

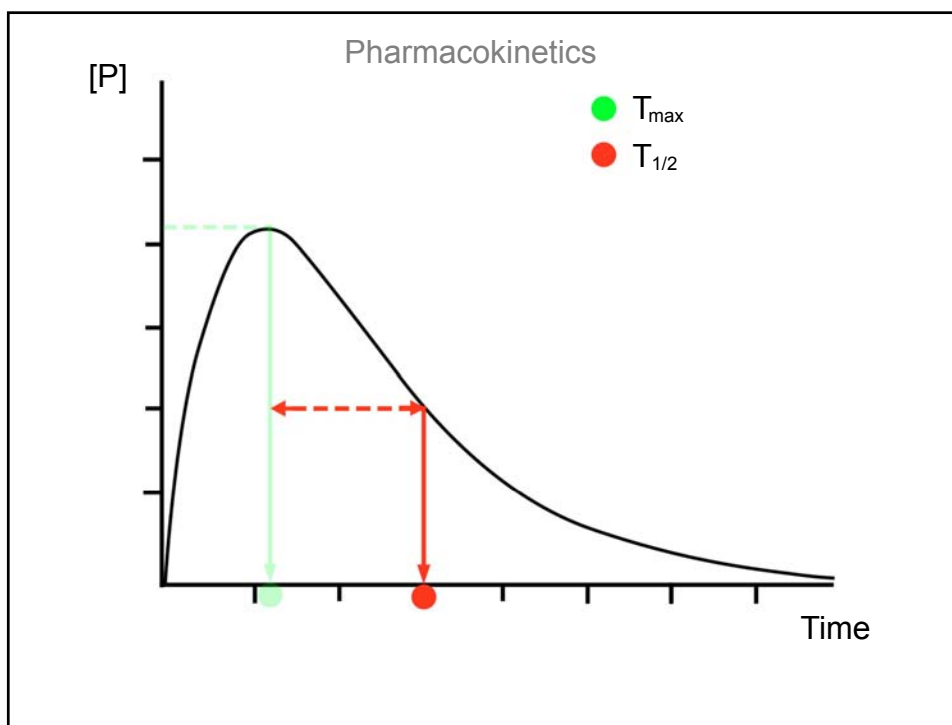
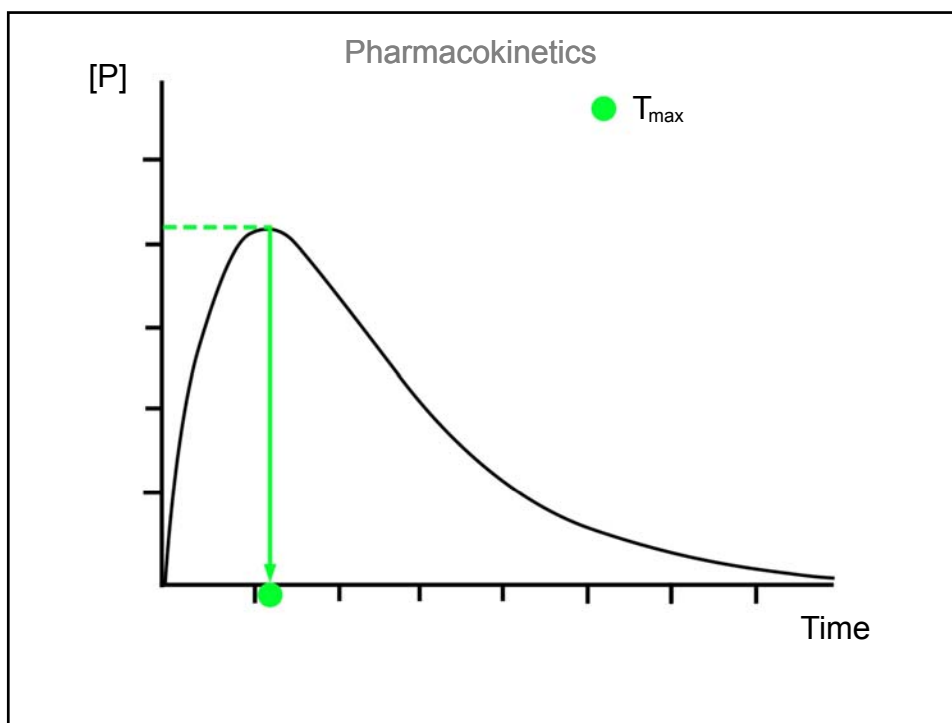


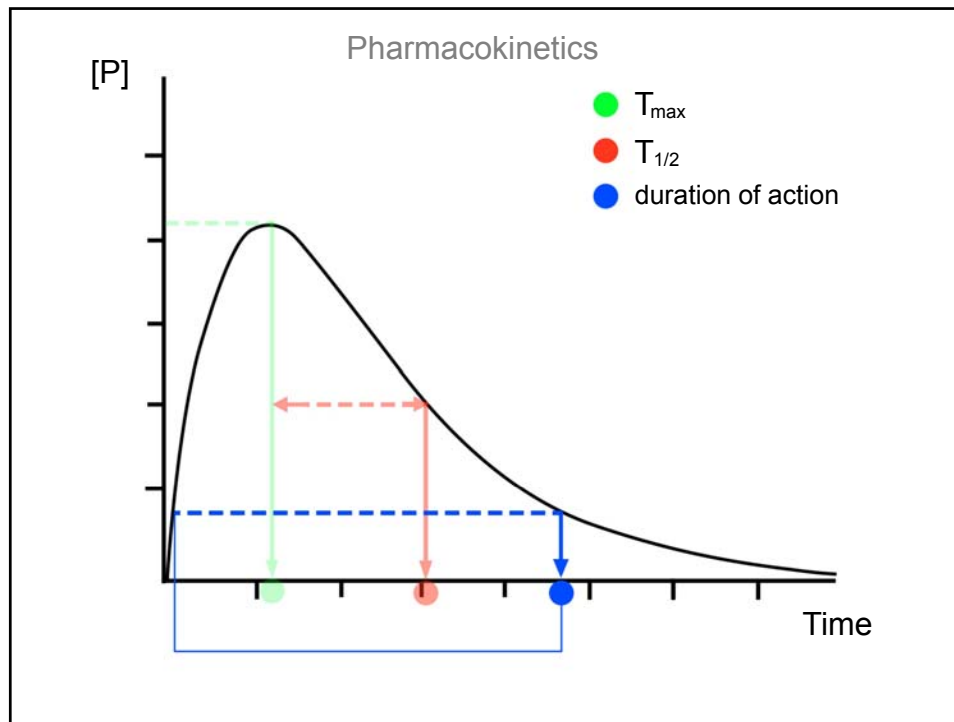
James MacFarlane
Asst Professor of Pediatrics & Psychiatry
University of Toronto
Director of Education, MedSleep
j.macfarlane@medsleep.com



