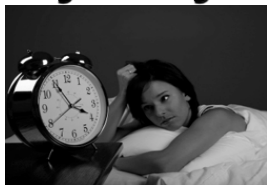


Insomnia: Help me make it though the night...



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Learning Objectives

- List 4 potential causes of chronic insomnia
- List 4 drugs that can worsen or cause insomnia
- Be familiar with 'proper' sleep hygiene techniques
- List the goals of therapy for insomnia
- Describe the short and long term benefits and risks associated with benzodiazepines
- Be familiar with the benefits and risks associated with the use of zopiclone and other medications used for treating chronic insomnia

Case 1. Ms. Jitters



- ID: 31 year old female with difficulty falling asleep (takes over 60 min) for the last month. She complains of daytime fatigue and takes naps
 - PMHx:
 - Generalized Anxiety Disorder x 2 years
 - Asthma x 15 yrs
 - Meds: Takes fluoxetine 40 mg daily x 1 year which is helpful for reducing GAD symptoms by about 60%
 - Salbutamol and betamethasone inhalers – helpful in controlling asthma
- How would you treat Ms. Jitters?

Case 2: Mr. Ian Somnia

- ID: 63 year old with fatigue, difficulty sleeping, poor concentration for 6 weeks
- HPI: otherwise healthy, no sleep apnea, no psychiatric conditions, etc.
- Social: occasional ethanol and caffeine; married; retired engineer
- Medications: occasional ibuprofen for pain, nicotine 14 mg patch (been on a patch x 7 wks)
- Physical exam and labs unremarkable

How would you treat Ian?

What is Insomnia?

- Difficulty falling asleep, maintaining sleep, or not feeling rested in spite of sufficient opportunity to sleep
- Most common sleep complaint
- Common reason to seek advice from a health care professional
- Can be transient or persistent

DSM IV Diagnostic Criteria for Primary Insomnia

- Difficulty initiating or maintaining sleep, or having nonrestorative sleep for at least a month
- Causes distress or impairment in social, occupational or other important areas of functioning
- Not related to medical disorder or other sleep disorder
- Not the result of substances

Classification of Insomnia

Primary:

Psychophysiological

Secondary:

Psychiatric, Medical, Substance Use

Categories

Transient	→	2-3 days
Short-term	→	< 3 weeks
Long-term	→	> 3 weeks

Goals of Therapy

- 1) Promote sound and restorative sleep
- 2) Minimize external (stress, noise, environment) and internal (anxiety, mood, pain) factors
- 3) Reduce daytime impairment (fatigue, poor concentration) and complications of lack of sleep
- 4) Improve the effectiveness of behavioural interventions in managing patients with primary, chronic insomnia

Treatment of Insomnia

Step 1: Get a good history, consider a sleep diary, look for potential underlying causes

Step 2: Nonpharmacological therapy

Step 3: Pharmacological options



What information do you need for both these cases?

Sleep History

- Time data
 - Napping, bed time, lights, how long to fall asleep, how many times awoken, longest awake period, time out of bed, hours of sleep
- Questions about the sleep period
 - Physical symptoms preventing sleep (pain), mental or emotional symptoms (worry, anxiety), what awakens during the night (snoring, gasping for air, nightmares), symptoms when you wake up (headache, confusion, sleepiness)
- Questions for the patient's bed partner
 - Snoring, gasping, breathing; leg twitching, jerking, kicking; alcohol, nicotine, caffeine, other drugs; change in mood or emotional state

