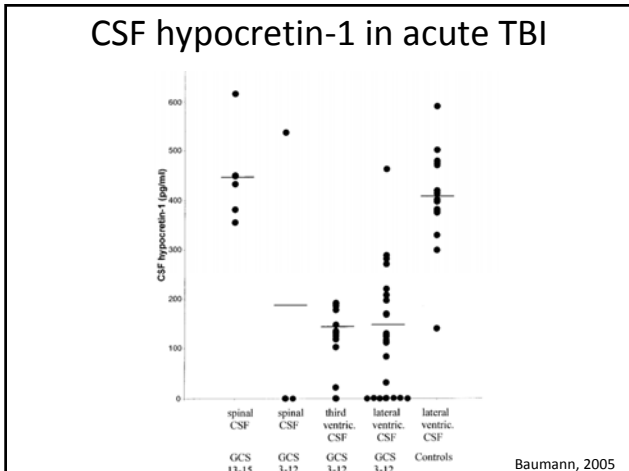
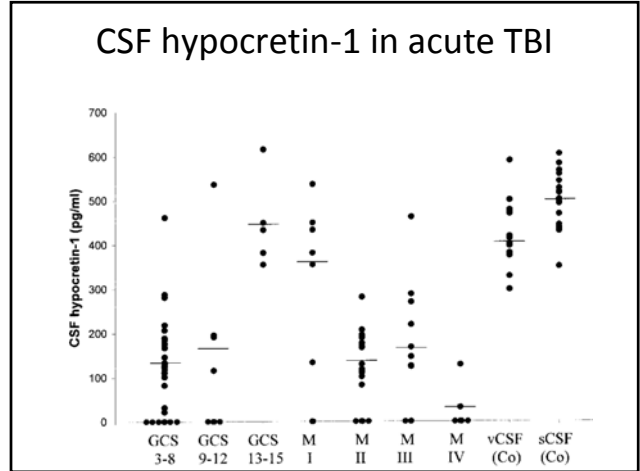
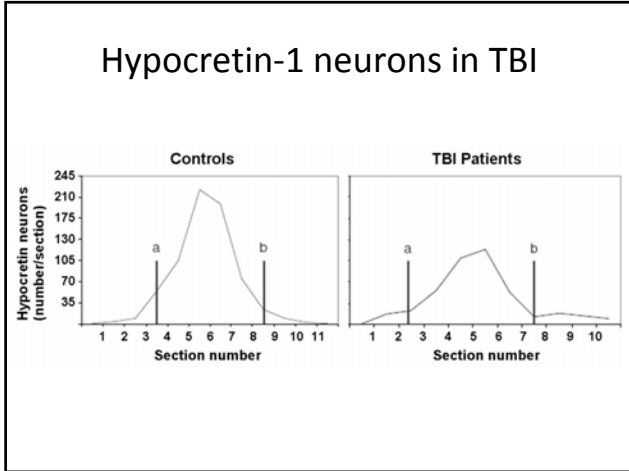
Melatonin levels for traumatic brain injury (TBI) and control groups



Hypocretin-1 neurons in 4 TBI cases



Baumann, 2009



- ### Sleep disorders and TBI
- Diagnosis and treat sleep disorders specifically
 - Screen for:
 - Insomnia's
 - Obstructive sleep apnea
 - Restless legs syndrome and periodic limb movements in sleep
 - Circadian rhythm disorders
 - Anxiety and depression

PTSD and sleep

- PTSD associated with certain types of TBI (military, blast, concussion)
- PTSD associated with sleep disturbance
- PTSD has specific treatments to reduce nightmares and insomnia:
CBT
Desensitization
Prazosin, nefazodone

Germain, 2011

Depression and sleep

- Association of sleep complaints in TBI most highly correlated with depression, anxiety, pain.
- No specific sleep disorder in depression:
 - More, less, sleep onset, sleep offset.

OSA

- Screen any patient who snores regardless of symptoms.
- Treatment trial when medically capable:
 - CPAP
 - Oral appliance
 - Position therapy

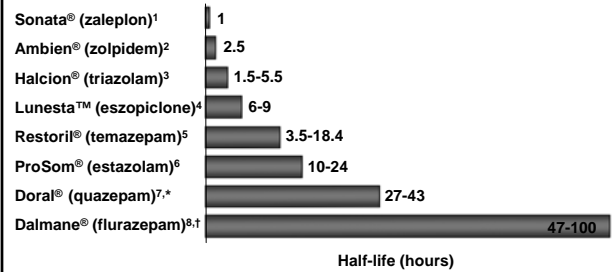
RLS and PLMS

- PLMS can contribute to poor sleep quality and daytime sleepiness
- Several FDA-approved treatments for RLS available which also decrease PLMS:
 - Pramipexole
 - Ropinirole
 - Horizant (gabapentin encarbil)

Insomnia

- Sleep onset, sleep maintenance, sleep offset
- Treat associated depression, anxiety, or other sleep disorder
- Assess timing of sleep
- Try short-acting hypnotics, low-dose sedating antidepressants, mood stabilizers, melatonin agonists (ramelteon)
- CBT when possible

BzRAs Approved for Insomnia



All brand names are the property of their respective owners. 1. Sonata® (zaleplon) package insert. 2. Ambien® (zolpidem) package insert. 3. Halcion® (triazolam) package insert. 4. Lunesta™ (eszopiclone) package insert. 5. Restoril® (temazepam) package insert. 6. ProSom® package insert. 7. Landolt HP, Gillin JC. CNS Drugs. 2000;13:185-199. 8. Dalmane® (flurazepam) package insert.

BzRAs Target GABA Receptors



α_1
 α_2
 α_3

Sieghart W, Sperk G. *Curr Top Med Chem*. 2002.

Circadian rhythms

- DSPD—Delayed sleep phase disorder
- ASPD—Advanced sleep phase disorder
- Free-running or non-24 hour cycle
- Treatments include appropriate timing of bright light and low-dose melatonin

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