Objectives

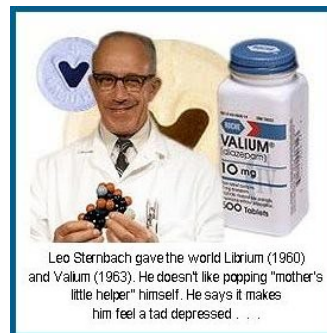
- To review basic principals
- CNS medications of interest
- To review 1^o and 2^o effects of various medication on the PSG
- Important notations

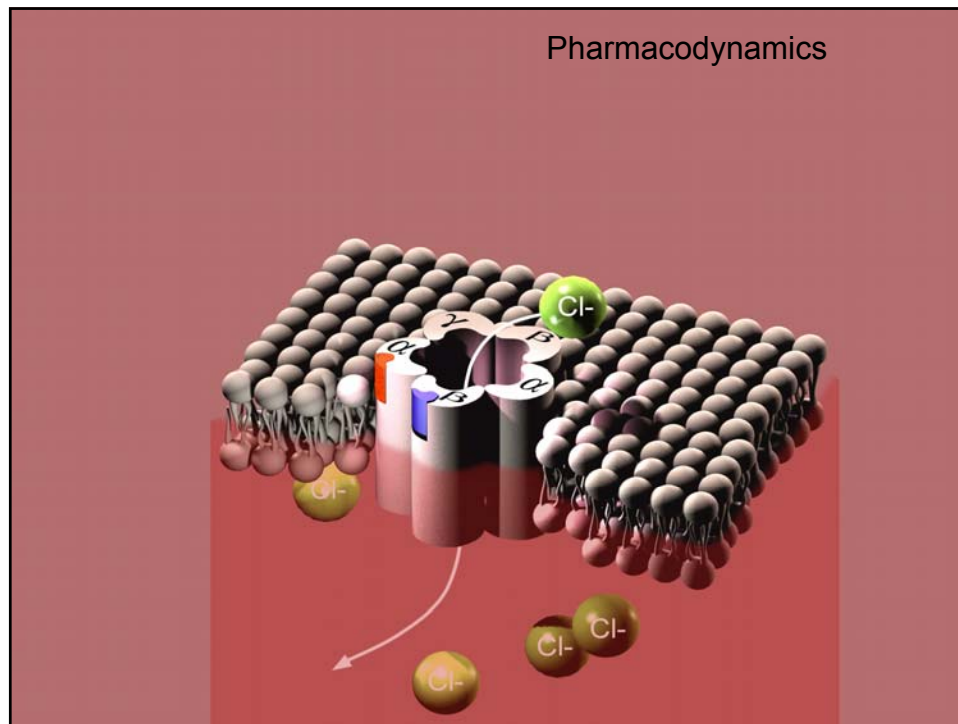




Benzodiazepines (BDZ)

AKA: GABA_A receptor





GABA_A α -receptor subtypes

- α 1 hypnotic properties
- α 2 anxiolytic properties
- α 3 myo-relaxant properties
- α 4 ?
- α 5 anti-convulsant properties
- α 6 alcohol induced properties



Various GABA_A Agonists

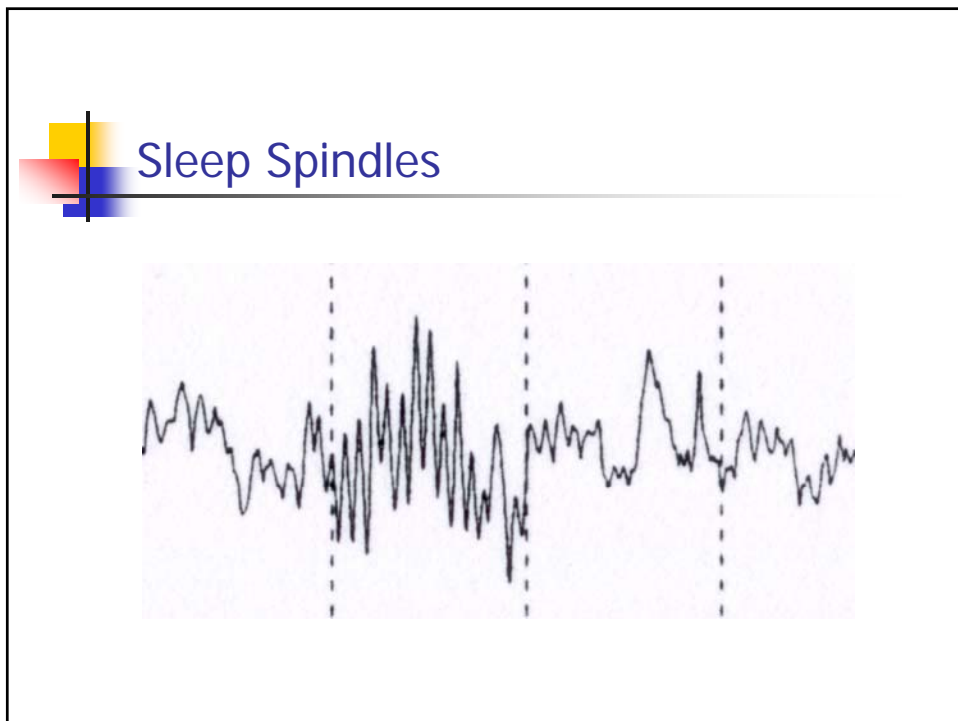
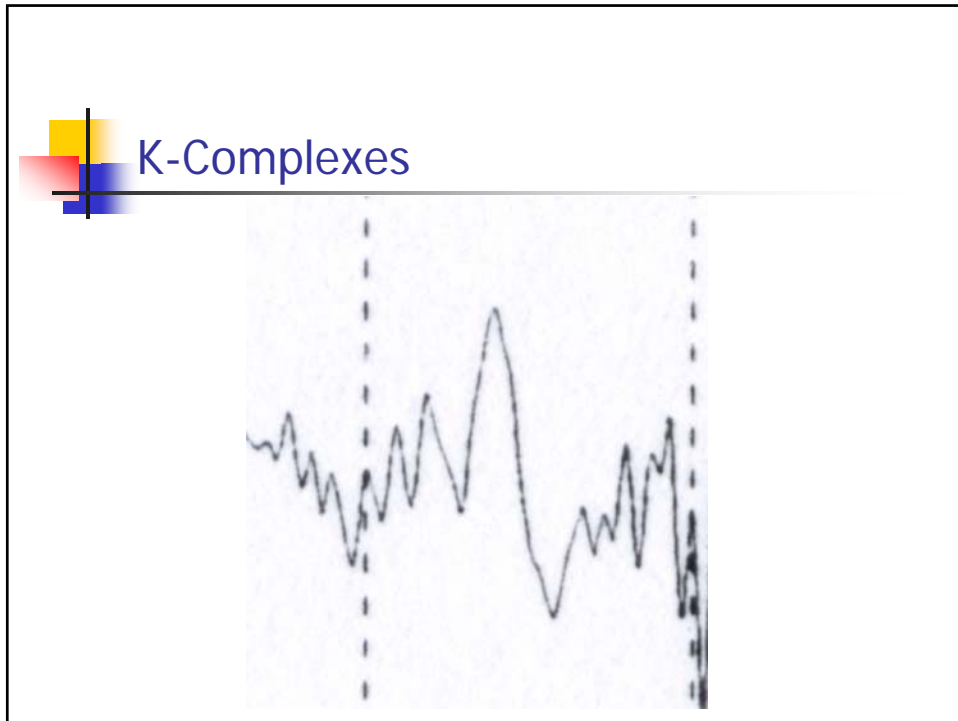
- Typical benzodiazepines (**non-specific**)
 - temazepam (Restoril) 15-30 mg
 - triazolam (Halcion) 0.125 - 0.25 mg
 - oxazepam (Serax) 10-30 mg
 - lorazepam (Ativan) 0.25-1.0 mg
- Typical non-benzodiazepines
 - zopiclone (Imovane) 3.75-7.5 mg (**more specific**)
 - zolpidem (Ambien) 5-10 mg (**α1 specific**)
 - zaleplon (Starnoc) 5-10 mg (**α1 specific**)