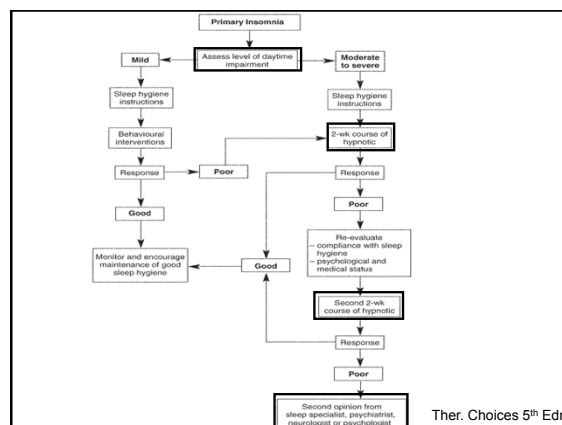
Sleep History Questionnaire		C. SLEEP PATTERN	
Name: _____ Date: _____		1. Circle the days of the week you work: _____	
Birthdate: _____ Age: _____ Occupation: _____		Monday Tuesday Wednesday Thursday Friday Saturday Sunday	
Sex: _____ Height: _____ Weight: _____ Weight Lost Year: _____		2. ON WEEKDAYS	
Referring Doctor: _____ Family Doctor: _____		a. What time do you go to bed? _____	
Describe your sleep problem: _____		b. What time do you get out of bed? _____	
What results do you expect: _____		3. ON WEEKENDS & HOLIDAYS	
A. MEDICATION SURVEY		a. What time do you go to bed? _____	
Please list all PRESCRIPTION and NON-PRESCRIPTION medications you're currently taking.		b. What time do you get out of bed? _____	
MEDICATION	REASON TAKEN	4. How long does it take for you to fall asleep? _____	
		5. How many times a night do you awaken? _____	
		a. How long do the awakenings last? _____	
		b. List any symptoms associated with the awakenings: _____	
		6. SLEEP TIME	
		a. How many hours do you usually sleep? _____	
		b. How many hours does it take to make you feel rested? _____	
		c. How many daytime naps do you take per week? _____	
		7. SLEEP QUALITY	
		a. Do you feel refreshed and still sleepy upon awakening? YES NO	
		b. How long does it take to fully awaken in the morning? _____	
		8. In the daytime, are you chemically sleepy, fatigued or tired? YES NO	
B. PLEASE LIST ALL PAST OR PRESENT MEDICAL CONDITIONS OR ILLS:		9. Grade your readiness to FALL ASLEEP during the following situations:	
		(Consider noise, sleep, bright lights of sleeping, pleasantness of sleeping, bright lights of sleeping)	
		a. Sitting and reading	
		b. Watching TV	
		c. Sitting in a car or in a public place (e.g. theater or meeting)	
		d. As a passenger in a car for an hour without a break	
		e. Lying down to rest in the afternoon	
		f. Sitting and talking to someone	
		g. Lying quietly after lunch without alcohol	
		h. In a car, while stopped for a few minutes	

