Toronto I-II 12:45 pm

Sweet Dreams – HIV + Sleep

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HIV and Sleep Problems

Sleep+ HIV

An Accredited, Case Based Discussion

By

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OHTN Nov 18, 2013

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Disclosure – Dr. Moscovitch

Grants/research support:	Neurocrine Biosciences,Wyeth, Novartis Bristol-Myers Squibb,Smith Kline, Pfizer Neuroscience Pharma,Merck Frost, Takeda Hoffman-La Roche,Vella,Lundbeck,Aventis Organon,Servier,Sanofi-Aventis,Cephalon Draxis,Eli-Lilly,Thera ,Janssen,Sepracor , Otsuka
Speaker's bureau/honoraria:	Pfizer, Bristol Myers Squibb, Valeant, Eli Lilly
Advisory Boards	Pfizer, Valeant, Merck, BMS
Other:	Transport Canada, US DOT, FMCSA, WSIB

Learning Objectives

After completing this program, participants should be able to:

- Incorporate sleep assessment as a regular component of follow-up of patients with HIV
- Screen for sleep problems among patients with HIV, including use of standardized tools
- Prescribe medications, when appropriate, to improve sleep in patients with HIV
- Know when to refer patients with HIV to specialist care to manage their sleep problems

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Program Outline

1. Presentation of two case studies
   - discussion about what to do in each case
2. Overview of sleep problems in HIV patients
   - epidemiology
   - impact
   - screening (including sleep questionnaire and how to interpret its results)
   - management
3. Revisit the case studies to discuss management in light of new information

William: Patient Overview

- 18-year-old male
- Diagnosed HIV+ two months ago
  - baseline CD4+: 390/mm^3
  - baseline viral load: 330,000 copies/mL
  - no resistance mutations
  - prescribed single-tablet efavirenz, emtricitabine and tenofovir as ART

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William: Presentation

- Patient returned two weeks after initiating ART
- Reported new-onset severe nightmares
  - vivid, caused him to relive sexual abuse suffered during childhood
  - frightened to go to sleep
  - new symptom since starting ART

William: Considerations for Management

- He is not receptive to changing therapy: strongly expresses wish to continue receiving ART in one pill
- Combined emtricitabine/rilpivirine/tenofovir is not an option since:
  - viral load > 100,000 copies/mL
  - patient eats at irregular and unpredictable hours
  - not covered by patient’s drug plan

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Discussion

- How would you further investigate William’s sleep disturbances? What questions would you ask him?

Lucien: Patient Overview

- 47-year-old male
- Immigrant from Senegal
- Being treated for pulmonary tuberculosis
- Recent diagnosis of HIV+
  - baseline CD4+: 135/mm^3
  - baseline viral load: 175,000 copies/mL
  - prescribed single-tablet efavirenz, emtricitabine and tenofovir as ART

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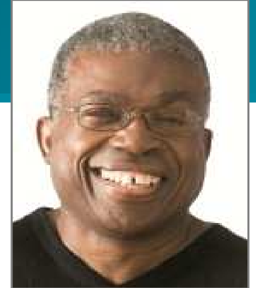
Lucien: Other Medical History



- Comorbidities
  - overweight (BMI 32.2)
  - type 2 diabetes
  - dyslipidemia
  - hypertension
  - pulmonary tuberculosis (two months)
- Medications
  - metformin
  - atorvastatin
  - HRZE (isoniazid, rifampin, pyrazinamide and ethambutol) for tuberculosis; responding well

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Lucien: Presentation
6 Months After Starting ART

- HIV status:
  - viral load: < 40 copies/mL
  - CD4+: 260/mm^3
- Reports increasing fatigue since starting ART therapy: is now exhausted
  - blames his ART and would like to switch regimens
- Other laboratory analyses normal (hemoglobin, TSH/free T4, free + AM testosterone, LFTs, A1C)

Discussion

- What do you think is causing Lucien’s fatigue?

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HIV and Sleep Problems

Overview of Sleep Problems in HIV patients

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Sleep Problems in HIV: Overview

- Effects on the central nervous system may be among the first physical manifestations of HIV infection
- Sleep problems are experienced by 30% to 100% of HIV-positive adults (depending on definitions)
- Fragmented sleep may not be perceived by patients and is rarely accompanied by initial insomnia (difficulty falling asleep), but commonly causes daytime sleepiness or fatigue
  - can lead to difficulty concentrating, poor cognitive functioning, depressive symptoms, loss of daytime productivity
- Sleep problems may be substantially underdiagnosed in HIV patients

Rubinstein ML, et al. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19(3):260-5.
Lee KA, et al. J Clin Sleep Med 2012; 8(1):67-75.