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Effects on PSG

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BDZ Effects on the PSG

- Reduce SOL
- Increase TST
- Decrease WASO
- Reduce K-complex frequency
- Increase sleep spindle frequency
- Decrease/eliminate slow wave sleep
- Some reduction of REM-sleep
- Increase apnea frequency & duration

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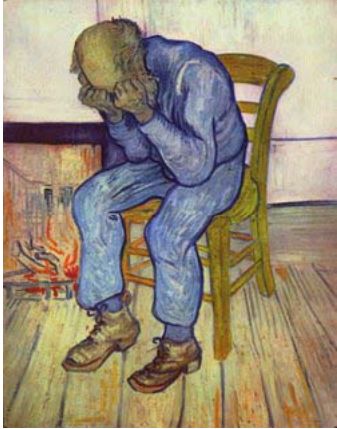


Other CNS Medications

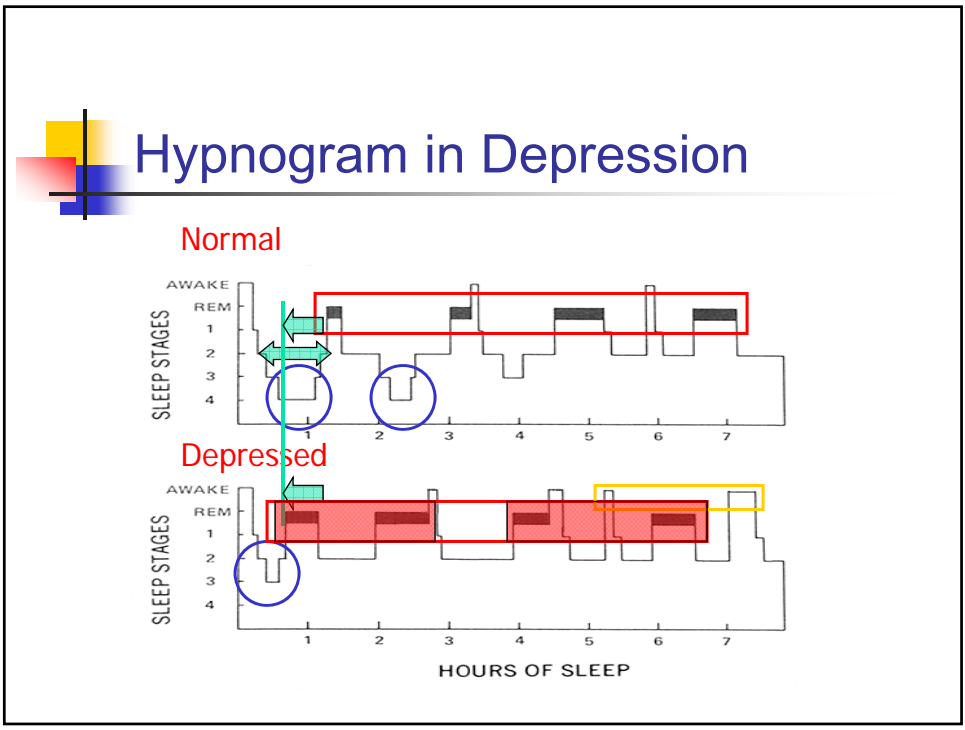
- Antidepressants
 - eg; fluoxetine (Prozac), citalopram (Celexa)
- Antiepileptics
 - eg; valproic acid, trileptal
- Narcotic analgesics
 - eg; oxycontin, methadone, fentanyl

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Antidepressants



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Case

- HPI: 38 Female with depression & insomnia
- PxExam: Normal
- Labs: Normal
- RFR to Lab:
 - Consultation in Sleep Clinic
 - Possible sleep study



Case

Patient description:


I used to be a good sleeper. I kept a crazy schedule in university. After my mother died, I noticed I used to wake-up very early in the morning (~3 AM) feeling very nervous. This got better after I was treated for depression. Now, I have trouble getting to sleep and my sleep seems very broken. My boyfriend say I twitch a lot.