<http://www.sjo.org/documents/1/sleephistoryquestionnaire.pdf>

D. SLEEP AND BREATHING		H. FAMILY HISTORY	
1. Do you snore?		AGE	
2. Do you snore loudly or frequently?		Father: _____	
3. Are the breathing pauses long enough to frighten your sleep?		Mother: _____	
4. Has your snoring driven your bed partner from the bed?		Sibling 1: _____	
5. Do you awaken with a dry mouth?		Sibling 2: _____	
6. Do you awaken with headaches?		Sibling 3: _____	
E. INSOMNIA		(continue below if necessary)	
1. Do you have trouble falling or staying asleep?		1. List any relatives who have sleep problems or snore? _____	
2. Do you worry about being able to fall asleep on time?			
3. Do you feel sleepy prior to getting into bed?			
4. Does your mind race with thoughts when lying awake?			
5. Do daytime worries keep you awake at night?			
6. Does pain disturb your sleep?			
7. Does heat, cold, hunger or thirst disturb your sleep?			
8. Is your stomach the primary reason your life is in a state of distress?			
9. Do you rely on a sleeping medication?			
10. Do you watch TV, read, or work in bed?			
11. Do you frequently travel across 2 or more time zones?			
F. SLEEP DISTURBANCES		I. PERSONAL HISTORY (Check any, not all that apply)	
1. Do you experience unpleasant leg sensations or twitches?		<input type="checkbox"/> slipped heart beat <input type="checkbox"/> heart failure <input type="checkbox"/> heart attack <input type="checkbox"/> heart murmur	
2. Do you kick or jerk your legs and/or arms during sleep?		<input type="checkbox"/> high blood pressure <input type="checkbox"/> thyroid problems <input type="checkbox"/> diabetes <input type="checkbox"/> stroke	
3. Do you have restless or awake from sleep feeling trouble?		<input type="checkbox"/> epilepsy <input type="checkbox"/> headache <input type="checkbox"/> hypertension <input type="checkbox"/> asthma	
4. Do you awaken with a bitter or acid taste?		<input type="checkbox"/> nasal congestion <input type="checkbox"/> deviated nasal septum <input type="checkbox"/> enlarged tonsils <input type="checkbox"/> sinusitis	
5. Do you frequently have nightmares or vivid dreams?		<input type="checkbox"/> reflux <input type="checkbox"/> glaucoma <input type="checkbox"/> depression/anxiety <input type="checkbox"/> bipolar disorder	
6. Have you ever woken or talked in your sleep?		J. BED PARTNER QUESTIONNAIRE (Please have your bed partner check any and all that apply)	
7. Have you ever been unable to sleep for a few seasons?		<input type="checkbox"/> Light snoring <input type="checkbox"/> Heavy snoring <input type="checkbox"/> Leg or body twitches <input type="checkbox"/> Leg kicking	
8. Have you ever been unable to sleep for a few seasons?		<input type="checkbox"/> Snoring in bed <input type="checkbox"/> Snoring in bed <input type="checkbox"/> Daytime sleepiness <input type="checkbox"/> Daytime confusion	
9. Have you ever experienced weakness when laughing or		<input type="checkbox"/> Snoring in bed <input type="checkbox"/> Snoring in bed <input type="checkbox"/> Daytime sleepiness <input type="checkbox"/> Daytime confusion	
10. Have you ever had unusual impressions or behaviors after		<input type="checkbox"/> Snoring in bed <input type="checkbox"/> Snoring in bed <input type="checkbox"/> Daytime sleepiness <input type="checkbox"/> Daytime confusion	
11. Have you ever had unusual impressions or behaviors after		<input type="checkbox"/> Snoring in bed <input type="checkbox"/> Snoring in bed <input type="checkbox"/> Daytime sleepiness <input type="checkbox"/> Daytime confusion	
Describe:		K. ADDITIONAL INFORMATION	
G. PERSONAL HABITS		1. Provide additional detail regarding any of the above. Please describe the activity, the time it occurs, and how often it occurs.	
1. Do you use tobacco now or have you in the past?			
2. If yes, how many per day and for how many years?			
3. If yes, what time of day is your last drink?			
4. Do you drink alcohol?			
5. If yes, how many drinks? _____ per day / per week			
6. If yes, what time of day is your last drink?			
7. How many caffeinated beverages do you drink per day?			
8. If yes, what time of day is your last drink?			

Medications that can Cause or Worsen Insomnia

- Antidepressants
 - bupropion, fluoxetine, SNRIs, MAOIs, TCAs
- Antihypertensives
 - beta blockers, methylodopa
- Nicotine
- Sympathomimetic Amines
 - amphetamines, methylphenidate, caffeine, cocaine, decongestants, appetite suppressants, bronchodilators (e.g., salbutamol),
- Miscellaneous
 - corticosteroids, anticonvulsants (e.g., phenytoin, valproic acid), levodopa, quinidine, hormones (e.g., thyroid supplements, estrogen)



Nonpharmacological Options

- Proper sleep hygiene (see slide in handout)
- Relaxation exercises and tapes
- Stimulus control
- Sleep restriction
- Sleep diary (see sample in handout)
- Increase aerobic exercise earlier in the day (~45 minutes and should induce sweating)
- Cognitive behavioural therapy for insomnia (CBTi)