Sleep Problems Are Highly Prevalent in HIV

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Systematic sample of outpatient HIV/AIDS clinic:[1]

- 73% had a sleep disturbance according to PSQI

Cross-sectional study of adults with HIV:[2]

- 45% slept < 6 hours per night
- 34% had difficulty falling asleep
- 56% had fragmented sleep

(34% and 56%:) 20% had both problems

BEAHIV national Canadian survey:[3]

- 62% had difficulty falling asleep and half of these (31% of total) reported this as bothersome

PSQI = Pittsburgh Sleep Quality Index; BEAHIV = Behaviour and Attitudes in HIV.

1. Rubinstein ML, et al. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19(3):260-5.
2. Lee KA, et al. J Clin Sleep Med 2012; 8(1):67-75.
3. Rachlis A, et al. Presented at CAHR 2010, Saskatoon. Oral Presentation 086.

Possible Causes of Sleep Problems in HIV

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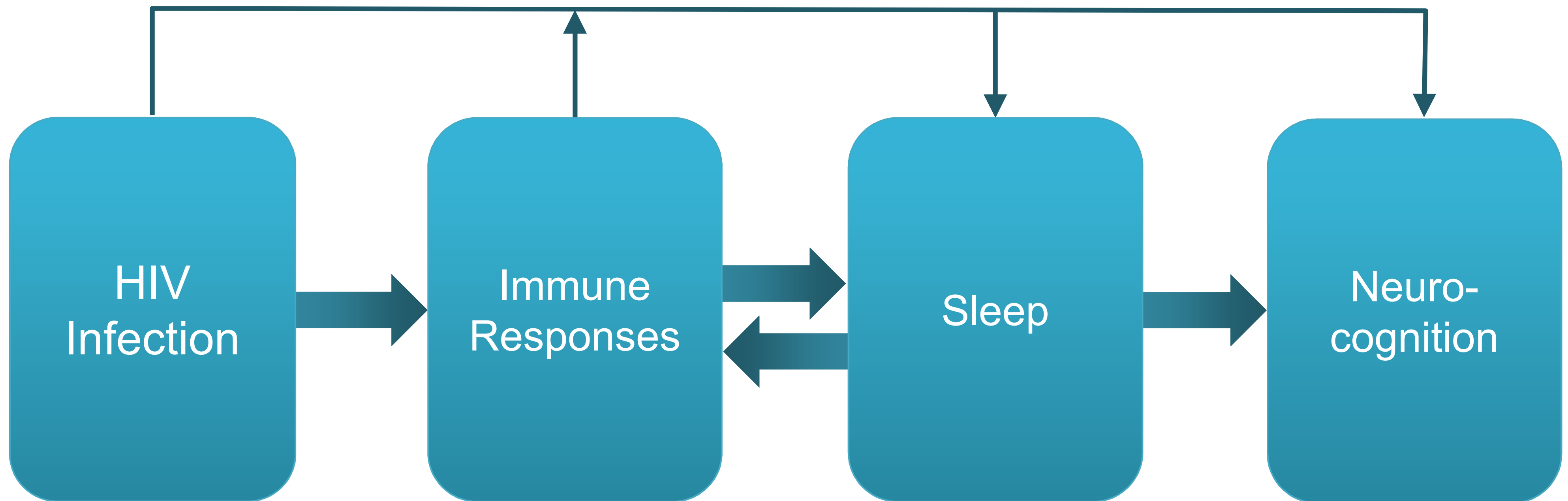
- Primary sleep disorders(ex. Sleep Apnea, RLS, PLMS, Primary Insomnia)
- Psychiatric disorders
- Psychosocial stressors
- Immune dysregulation
- Virus progression
- Neuronal damage
- Comorbid medical conditions
- Adverse drug effects

Reid S, et al. Psychosom Med 2005; 67(2):260-9.
Low Y, et al. Clin Neurophysiol 2012; June 22 [Epub ahead of print].

Proposed Associations



Foster SB, et al. Clin Immunol 2012; 144(1):13-23.