Tech observations:

Patient friendly and talkative. She says her mood has been so much better in the last year, but her sleep has gotten worse. She awakens at night for no reason. Her restlessness disturbs her boyfriend, and he now often sleeps on the couch. She been snoring more too.

Tech Notes:

- took fluoxetine 60 mg prior to lights out as prescribed.
- Appeared tired, and wanted to go to bed.
- Restless before sleep - generalized.
- Delayed sleep onset (~76 mins); frequent spontaneous wakes; ++WASO



Case

MD Observations:

- Frequent PLMs, in the absence of significant PLM arousals.
- Frequent spontaneous movement arousals
- Significant sleep fragmentation.
- Alterations in sleep architecture.

MD Interpretation:

- 1) 1^o insomnia after successful resolution of mood disorder
- 2) Possible SSRI-induced insomnia.

The Effects of Psychotropic Medications on Sleep

Medication	T _{max} (Hrs)	T _{1/2} (Hrs)	Sleep latency	Sleep efficiency	% SWS	% REM	Daytime Sedation	Motor Restless
3^o amines:								
Amitriptyline	3.6	21	↓	↑	↑	↓	Yes	---
Imipramine	4	16	↓	↑	↑	↓	Mild	---
Trimipramine	N/A	16	↓	↑	↑	↓	Yes	---
2^o amines:								
Desipramine	N/A	30	↓	↑	↑	↓	Yes	↑
Protriptyline	N/A	80	↓	↑	↑	↓	Yes	---
SSRIs:								
Fluvoxamine	5	17	↑	↓	N/A	↓	Yes	N/A
Fluoxetine	6	50	↑	↓	---	↓	No	↑↑
Paroxetine	5	17	↑	↓	---	↓	Yes	↑
Sertraline	7	24	↑	↓	---	↓	No	↑
Venlafaxine	2	5	↑	↓	---	↓	Mild	↑
Citalopram	4	36	---	---	---	↓	Mild	↑
Atypical agents:								
Bupropion	1.6	12	---	---	---	↑	No	↓
Mirtazapine	1.5	16	↓	↑	↑	---	Yes	↓
Nefazodone	1.5	3	↓	↑	↑	---	No	↓
Trazodone	2	6	↓	↑	↑	---	No	↓
Antipsychotics:								
Clozapine	2	12	↓	↑	↑	↓	Yes	---
Loxapine	1.5	8	↓	↑	↑	↓	Mild	↑
Olanzapine	6	33	↓	↑	↑	↓	Mild	---
Risperidone	1	3.2	--	↑	↑	↓	Mild	↑
Haloperidol	2.5	18	---	---	---	---	Mild	↑↑
Hypnotics:								
Flurazepam	2	16	↓	↑	↓	↓	Yes	↓
Clonazepam	2.5	23	↓	↑	↓	↓	Yes	↓
Temazepam	1	9	↓	↑	↓	↓	Mild	↓
Zopiclone	1	6	↓	↑	↑	---	No	---
Zaleplon	1	1	↓	↑	↑	---	No	---

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Zopiclone	1	6	↓	↑	↑	---	No	---
Zaleplon	1	1	↓	↑	↑	---	No	---

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The Effects of Psychotropic Medications on Sleep

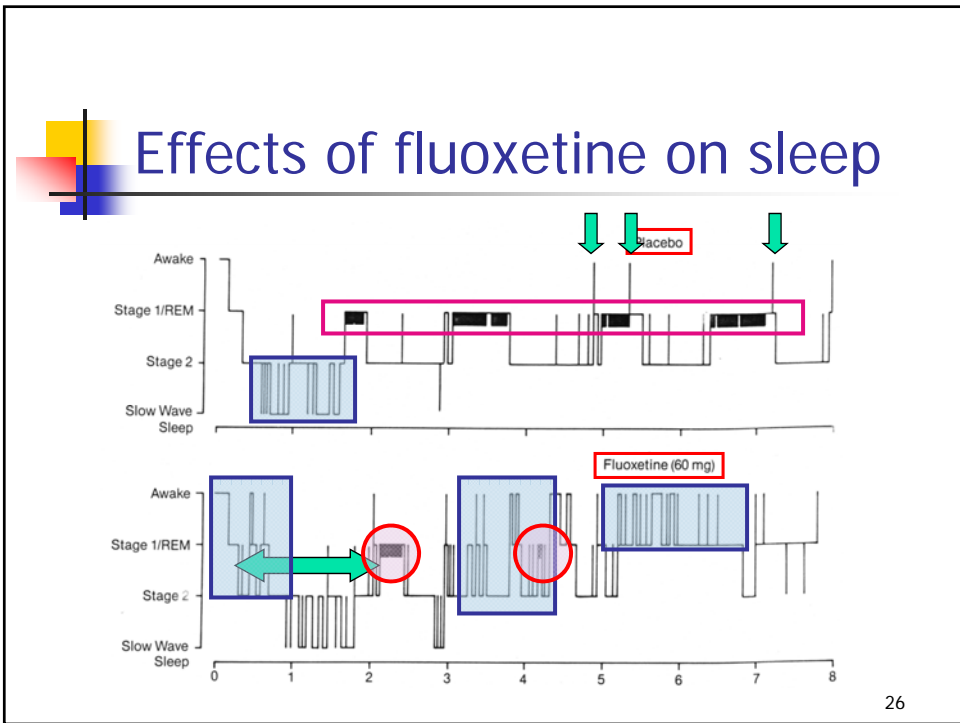
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Zopiclone	1	6	↓	↑	↑	---	No	---
Zaleplon	1	1	↓	↑	↑	---	No	---

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The Effects of Psychotropic Medications on Sleep

