Sleep Disorder

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Socioeconomic Consequences

- 40 million Americans suffer form chronic disorders of sleep and wakefulness
- 95% of these remain unidentified and undiagnosed
- The annual direct cost of sleep-related problems is $16 billion, with an additional $50-$100 billion in indirect costs (accidents, litigation , property destruction, hospitalization and death)

Sleep

- A very complex orchestration of physiological and behavioral processes
- Unlike coma: physiologic, recurrent and reversible

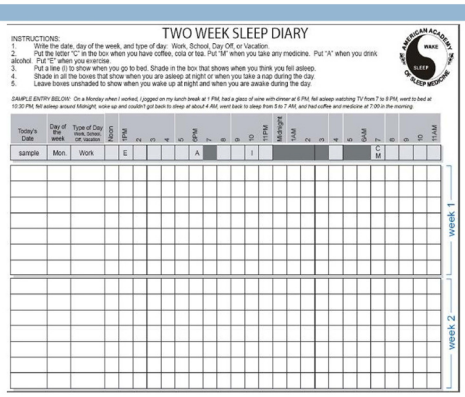
Sleep disorders

- Breathing disorders
  - Sleep apnea
- Neurological
  - Restless legs syndrome
- Psychiatric
  - Insomnia
- Medical
- Drug associated
  - Alcohol, hypnotics, stimulants
- Circadian rhythms
  - Phase shift syndrome
- Abnormal behavior
  - Sleep walking
  - Night terrors

Approach to and evaluation of sleep disorders

- Sleep history
- Use of prescription drugs
- Sleep diary or sleep log
- Sleep and psychological rating scale
- Focused physical examination
- Polysomnography
- Actigraphy
- Blood tests

수면일지 (sleep log)


TWO WEEK SLEEP DIARY

INSTRUCTIONS:
1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (|) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 9 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't get back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

Today's Date	Day of the week	Type of Day (work, school, off, vacation)	Noon	1PM	2	3	4	5	6PM	7	8	9	10	11PM	Midnight	1AM	2	3	4	5	6AM	7	8	9	10	11AM
sample	Mon.	Work		E					A					I							C M					

week 1

week 2

Evaluation of Sleep

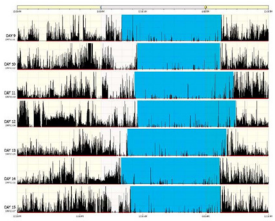
- Polysomnography
  - EMG
  - Airflow
  - EEG, EOG
  - Oxygen saturation
  - Cardiac rhythm
  - Leg movements
  - AI, HI, AHI, RDI

Sleep stage

Sleep stage assigned to each epoch (30 seconds) : stage occupying the majority of time within that epoch

Awake	Stage W (Wakefulness)
Stage 1 sleep	Stage N1 (NREM 1 sleep)
Stage 2 sleep	Stage N2 (NREM 2 sleep)
Stage 3 sleep	Stage N3 (NREM 3 sleep)
Stage 4 sleep	
REM	Stage R (REM sleep)

Actigraphy



- Circadian rhythms and sleep patterns
- number of awakenings, wake time after sleep onset, total sleep time, and sleep efficiency

증례

10년 된 불면증으로 48세 여자 환자가 내원하였다.

환자는 밤에 잠일 들기가 어려우며 잠을 자더라도 깊은 잠이 들지 않아 자주 깨며 잠에서 깨면 다시 잠들기가 어렵다고 한다. 환자는 아침에 개운한 느낌이 전혀 없으면서 낮 동안 계속 피곤하고 머리가 아팠으나 낮잠이 들지는 않았다고 한다. 환자는 과거력상 특이 소견이 없었으며 평소에 두통약을 자주 복용하였다고 한다. 환자는 자녀문제 등으로 스트레스를 많이 받고 있으나 정신과 치료는 받지 않고 있다고 한다. 가족들이 환자가 코를 골거나 수면무호흡은 없었다고 한다.

진찰 상 신장 159cm에 체중은 48kg이고 목 둘레는 28cm이었다.