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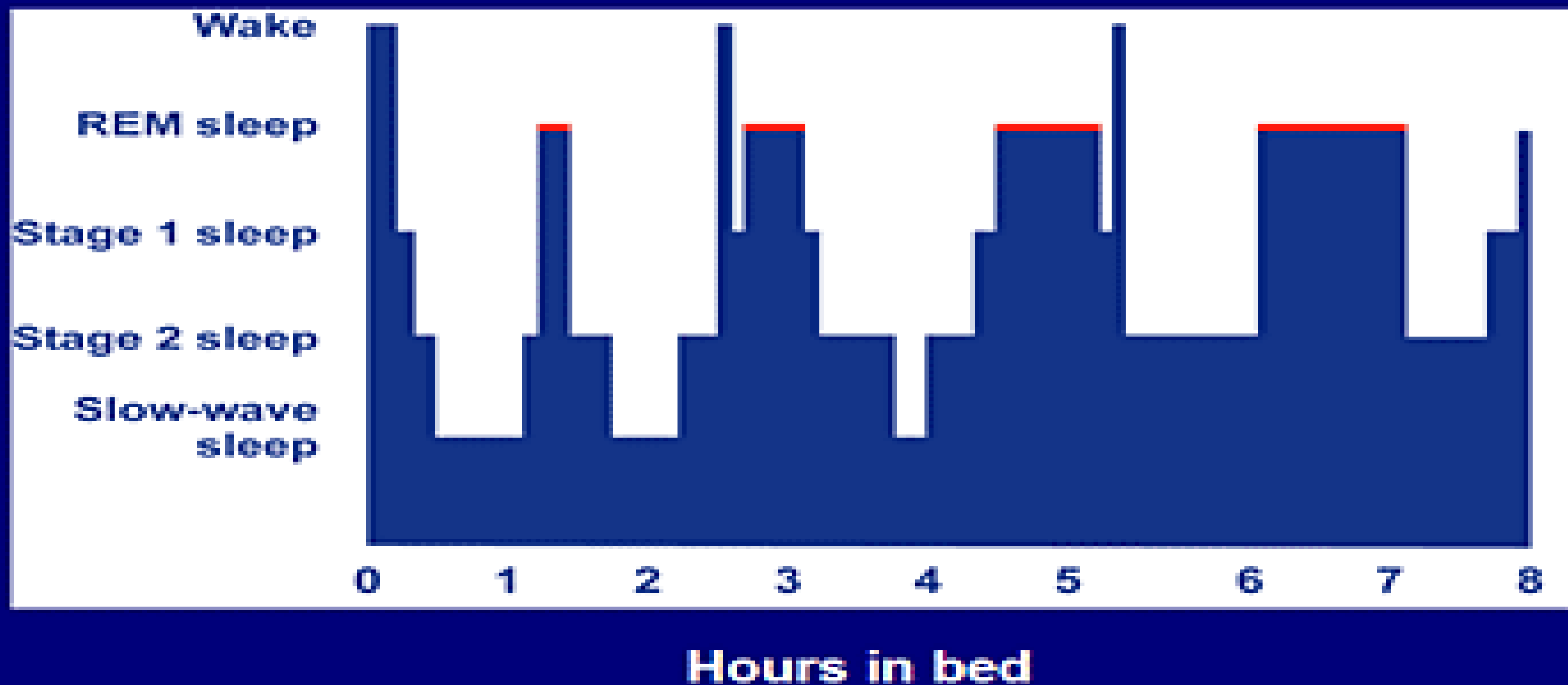
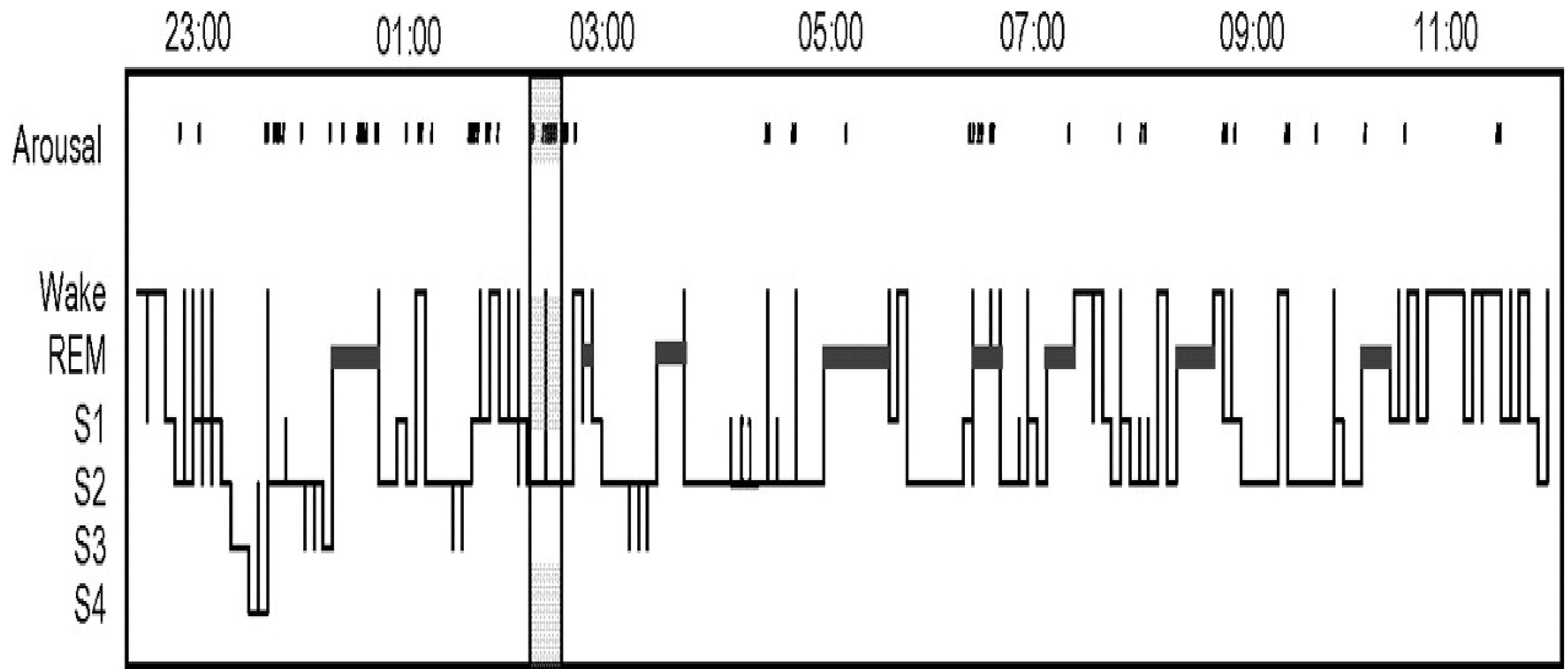
Picture of Normal Sleep