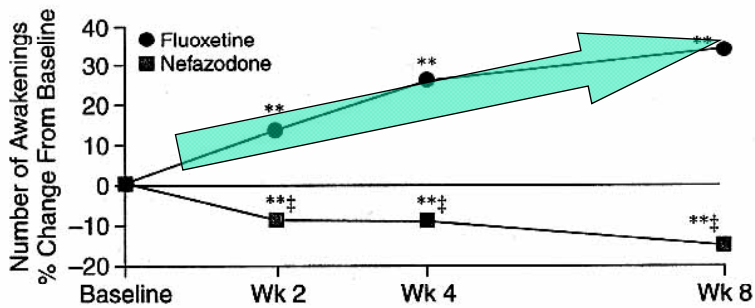
Medication	T _{max} (Hrs)	T _{1/2} (Hrs)	Sleep latency	Sleep efficiency	% SWS	% REM	Daytime Sedation	Mood/ Restless
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Zaleplon	1	1	↓	↑	↑	—	No	—

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Figure 1. Effects of Nefazodone and Fluoxetine on Objective Sleep Measures: Number of Awakenings^a



^aFrom Rush et al,¹⁹ with permission. Nefazodone baseline (mean = 25.8), N = 59; fluoxetine baseline (mean = 22.1), N = 57.
 **p ≤ .01 compared with baseline.
 †p ≤ .01 compared with fluoxetine.

Thase, ME: J. Clin Psychiatry 2000; 61 Suppl 11, 46-50

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PLMS & Antidepressants (Biol Psychiatry 2005; 58(6):510-514)

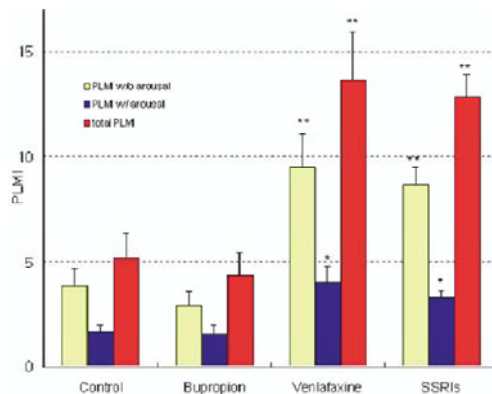
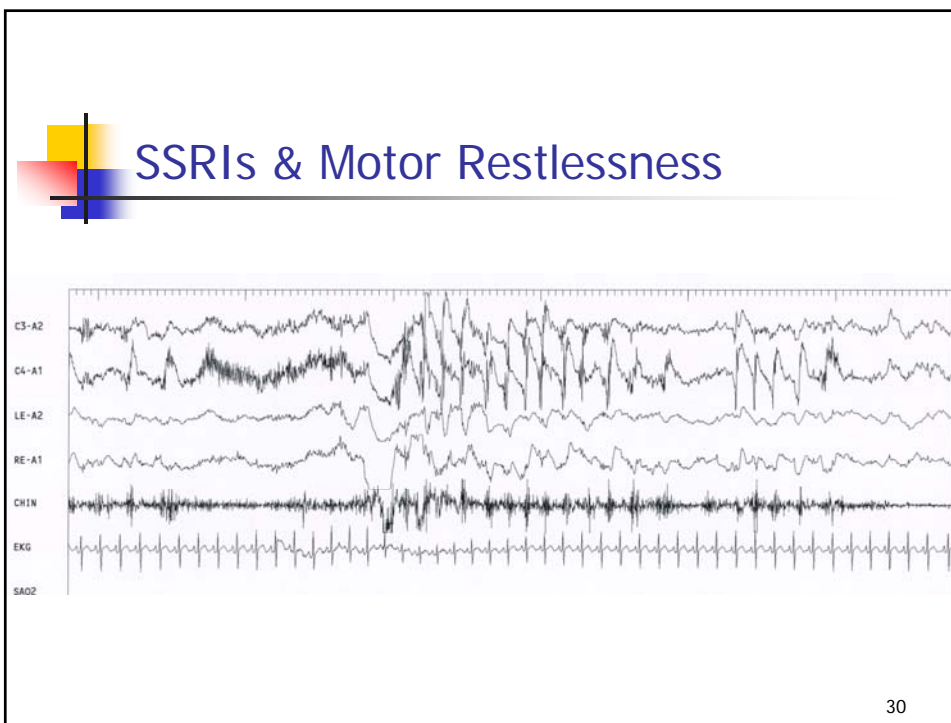
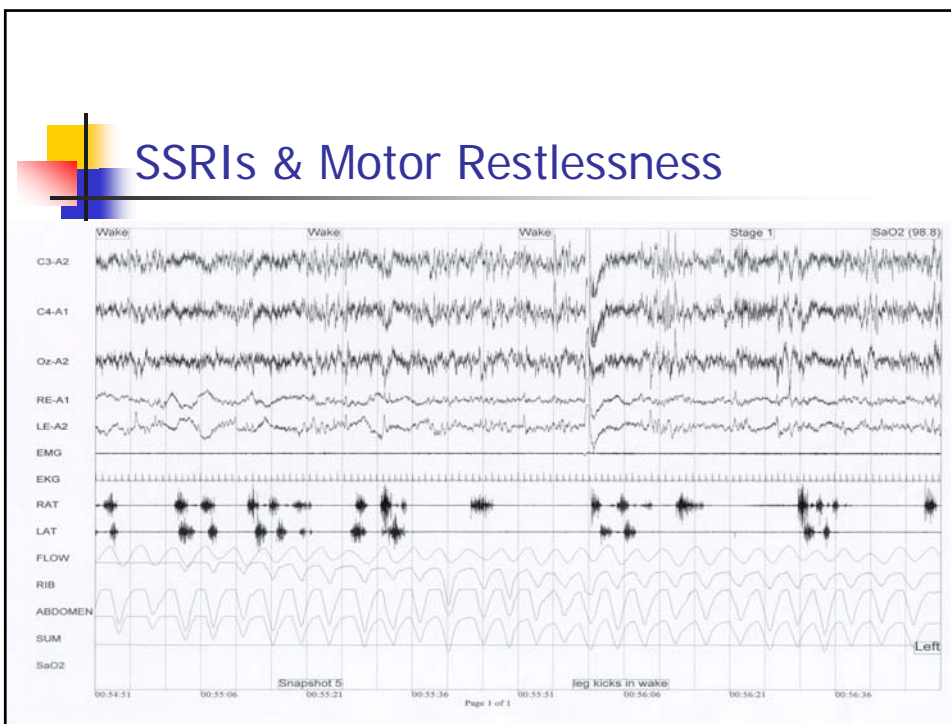
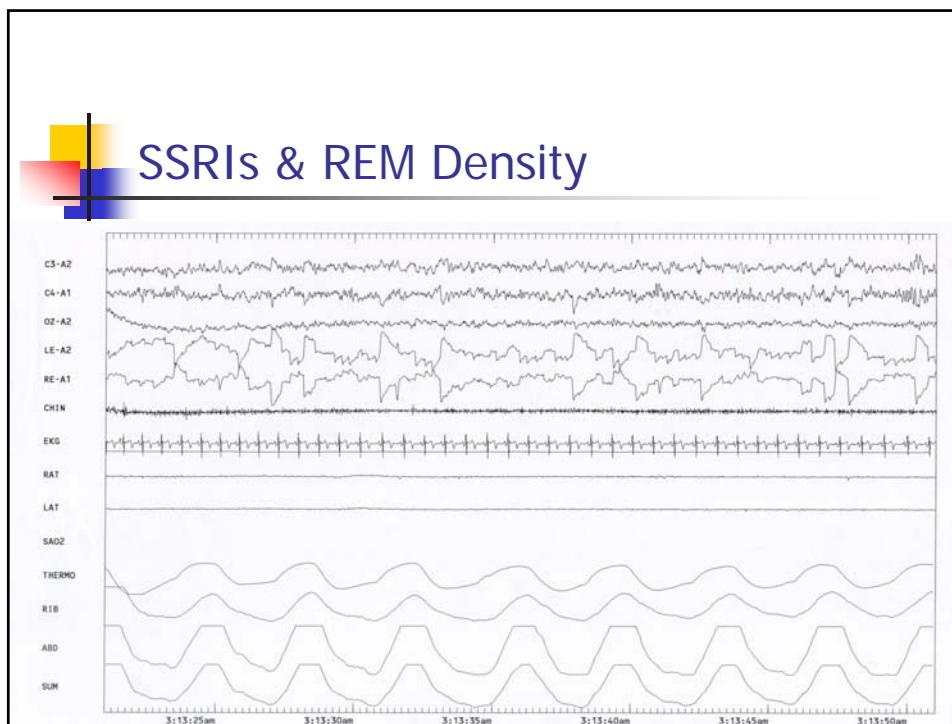