National Sleep Foundation Sleep Diary												
COMPLETE IN MORNING										COMPLETE AT END OF DAY		
Fill out days 1-4 below and days 5-7 on page 2	I went to bed last night at:	I got out of bed this morning at:	Last night I fell asleep in:	I woke up during the night:	When I woke up for the day, I felt:	Last night I slept a total of:	My sleep was disturbed by:	I consumed caffeinated drinks in the last 24 hours:	I exercised at least 20 minutes in the last 24 hours:	Approximate time before going to bed I consumed:	Medication I took during the day:	About 1 hour before going to sleep, I did the following activity:
			Overseas time	Overseas time	(Poor)	Hours (Poor)	(By coffee, etc.)	(By coffee, etc.)				(Locality & week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12)
DAY 1												
DATE												
DAY 2												
DATE												
DAY 3												
DATE												

Sleep Hygiene

1. Keep a regular sleep/wake schedule 7 days a week
2. Limit daily "in-bed" time to average sleep time prior to the sleep disturbance
3. Avoid sleeping in or daytime naps
4. Stop offending medications/substances (caffeine, nicotine, alcohol, stimulants)
5. Avoid evening stimulation
6. Try a warm, 20 minute bath near bedtime
7. Eat regularly during the day and avoid large meals near bedtime
8. Use bedroom only for sleep and intimacy – not for TV or something that keeps you too alert

Pharmacological Options

- Antihistamines
- Benzodiazepines
- Zopiclone
- Eszopiclone*
- Zaleplon*/Indiplon*
- Zolpidem*
- Antidepressants (e.g., trazodone, doxapin)
- Alcohol?
- Melatonin
- Ramelteon* (melatonin receptor agonist)
- Chloral Hydrate
- Antipsychotics
- L-Tryptophan
- Herbs (valerian, chamomile)

*Not available in Canada

6 Basic Principles

- Use lowest effective dose
- Intermittent dosing (PRN) – e.g., <4/week
- Short term treatment (2-4 weeks) depending on presentation
- Need for medication tapering if longer term
- Select and monitor medications by assessing daytime functioning and adverse effects
- Patient plays an active role in treatment

Benzodiazepines

- Effective in promoting sleep onset and maintaining sleep
- Consider half-life and metabolites
 - Particularly for the elderly
 - Increased risk of higher cortical impairment
 - Confusion and falls
 - Reduced Phase I metabolism
 - Reduced GFR and hepatic blood flow
 - "LOT" – lorazepam, oxazepam, temazepam

Benzodiazepines

- Bind to gamma sub-unit of GABA-A receptor, resulting in an increase in GABA-A receptor activity
- Improve insomnia by:
- Reducing REM sleep
 - Decreasing sleep latency
 - Decrease nocturnal awakenings
 - Tolerance develops with repeated administration

Problems with Benzodiazepines

- | | |
|-----------------------|--------------|
| • Short-term | • Long-term |
| – Adverse effects | – Tolerance |
| – Carry-over effects | – Withdrawal |
| – Cognition | – Rebound |
| – Anterograde amnesia | – Dependence |

Adverse Effects of BDZs

- Daytime drowsiness/tiredness
- Cognitive impairment
- Rebound insomnia (even after 2 wks)
- Anterograde amnesia
- Incoordination and falls
- Paradoxical effects
- Respiratory depression
- Dependence/tolerance
- Sleep walking?

Physical Dependence vs. Abuse

- Physical Dependence:
 - Down regulation of benzodiazepine receptor sensitivity
 - Need to continue to use a drug to relieve or avoid physical withdrawal symptoms
- Abuse
 - Recreational use
 - Continued use despite negative consequences
 - Dose escalation
 - Loss of control over use

Zopiclone

- Acts at the benzodiazepine receptor
 - Not a benzodiazepine
- Compared to benzodiazepines, zopiclone appears to have less or no:
 - Rebound insomnia
 - Tolerance and dependence
 - Amnesic effects
 - Morning hang-over (short half life)