Hypnogram in a Patient



Differential Diagnosis of Insomnia in HIV

Etiologies	Considerations
Primary insomnia not related to underlying condition/treatment	Should be treated with consideration given to the role of sleep hygiene counselling and to concomitant medications
Non-HIV medications that may cause insomnia side effects	Beta-blockers, bronchodilators, calcium channel blockers, corticosteroids, decongestants, immunomodulators (*e.g.,* interferons), trimethoprim-sulfa, dapsone, amphotericin, fluconazole, isoniazid, diuretics taken at bedtime, varenicline
Medical conditions	Hyperthyroidism, chronic renal failure, lung disease, congestive heart failure, pain, diarrhea, incontinence, fever, dyspnea & sleep apnea, periodic limb movements in sleep or restless limb syndrome
Mental health etiologies	Side effects of psychotropic medications, including SSRIs; psychiatric disorders, including mood and anxiety disorders, mania & psychosis
Substance-use etiologies	Illicit drug use, particularly stimulant drugs; alcohol and caffeine consumption; nicotine
ARV medications	[See following slides]

SSRIs = selective serotonin reuptake inhibitors.

Adapted from: New York State Department of Health AIDS Institute. *Mental Health Approach and Differential Diagnosis*.
Omonuwa TS, et al. J Clin Sleep Med 2009; 5(3):251-62.

Sleep Problems in HIV: Impact

- Sleep problems have been linked to:
  - reduced quality of life
  - treatment non-adherence
  - neurocognitive impairment

Crum-Cianflone NF, et al. Clin Infect Dis 2012; 54(10):1485-94.

Self-reported Symptoms, Including Insomnia, Impact Adherence to ART

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Self-reported Symptom	Odds Ratio for Non-adherence (95% CI)	*p* value
Vision problems	6.06 (1.92 – 19.1)	0.002
Nausea	5.80 (2.38 – 14.1)	< 0.001
Confusion	4.27 (1.74 – 10.4)	0.002
Taste perversion	3.31 (1.24 – 8.91)	0.03
Anxiety	3.30 (1.80 – 6.04)	< 0.001
Anorexia	3.07 (1.23 – 7.71)	0.02
Insomnia	**2.32 (1.19 – 4.48)**	**0.02**
Abnormal fat accumulation	2.06 (1.06 – 4.06)	0.04

Univariate analysis.

Ammassari A, et al. J Acquir Immune Defic Syndr 2001; 28(5):445-9.