이 환자에게 알맞은 치료 법은 무엇인가?

① Cognitive-behavioral therapy

② Positional therapy

③ Benzodiazepin medications

④ Weight control

Insomnia

Insomnia

- Affecting up to 30% of adult population at one time
- Chronic insomnia
  8% of men; 12% women
- Usually a symptom of many underlying medical, psychiatric (depression) and psychological conditions
- Insomnia may be the presenting symptom of primary sleep disorders
- 15-20% of insomnia are “primary” meaning have no organic or psychological cause

Diagnostic Criteria for Insomnia (ICSD-2)

A. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, or sleep that is chronically nonrestorative or poor in quality.

B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:

1. Fatigue or malaise;
2. Attention, concentration, or memory impairment;
3. Social or vocational dysfunction or poor school performance;
4. Mood disturbance or irritability;
5. Daytime sleepiness;
6. Motivation, energy, or initiative reduction;
7. Proneness for errors/accidents at work or while driving;
8. Tension, headaches, or gastrointestinal symptoms in response to sleep loss; and
9. Concerns or worries about sleep.

DSM V criteria of Insomnia disorder

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:

1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention)
2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

E. The sleep difficulty occurs despite adequate opportunity for sleep.

F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia)

G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).

H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia

Impact of Insomnia

Biological

- Increased surveillance of immune system

Functional impairments

- Increased risk of accidents
- More likely to report lack of concentration and motivation
- Reduced productivity, work absenteeism
- Increased use of medical services

Psychological health

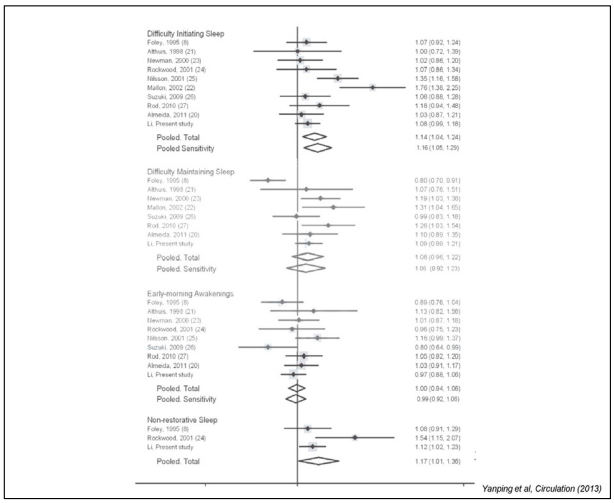
- Increases risk of developing depression, anxiety or substance, dependence
- Risk factor in suicide

Insomnia Symptoms and Mortality

- prospective cohort study of 23,447 US men in 2004 were followed through 2010
- 4 questionnaire

Insomnia symptoms	CVD mortality (case #=741)	Cancer mortality (case #=493)	Others (case #=791)
Difficulty initiating sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.06(0.89-1.25)	0.96(0.78-1.19)	1.11(0.95-1.30)
Most of the time	1.55(1.19-2.04)	1.04(0.69-1.58)	1.02(0.75-1.40)
P for trend	0.01	0.90	0.38
Difficulty maintaining sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.02(0.85-1.22)	1.20(0.96-1.50)	1.05(0.88-1.25)
Most of the time	0.99(0.81-1.21)	1.12(0.87-1.44)	1.12(0.92-1.36)
P for trend	0.94	0.37	0.26
Early-morning awakenings			
Rarely or never	Reference	Reference	Reference
Sometimes	1.04(0.89-1.21)	0.96(0.79-1.15)	0.91(0.78-1.05)
Most of the time	1.09(0.83-1.43)	1.08(0.77-1.51)	0.97(0.74-1.27)
P for trend	0.49	0.99	0.39
Non-restorative sleep			
Rarely or never	Reference	Reference	Reference
Sometimes	1.32(1.12-1.57)	0.88(0.70-1.10)	1.02(0.86-1.21)
Most of the time	1.32(1.02-1.72)	1.14(0.80-1.61)	1.16(0.89-1.50)
P for trend	0.002	0.92	0.35