Figure 1. Comparison of mean periodic leg movement index (PLMI) during sleep by group. Values indicate Mean ± SE. SSRIs, selective serotonin reuptake inhibitors. *p < .001, control, bupropion versus venlafaxine, SSRIs; **p < .0001) control versus venlafaxine, SSRIs.

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Effects of A/Ds on Sleep

- Normal controls
 - Prolongs REM latency
 - Increases total NREM sleep
 - Decreases total REM sleep
- Sleep disruption proportional to dose and age
- Other Specific Effects
 - Increased motor restlessness (PLMS, bruxism)
 - Increased REM density (Prozac eyes)

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Key Points

- 1) Insomnia is common in major affective disorder.
- 2) Insomnia often resolves with effective treatment.
- 3) SSRI medications induce specific changes in sleep architecture.
- 4) SSRIs increase sleep-related motor restlessness.
- 5) SSRIs often increase WASO



Anti-Epileptic Mediations



Anti-Epileptic Mediations (Neurology 2000; 54(5):S16-S24)


Table 2 Chronic polysomnographic effects of antiepileptic drugs on sleep: consensus of available studies

AED	TST	Sleep efficiency	% Stage 1	% Stage 2	% SWS	% REM	# Full AW	RD rate	PLM rate	Total arousal rate	EDS by MSLT
AZM	?	?	?	?	?	?	?	+	?	?	?
CBZ	0	+	0	0	+	0	?	?	?	?	-
CZP	+	-	+	+	-	-	±	-	±	+	-
ESM	±	-	-	0	-	±	-	?	?	?	?
GBP	+	+	+	0	+	+	+	0	+	+	?
LTG	?	?	?	?	?	?	?	?	?	?	?
PHB	0	-	-	+	0	-	+	?	?	±	-
PHT	0	-	-	+	-	0	-	?	?	-	?
TPM	?	?	?	?	?	?	?	?	?	?	?
VPA	±	0	+	0	+	±	±	?	?	?	0

% Stage 1,2 = percent TST in stage 1 or 2; % SWS = percent TST in stages 3 + 4; % REM = percent TST in rapid eye movement sleep; # Full AW = number of full awakenings; AED = antiepileptic drug; AZM = acetazolamide; CBZ = carbamazepine; CZP = clonazepam; EDS = excessive daytime sleepiness; ESM = ethosuximide; GBP = gabapentin; LTG = lamotrigine; MSLT = multiple sleep latency test; PHB = phenobarbital; PHT = phenytoin; PLM rate = periodic limb movements per hour of TST; PRM = primidone; RD rate = respiratory disturbance events per hour of TST; Total arousal rate = rate of arousals/subarousals per hour of TST; TPM = topiramate; TST = total sleep time; VPA = valproate.

+ = improves; - = worsens; 0 = no effect; ? = insufficient data; ± = conflicting data. (Note: a decrease in % Stage 1 is considered a "+".)

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Anti-Epileptic Mediations (Neurology 2000; 54(5):S16-S24)


Table 2 Chronic polysomnographic effects of antiepileptic drugs on sleep: consensus of available studies

AED	TST	Sleep efficiency	% Stage 1	% Stage 2	% SWS	% REM	# Full AW	RD rate	PLM rate	Total arousal rate	EDS by MSLT
AZM	?	?	?	?	?	?	?	+	?	?	?
CBZ	0	+	0	0	+	0	?	?	?	?	-
CZP	+	-	+	+	-	-	±	-	±	+	-
ESM	±	-	-	0	-	±	-	?	?	?	?
GBP	+	+	+	0	+	+	+	0	+	+	?
LTG	?	?	?	?	?	?	?	?	?	?	?
PHB	0	-	-	+	0	-	+	?	?	±	-
PHT	0	-	-	+	-	0	-	?	?	-	?
TPM	?	?	?	?	?	?	?	?	?	?	?
VPA	±	0	+	0	+	±	±	?	?	?	0

% Stage 1,2 = percent TST in stage 1 or 2; % SWS = percent TST in stages 3 + 4; % REM = percent TST in rapid eye movement sleep; # Full AW = number of full awakenings; AED = antiepileptic drug; AZM = acetazolamide; CBZ = carbamazepine; CZP = clonazepam; EDS = excessive daytime sleepiness; ESM = ethosuximide; GBP = gabapentin; LTG = lamotrigine; MSLT = multiple sleep latency test; PHB = phenobarbital; PHT = phenytoin; PLM rate = periodic limb movements per hour of TST; PRM = primidone; RD rate = respiratory disturbance events per hour of TST; Total arousal rate = rate of arousals/subarousals per hour of TST; TPM = topiramate; TST = total sleep time; VPA = valproate.