HIV and Sleep Problems

Screening for Sleep Problems in HIV

Screening for Sleep Problems Should be Routine in HIV Management

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- Healthcare professionals should ask patients, at routine monitoring visits, about quality of sleep and difficulty initiating or maintaining sleep
- Healthcare professionals should determine whether a patient's insomnia is acute, chronic, primary, or secondary

Adapted from: New York State Department of Health AIDS Institute. *Mental Health Approach and Differential Diagnosis*.

Insomnia: Time-based Classification

- Acute
  - transient or short-term insomnia (< 1 months)
- Chronic
  - persistent insomnia (≥ 1 month)
  - Lasting frequently for years

Roth T, et al. Clin Cornerstone 2003; 5:5-15.

Primary Insomnia

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- Diagnosis of exclusion
- Common characteristics:
  - "light" sleepers
  - inability to relax
  - often sleep better away from home
  - insomnia becomes pronounced during stress

American Psychiatry Association. In: DSM-IV-TR. Fourth edition, text revision. Washington, 2000, pp. 597-662.
Walsh JK, et al. NIH Publication No. 98-4088.

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Secondary Insomnia

- Associated with:
  - medical, psychiatric, and neurological disorders
  - certain medications
  - alcohol/stimulants
  - specific sleep disorders
    - restless legs syndrome
    - sleep apnea
    - circadian rhythm sleep disorder

Doghramji PP. J Clin Psychiatry 2001; 62 (suppl 10):18-26.
Jiva TM. Sleep Rev 2003; 4.
Roth T, et al. Clin Cornerstone 2003; 5:5-15.
Harvey AG. Clin Psychol Rev 2001; 21:1037-59.

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Sleep & Fatigue Wellness Screening Questionnaire

Sleep and Fatigue Wellness Screening Questionnaire

Sleep and Fatigue Wellness Screening Questionnaire (cont'd)

Risk Analysis Scoring

Adapted from: Moscovitch A, et al. Available at: *www.npao.org.*

Consider Recommending a Sleep Diary

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Sleep Diary:

Keeping a sleep diary can help you avoid activities that worsen your chances of restful sleep. It will also help your doctor decide if drug therapy would help and to choose the best method of treatment. It is important that you complete this chart on a daily basis.

IN THE COLUMNS BELOW, MARK THE DIARY AS FOLLOWS

- **A** = Time of wake-up alarm
- **C** = Caffeinated drink
- **D** = Alcoholic drink
- **E** = Exercise
- **M** = Meal
- **S** = Snack
- **N** = Noise disturbing sleep
- **B** = Bathroom use during sleep-time
- **Z** = Sleeping pill
- ↓ = Each time you get into bed
- ↑ = Each time you get out of bed
- — = Beginning/end of sleep — join the lines to indicate sleep periods

WEEK OF __/__/__ TO __/__/__

SUN MON TUE WED THU FRI SAT

00:00 01:00 02:00 03:00 04:00 05:00 06:00 07:00 08:00 09:00 10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00 19:00 20:00 21:00 22:00 23:00

Total sleep (hours):

EXAMPLE:

	SUN
00:00	↓ —
01:00	|
02:00	|
03:00	|
04:00	— ↑
05:00	
06:00	↓ —
07:00	|
08:00	A —
09:00	M
10:00	
11:00	
12:00	M
13:00	
14:00	
15:00	
16:00	
17:00	D
18:00	MD
19:00	
20:00	D
21:00	
22:00	M
23:00	
Total sleep (hours):	4.5

WEEK OF __/__/__ TO __/__/__

SUN MON TUE WED THU FRI SAT

00:00 01:00 02:00 03:00 04:00 05:00 06:00 07:00 08:00 09:00 10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00 19:00 20:00 21:00 22:00 23:00

Total sleep (hours):

http://www.sleeplab.ca/SleepDiary.pdf

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Sleep Hygiene Program:

Dr. Adam's Commandments for Better Sleep

Patient Name: ______________________________ **Date:** ______________________________

Start this program only after you have filled out one week of the accompanying sleep log, as your baseline (starting point).