Zopiclone Pharmacokinetics

- Absorption: Elderly: 75% to 94%
- Protein binding: ~45%
- Metabolism: Extensively hepatic
- $T_{1/2}$: 5 hours; Elderly: 7 hours; Hepatic impairment: 11.9 hours
- Time to peak, serum: <2 hours; Hepatic impairment: 3.5 hours
- Excretion: Urine (75%); feces (16%)

Zopiclone

- Drug interactions:
 - CNS depressants
 - CYP2C9 and CYP3A4 drugs (inducers and inhibitors)
- Adverse effects: bitter taste, dry mouth, headache, somnolence
- Serious AEs: suicidal ideation, aggression, worsening of depression
- Eszopiclone (Lunesta) available in the US

Zolpidem (Ambien or Sublinox)*

- Non-benzodiazepine, binds to the omega -1 (BZ-1) receptor subtype of the GABA-A receptor complex.
- Rapid onset of action; sleep onset/duration
- $T_{1/2}$: 2.5 - 3 h
- 5 – 10 mg Sublingual (sublinox), 6.25 mg CR (Ambien) before bedtime
- Common SE: nausea, dizziness, drowsiness, rebound insomnia
- Serious SE: suicidal ideation, worsening of depression, aggressive behaviour
- Contraindications: severe hepatic impairment, respiratory insufficiency

*Not currently sold in Canada

Trazodone

- Limited data in primary insomnia (only 2 studies)
- Lack of objective efficacy measures
- Short duration of trials (longest is 6 weeks)
- Consideration for side effects (sedation, dizziness, orthostasis, psychomotor impairment, priapism, etc.)

Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005 Apr;66(4):469-76.

Trazodone vs. zolpidem

- 14 day, placebo controlled, primary insomnia
- Subjective sleep latency and duration showed significant improvement with both trazodone and zolpidem vs. placebo
- Effect was greater with zolpidem

Silber MH. Clinical practice. Chronic insomnia. N Engl J Med. 2005 Aug 25;353(8):803-10.

Other Non-Prescription Products

Agents	Usual Dose	Comments
Diphenhydramine • Benadryl® • Sleep Eze • Simply Sleep • Nytol® • Unisom®	25-50 mg hs	Potential for serious side effects arising from anticholinergic properties (especially in elderly): residual daytime sleepiness, diminished cognitive function, dry mouth, blurred vision, constipation, urinary retention, etc. These products are not intended for long term use and tolerance to sedative effects likely develops rapidly (3 days)
Dimenhydrinate • Gravol	25-50 mg hs	Gravol not approved in Canada as a sleep aid
Doxylamine • Unisom 2	25-50 mg hs	

Toward Optimized Practice Program. Guideline for adult primary insomnia. 2010 Feb

Not Recommended

The following agents are not recommended for the management of conditioned insomnia except in cases where the agent is being used specifically to manage a co-morbidity such as depression.

Agents	Comments
Antidepressants - mirtazapine, fluvoxamine, tricyclics	Relative lack of evidence
Amitriptyline	Relative lack of evidence and significant adverse effects (such as weight gain)
Antihistamines - chlorpheniramine	Relative lack of evidence or excessive risk of daytime sedation, psychomotor impairment and anticholinergic toxicity
Antipsychotics (Conventional or 1st-Generation) - chlorpromazine, methotrimeprazine, loxapine	Relative lack of evidence and unacceptable risk of anticholinergic and neurological toxicity
Antipsychotics (Atypical or 2nd-Generation) - risperidone, olanzapine, quetiapine	Relative lack of evidence and unacceptable cost and risk of metabolic toxicity
Benzodiazepines (Intermediate and Long-Acting) - diazepam, clonazepam, flurazepam, lorazepam, nitrazepam, alprazolam, oxazepam	Excessive risk of daytime sedation and psychomotor impairment No longer recommended due to unacceptable risk of memory disturbances, abnormal thinking and psychotic behaviors
Benzodiazepines (Short-Acting) - triazolam	

Toward Optimized Practice Program. Guideline for adult primary insomnia. 2010 Feb

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QUESTIONS???