Yanping et al, Circulation (2013)



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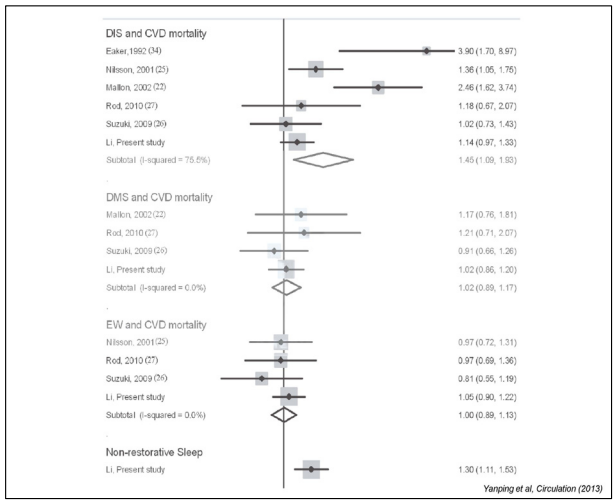


Yanping et al, Circulation (2013)

Sleeping Problems and Suicide in 75,000 Norwegian Adults

- Prospective cohort study 1984-2004
- questionnaire

	Crude[a]		Model I[b]		Model II[c]	
	HR CC[d]	95% CI	HR CC[d]	95% CI	HR CC[d]	95% CI
Total						
No problems falling asleep or other sleep disorders	1.0	Ref.	1.0	Ref.	1.0	Ref.
Sometimes	1.6	1.3-2.6	1.6	1.2-2.5	1.2	0.9-1.9
Often	2.3	1.4-5.0	2.1	1.2-4.5	1.2	0.7-2.8
Almost every night	4.9	2.3-8.3	4.3	1.9-7.4	2.1	0.9-4.0
P for trend	< 0.001		< 0.001		0.05	

Bjorngaad et al, Sleep (2011)

Insomnia treatment

- Treat underlying medical or psychiatric condition if there is one
- Cognitive-Behavioral therapy
  - Most useful for chronic insomnia
  - Sleep habits and behavioral modification
- Pharmacologic : sleep pills
  - For transient insomnia
  - Less useful for chronic insomnia – but used in selected cases

Non-pharmacologic Tx

- stimulus control
- relaxation training
- sleep restriction
- paradoxical intention
- biofeedback
- cognitive behavioral therapy (CBT-1)

Inadequate Sleep Hygiene

- Fix a bedtime and fix an awakening time
- Avoid napping during the day
- Avoid alcohol before bed
- Avoid caffeine containing beverages 4 – 6 hours before bedtime
- Avoid heavy, spicy, or sugary foods before bed
- Regular exercise is good, not before bedtime
- Comfortable bedding
- Bedroom cool, dark, quiet
- Bedroom reserved for sleep and sex – NOT a work room

Psychological and Behavioral Therapies

- Psychological and behavioral interventions are effective and recommended in the treatment of chronic primary and comorbid (secondary) insomnia.
- These treatments should be utilized as an initial intervention when appropriate and when conditions permit
- Initial approaches to treatment should include at least one behavioral intervention such as *stimulus control therapy or relaxation therapy, or the combination of cognitive therapy,* cognitive behavioral therapy for insomnia (CBT-I). Other common therapies include *sleep restriction, paradoxical intention*, and *biofeedback therapy*
- Sleep restriction and multicomponent CBT are effective in the treatment of elderly
- Although all patients with chronic insomnia should adhere to rules of good *sleep hygiene*, there is insufficient evidence to indicate that sleep hygiene alone is effective. It should be used in combination with other therapies
- When an initial psychological/ behavioral treatment has been ineffective, other psychological/ behavioral therapies, combination CBT-I therapies, combined treatments or occult comorbid disorders may next be considered