1. Time in bed is restricted to _____ hours, between _____ and _____. Keep this schedule **7 days per week**, within reason.
2. Two hours before bed begin to disengage from the day's activities. You can have a hot bath to slightly raise your body temperature. Do something relaxing after that until bedtime.
3. Your bedroom should be dark, quiet and comfortable. Use it only for sleep and sex. Remove the **clock** from your bedroom or at the very least, turn it around so you can't see it. If you get up during the night, **DO NOT** look at the clock.
4. If you have not fallen asleep within 20-30 minutes (just estimate), or if you wake up and can't get back to sleep again, get up and go to another room, to do something relaxing and non-stimulating. Go back to bed only when you feel sleepy. If you are not sleepy, don't go back to bed.
5. Within two hours of awakening in the morning, get approximately 30 minutes of **direct sunlight** (outside, no sunglasses), or discuss with your Dr. use of a **light unit** to be prescribed. Do not use one without medical supervision.
6. Eat **regular meals** and a balanced diet. Avoid heavy, spicy meals close to bedtime.
7. Try to get some **exercise** every day, but nothing strenuous within 4 hours of bedtime.
8. Either **stop smoking** totally or do not smoke after 7PM or during the night. Avoid **caffeine** or drink no more than 3 cups of caffeinated beverages a day, none later than 2PM. Have no more than 2-3 drinks of **alcohol** on any given day.
9. Learn simple **relaxation methods** to help you get to sleep and turn your mind off, such as progressive relaxation techniques, self-hypnosis, meditation etc. Our therapist can help guide you with that.
10. ☐ Do not nap during the day ☐ Take naps consistently around _____ for 20-30 minutes. Discuss the **catnap** tape with your sleep clinician.
11. Take **Calcium 500 mg and Magnesium 250 mg** approximately 30 minutes before bedtime with a light snack and a glass of apple or grape juice.
12. Medications – sleeping pills are used as an aid only, until the non-medication measures become effective.
13. Take _________mg of ______________________ ☐ at bedtime ☐ 30 minutes before bedtime.
14. Other Instructions: ____

BE PATIENT. The first few weeks can be quite difficult, but most people will notice some improvement in the first month. However, it usually takes between 3-6 months to obtain the full benefits from this program. Your sleep problem did not develop overnight. There are no instant fixes either.

DON'T GIVE UP! YOU CAN HAVE A RESTFUL AND REFRESHING SLEEP.

If you have any questions or concerns, call Debbie at (416) 784-1430

Considerations for Pharmacotherapy (1)

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Select the agent with the best likelihood of addressing (or at least not exacerbating) the underlying symptoms contributing to the patient's insomnia

– *e.g.*, depression, anxiety, neuropathic pain

Ensure that the agent selected does not have potentially deleterious effects on comorbid conditions

– *e.g.*, benzodiazepines: contraindicated in untreated obstructive sleep apnea; may cause cognitive impairment which also impacts sleep; have long half-lives which contribute to increased adverse effects in patients with liver disease

Omonuwa TS, et al. J Clin Sleep Med 2009; 5(3):251-62.

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HIV and Sleep Problems

Case Studies Revisited

William: Review

- 18-year-old male
- Returned two weeks after initiating single-tablet efavirenz, emtricitabine and tenofovir
- Reported new-onset severe nightmares
  - vivid; caused him to relive sexual abuse suffered during childhood
  - frightened to go to sleep
  - insists on single-tablet therapy

Discussion

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- Given what we have just discussed, how would you recommend managing William's nightmares?

William: Management

- Information and counselling about sleep hygiene
- Short-term benzodiazepine (lorazepam 1 mg po qhs x 2 weeks)
  - plan to treat to desired effect, then attempt to wean the patient back off the medication
- With lorazepam therapy, the nightmares stopped
  - at end of 2 weeks, dose reduced to 0.5 mg qhs for 1 week and then, with no return of the nightmares, cessation of lorazepam
- Nightmares have not returned

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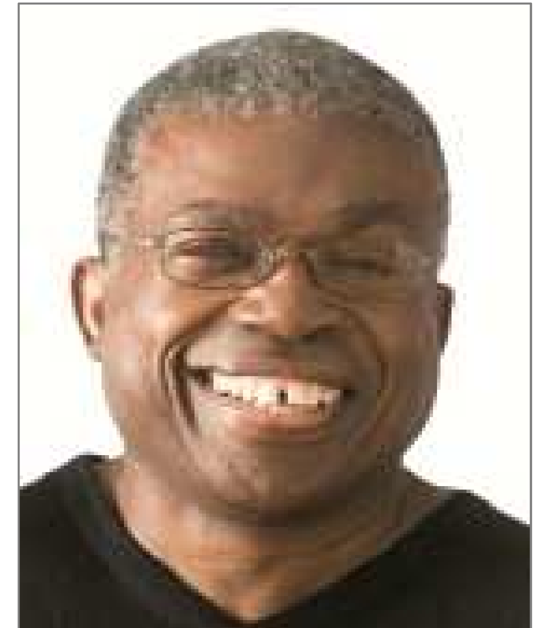
Lucien: Review

- 47-year-old man from Senegal
- Reports increasing fatigue since starting single-tablet efavirenz, emtricitabine and tenofovir; is now exhausted
  - blames his ART and would like to switch regimens



Discussion

- Given what we have just discussed, how would you recommend managing Lucien's fatigue?