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Pregabalin (Lyrica) & Sleep Architecture

Sleep stage, % of SPT	Pregabalin	BDZ	Placebo
REM	18.4	19.5	21.9
Stage 1	2.4	4.1	4.8
Stage 2	36.3	54.4	41.3
Stage 3	11.3	7.0	9.3
Stage 4	30.0	11.9	16.4

Hindmarch I, Dawson j, Stanley N. SLEEP 2005. Vol. 28 (2):187-193

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Hindmarch I, Dawson j, Stanley N. SLEEP 2005. Vol. 28 (2):187-193

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Case

- HPI: 38 male with severe insomnia
- PxExam: Normal; previous hx of severe back injury; pain now well controlled
- Labs: Normal
- RFR to Lab:
 - Consultation in Sleep Clinic
 - Possible sleep study



Case

Patient description:

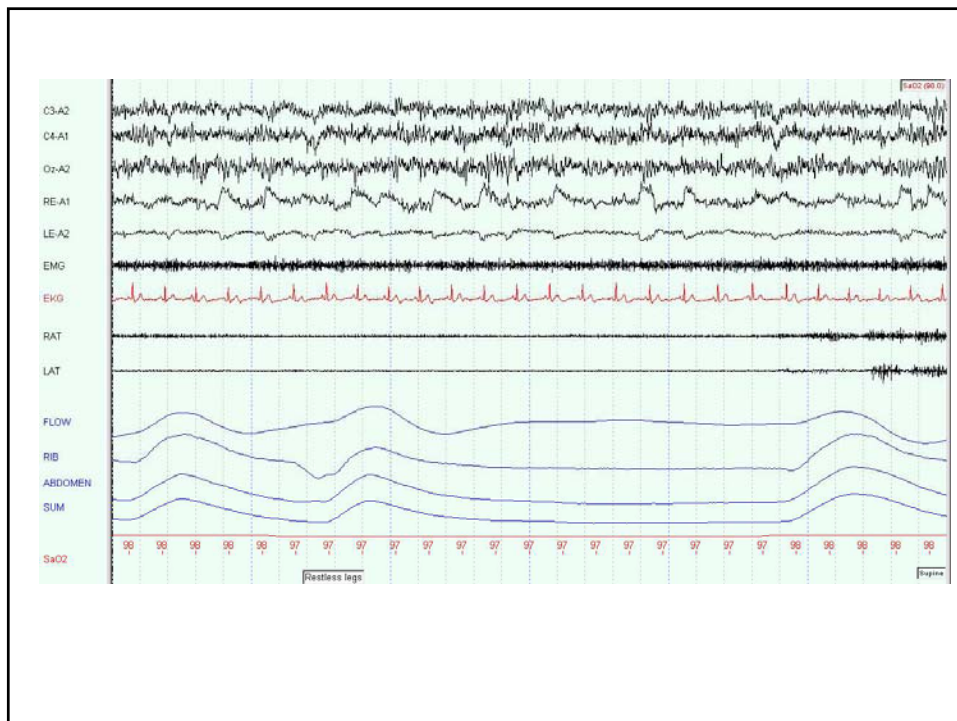
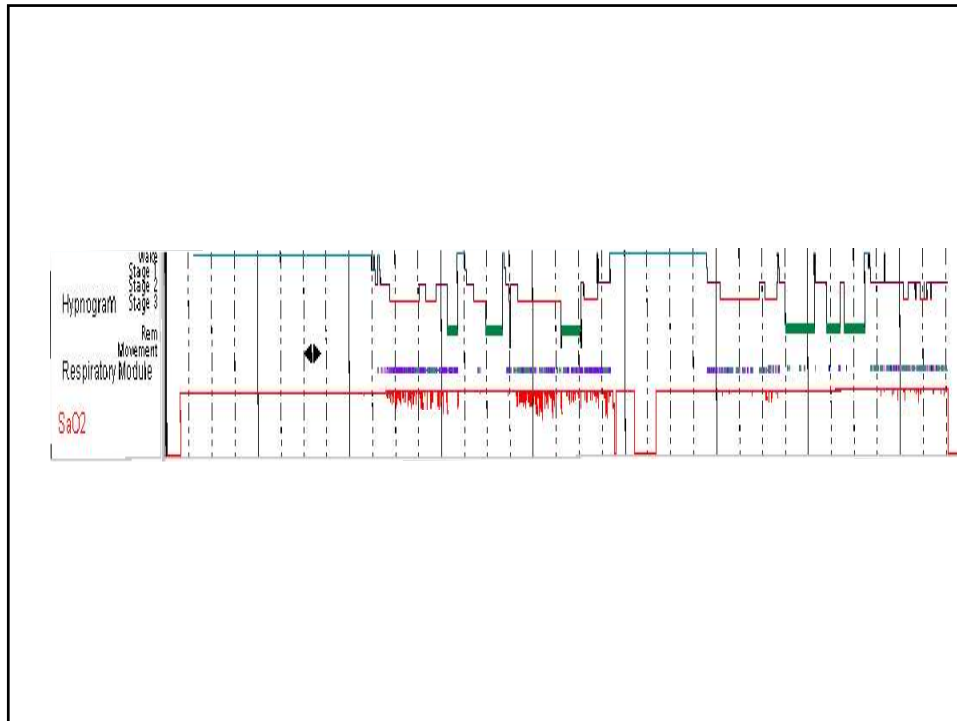
It takes me hours to get to sleep. If I wake-up, I can't get back to sleep.