Pharmacologic Tx

- use of the lowest effective dose
- use of intermittent dosing (2 to 4 times weekly)
- short-term medication prescribing (regular use for not more than 3 to 4 weeks)
- gradual medication discontinuation to reduce rebound insomnia

Benzodiazepines

Agent	Dose (mg)	Half life (h)	Receptor	S/E	Comments
Flurazepam	15, 30	48-120	GABA-BZD	Dizziness drowsiness ataxia amnesia falls GI upset	FDA approved for insomnia; Abuse potential rebound insomnia; tolerance and dependence; hangover effect; increased fall risk; cytochrome P450 metabolism
Estazolam	1, 2	10-24			
Temazepam	7.5-30	8-20			
Triazolam	0.125-0.25	2-5			
Quazepam	7.5, 15	48-120			

Non-Benzodiazepine Medications

Agent	Dose (mg)	Half life (h)	Receptor	S/E	Comments
Zolpidem	5, 10	1.5-2.4	GABA-A; alpha-1	Dizziness drowsiness amnesia headache GI upset	For sleep-onset insomnia risk of dependence & rebound abuse potential
Zaleplon	5, 10	1.0	GABA-A: omega 1	Headache dizziness myalgia amnesia	For sleep-onset insomnia; no tolerance or hangover
Eszopiclone	1–3	5-7	GABA-A	Dry mouth unpleasant taste dizziness amnesia GI upset	Studied in elderly; favorable side effect profile; FDA approved for long-term use

MT1/MT2 Receptor Agonist

- Ramelteon

Dose (mg)	Half life (h)	Receptor	S/E	Comments
8	1-2.6	M1, M2	Headache Somnolence dizziness	Elderly; favorable S/E profile

Antidepressants

Agent	Dose (mg)	Half life (h)	Receptor	S/E	Comments
Trazodone	50-150	Early: 3–6 Late: 5–9	Possible: 5-HT2	Antidepressant dry mouth dizziness headache nervousness orthostasis	Not FDA approved for insomnia; primary use: Depression
Amitriptyline	10-100	12-24	5-HT2 noradrenaline	Dry mouth dizziness QTc prolongation constipation orthostasis	Not FDA approved for insomnia; narrow therapeutic window;anticholinergic S/E;cardiotoxic; overdose potential
Doxepin	3, 6	Early: 17 Late: 52	Postsynaptic: H1, H2, Alpha-1, 5-HT2, muscarinic	Somnolence/sedation, nausea, URI	FDA approved for insomnia
Trimipramine	25-100	11-23			Not FDA approved for insomnia

Non-prescription Medications

Agent	Dose (mg)	Half life (h)	Receptor	S/E	Comments
Diphenhydramine	25-50	2-9	Antihistamine; H-1	Drowsiness dry mouth dizziness Constipation	Not FDA approved for insomnia; Anti-cholinergic S/E
Melatonin	1-3	1-2	melatonin	Headache, irritability, dizziness	No quality controls Not FDA-regulated
Valerian	400-900	1-2	Possible: GABA-A, Adenosine 5HT-5a	Headache, restlessness, GI upset	No quality controls not FDA-regulated

Prolonged release melatonin

- Melatonin is available as a prolonged-release prescription drug, trade-name Circadin®
- The European Medicines Agency (EMA)
  - approved Circadin 2 mg (prolonged-release melatonin) for patients aged 55 or over, as monotherapy for the short-term treatment (up to 13 weeks) of primary insomnia

Restless Leg syndrome

Restless legs syndrome and periodic limb movements of sleep

- RLS is a syndrome characterized by sensory and motor disturbances of the lower extremities occurring primarily at rest
- Episodes are often painful and result in severe insomnia
  - A desire to move the limbs, usually associated with parasthesias and dysesthesias
  - Motor restlessness causing voluntary limb movements
  - Nocturnal worsening of symptoms

Essential Diagnostic criteria for RLS

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relived by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)