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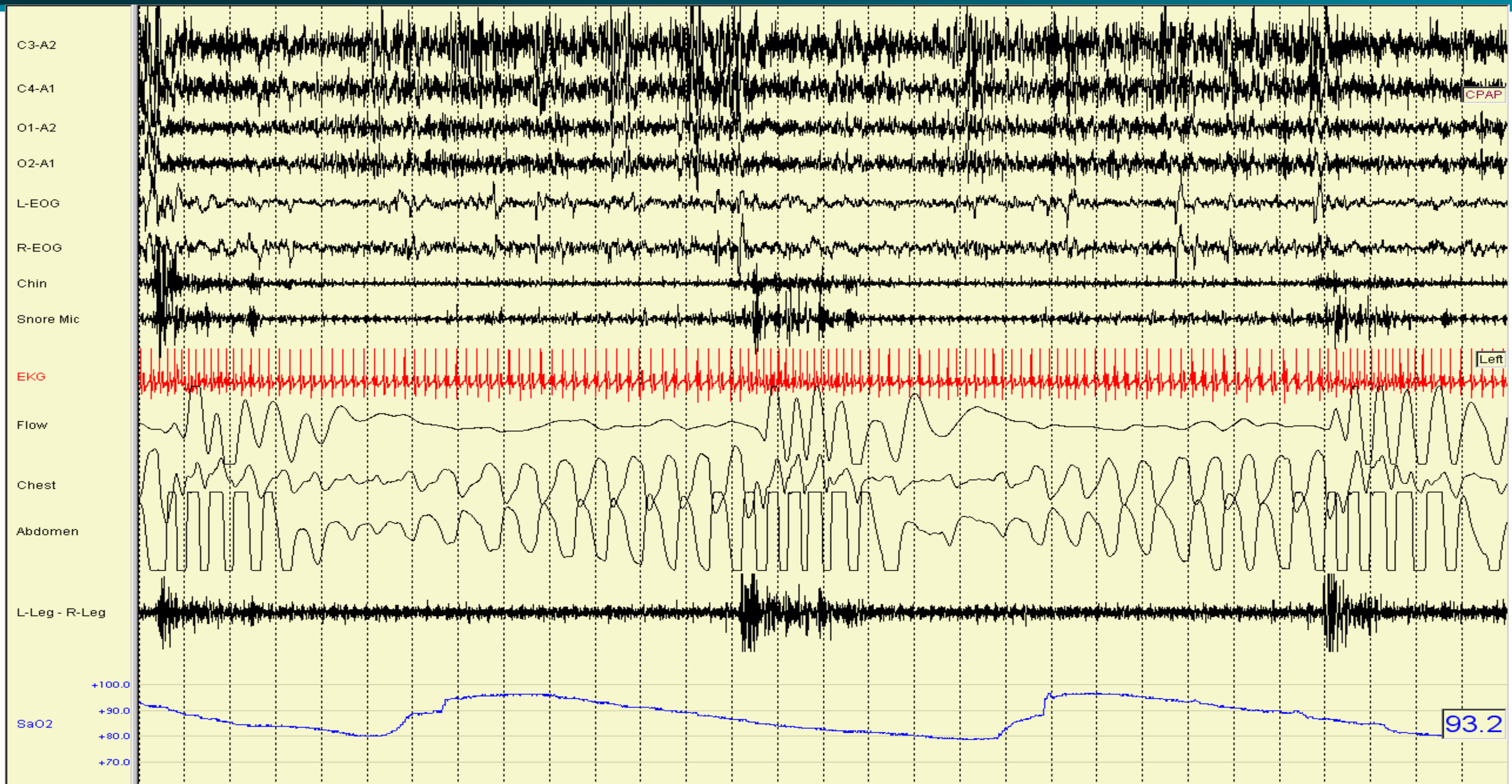
Lucien: Management

- Responses to sleep questionnaire indicated high risk for sleep apnea
- Assessment by a sleep specialist was recommended
  - patient was receptive to this suggestion
- Sleep study showed that the patient had obstructive sleep apnea
  - sleep specialist recommended management with a continuous positive airway pressure (CPAP) device
- Once this treatment was initiated, the patient reported a resolution of his fatigue