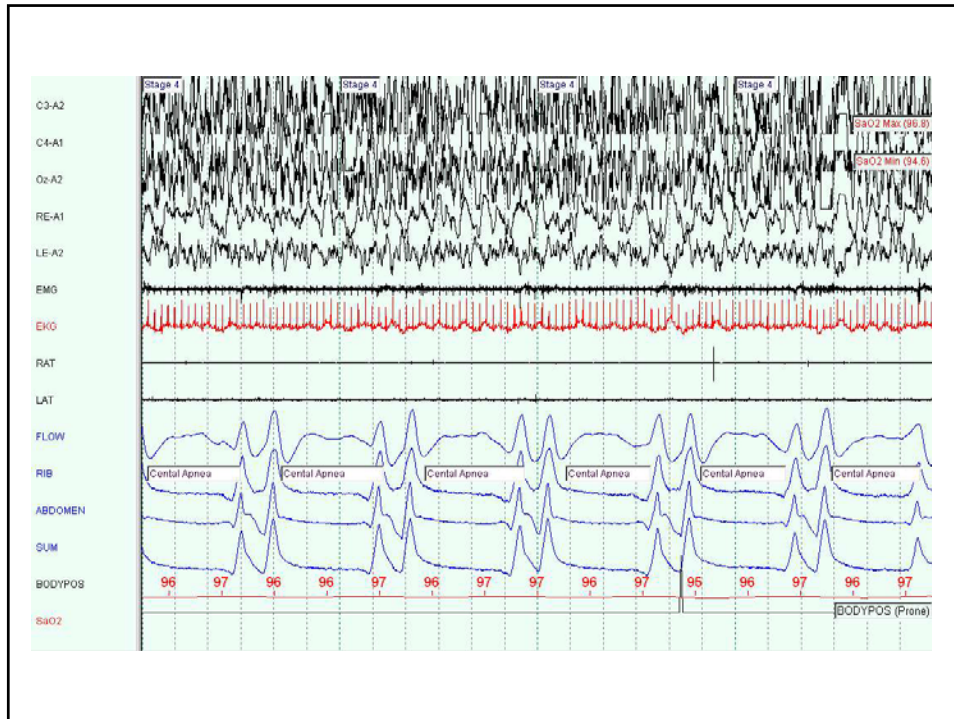
Technical observations:

Patient appears to be uncomfortable. Goes on to discuss his pain symptoms. Mechanic - tried to brace a car engine that swung free with too much momentum, - felt snapping sensation in his lower back and fell to the floor, unable to move. He ended up with two ruptured lumbar discs (L4, L5), nerve root injury, and intermittent severe lower back pain. The pain is better with his meds, but the sleep is worse!

Tech Notes:

- took Methadone 30 mg prior to lights out as prescribed.
- listened to his IPOD for about 35 minutes.
- patient was very still in bed.
- delayed sleep onset; frequent S/O resp events.
- Increased WASO.
- No pain complaints





Variable	1 st study
Age	38
BMI	27.6
Stage1%	19.1
Stage2%	38.5
SWS%	18.2
REM%	15.5
TST (mins)	227
Sleep Latency (mins)	105.7
REM Latency (mins)	67.5
Sleep Efficiency	58%
RDI	88
Hypopneas/hr	24.0
Central Apneas/hr	66.7
Obst. Apneas/hr	7.3
Low SaO2	78.1
PLMS/hr	6.3
Arousals/hr	41.0

Variable	1 st study
Age	38
BMI	27.6
Stage1%	19.1
Stage2%	38.5
SWS%	18.2
REM%	15.5
TST (mins)	227
Sleep Latency (mins)	105.7
REM Latency (mins)	67.5
Sleep Efficiency	58%
RDI	88
Hypopneas/hr	24.0
Central Apneas/hr	66.7
Obst. Apneas/hr	7.3
Low SaO ₂	78.1
PLMS/hr	6.3
Arousals/hr	41.0



Narcotics

- The term opiate refers to medications chemically related to opium.
- The term narcotic refers to a broader variety of alkaloids often denoting a high potential for dependency.
- Morphine was the first pure alkaloid to be isolated from opium in 1806
- All bind at the μ -receptor subtype of the endogenous opioid receptors.



Narcotics

- Increased risk for sleep related central apnea more recently demonstrated
- Nonspecific pathogenesis of apneas, which may include disturbances in regulatory activity related to:
 - i) medullary centers and brain stem structures
 - ii) afferent influx to CNS
 - iii) sleep stages
 - iv) upper airways, lungs, respiratory muscles.



Case I PSG

- patient often unaware of breathing problems during sleep.
- difficult for the bed partner to add a corollary history, as snoring patterns may be unchanged



Case I PSG

- Downward titration of narcotic
- Follow-up sleep study

Variable	1 st study	2 nd study
Methadone dose	30 mg tid	20 mg bid
BMI	27.6	28.3
Stage1%	19.1	15.7
Stage2%	38.5	53.2
SWS%	18.2	12.2
REM%	15.5	16.4
TST (mins)	227	335
Sleep Latency (mins)	105.7	15.3
REM Latency (mins)	67.5	140.8
Sleep Efficiency	58%	73.5%
RDI	88	30.9
Hypopneas/hr	24.0	14.9
Central Apneas/hr	66.7	11.4
Obst. Apneas/hr	7.3	5.6
Low SaO ₂	78.1	88.7
PLMS/hr	6.3	20.4
Arousals/hr	41.0	25.1



Case Conclusions:

MD Observations:

- The patient complains reports a reduction of pain symptoms, but increased sleep disruption.
- Polysomnographic evidence of difficulty initiating and maintaining sleep, in the absence of significant motor restlessness.
- Evidence of sleep-onset central apneas or hypopneas; overt central apneas during sleep; possible concomitant increase of OSA.

MD Interpretation:

- 1) Narcotic-induced central apnea.
- 2) The pain management physician should be alerted, and downward titration of narcotic analgesic should be considered.
- 3) Repeat baseline assessment after reduction of narcotic dose.
- 4) Consideration of adapted-servo ventilation (ASV) if required.



Pain Medications

- Codeine
- Oxycodone
- Fentanyl
- Methadone
- Morphine
- MS-contin

Other Meds

- Diuretics
- Beta-blockers
- OTCs
 - valerian
 - lavender
 - melatonin



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Notations

- What medications have you been taking?
- When did/will you take your medication?
- What is the dose of your medication?
- Have you recently discontinued any medications?
- Scorers comments on PSG effects – be descriptive

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