Sleep Apnea - Before Treatment



Sleep Apnea on PAP Treatment

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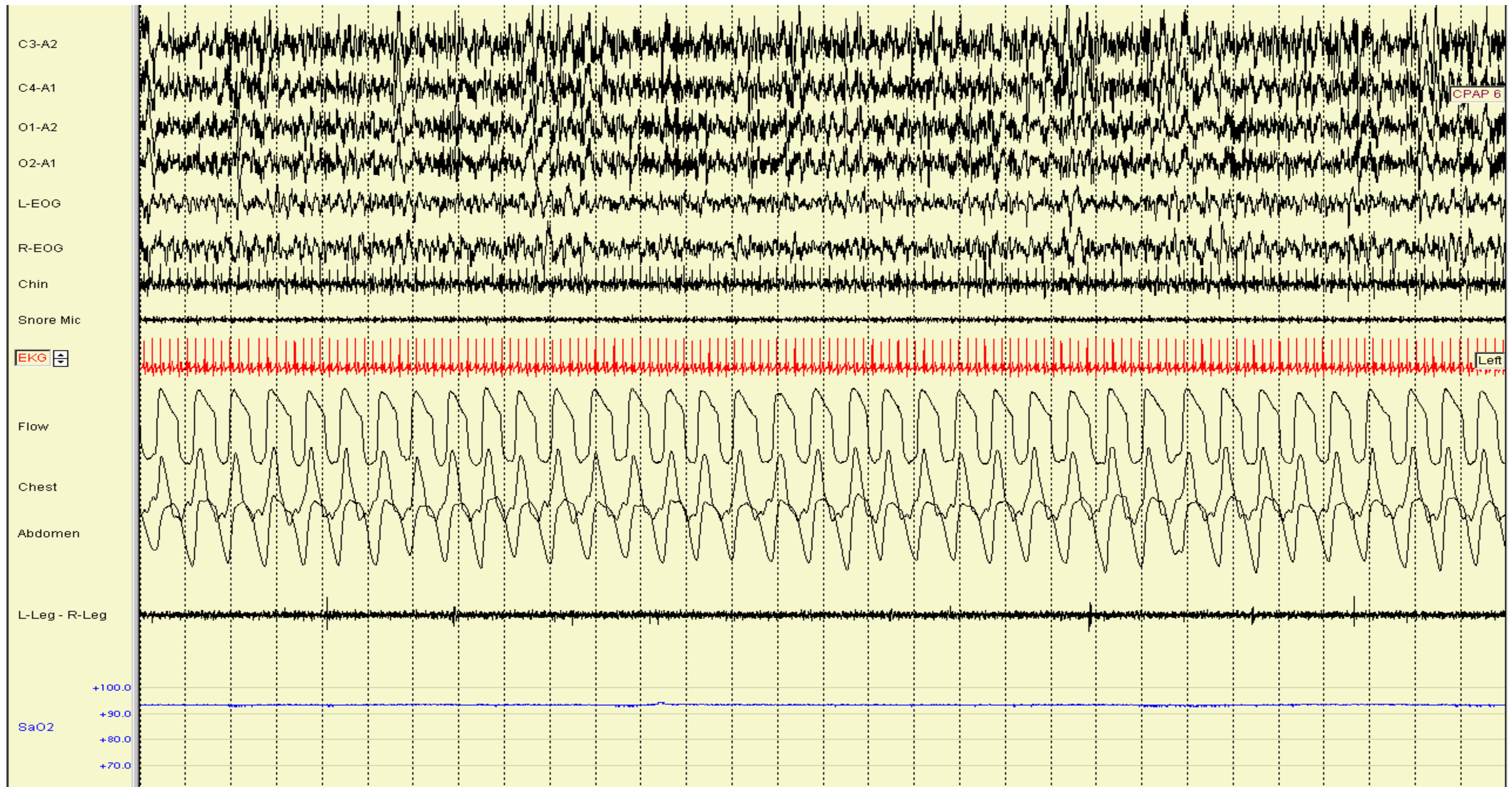

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Specialized Sleep Centres

- Approximately 150 sleep labs/clinics in Canada (about 125 in Ontario)
- Most consultations and many specialized services at these clinics are covered by provincial healthcare with appropriate referrals
- **Multidisciplinary** labs/clinics tend to be those based in universities or major teaching hospitals
- Canadian Sleep Society website provides a listing/map of sleep clinics
  - *www.canadiansleepsociety.ca/usermap/action/nationalmap*

HIV and Sleep Problems: Summary

- When faced with HIV-positive patients with sleep-related complaints, use a sleep questionnaire and take a full history to fully understand the cause(s) of the sleep problems
- An interdisciplinary approach is needed to diagnose and manage sleep problems in patients with HIV

Q & A