RLS and PLMD

- Characterized by an almost irreversible urge to move, usually associated with disagreeable leg sensations, worse during inactivity and often interfering with sleep (akisthesia)
- Symptoms worse at rest, partially relieved by activity
- Symptoms worse in the evening or at night
- Periodic limb movements : found on polysomnography
- Stereotypic movements of legs (or arms) during sleep
- 90% pts with RLS
- May be independent
- May disturb sleep

Evaluation and Diagnosis

- RLS - diagnosed from the H&P
- PLMD requires a PSG
- Labs : CBC, BUN, Cr, fasting glucose, Fe, **Ferritin,** folate and TSH
- Consider EMG/NCV as indicated for neuropathy symptoms

Treatment For RLS And PLMD

Medications for Restless Legs Syndrome and Periodic Limb Movement Disorder

Agent	Major Side Effects	Examples	Dosage
Dopamine receptors	Nausea, postural hypotension	Pergolide mesylate,* ropinirole,* bromocriptine mesylate,* pramipexole*	Start at lowest dose before bed; titrate for effectiveness
Dopamine precursors	Nausea, constipation, rebound, sleep augmentation	Levodopa/carbidopa*	Start at lowest dose (25 mg carbidopa/100 mg levodopa) before bed; titrate for effectiveness
Benzodiazepines	Excessive sedation	Clonazepam*	Start at lowest dose (0.5 mg) before bed; titrate for effectiveness
Opiates	Addiction, constipation	Propoxyphene*	Start at lowest dose (65 mg) before bed; titrate for effectiveness
Anticonvulsants	Fatigue, somnolence	Carbamazepine,* gabapentin*	Start at lowest dose (carbamazepine 100 mg, gabapentin 300 mg) before bed; titrate for effectiveness

증례

주간 졸리움으로 54세 남자환자가 내원하였다. 환자는 매일 7시간 씩 자도 다음날 아침에 일어날 때 머리가 띵하고 개운하지 않았다고 하며 겨울에 자고 나면 입이 마르고 목이 아픈 경우가 흔하다고 하였다. 환자는 낮에 사무직으로 근무를 하며 일 하다가 자주 조는 경우가 많아 커피를 하루에 3-4잔 복용하고 있다고 한다. 장거리 운전을 할 때는 조는 경우가 흔하게 있어 부인이 운전하는 경우도 많았다고 한다.

환자는 보호자가 코를 많이 골다가 가끔 숨을 멈추기도 한다고 하였으나 본인은 코를 심하게 고는지는 모르겠다고 하였다.

환자의 신장은 173cm에 목둘레 46cm, 체중은 85kg이었다.

수면다원 검사상 환자의 평균Apnea-hypopnea index가 55/hr 이었고 lateral decubitus 자세로 자는 경우에도 AHI 가 32/hr 였다.

이 환자에서 가장 효과적인 치료 법은 무엇 인가 ?

① O_2 supply during sleep

② Continuous positive airway pressure (CPAP)

③ Tongue retaining device

④ Uvulopalatopharyngoplasty

Sleep Apnea

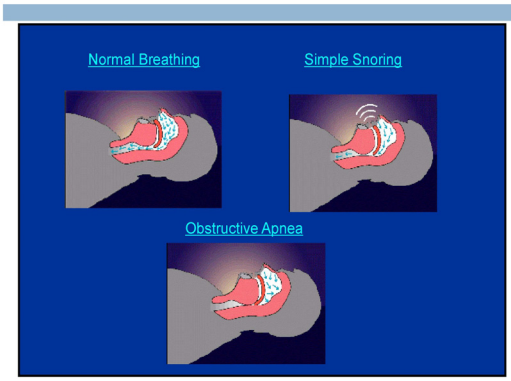
Sleep Apnea Syndrome

- Is characterized by repetitive episodes of decreased airflow that occur during sleep. Decreased airflow may be associated with a reduction in blood oxygen saturation, and enhanced autonomic activity.
- Apneic events may terminate in arousals with resultant sleep fragmentation.

Sleep Apnea type

- Obstructive Sleep Apnea (OSA) : most common
- Central Sleep Apnea

Obstructive Sleep Apnea (OSA)



Prevalence of Obstructive Sleep Apnea

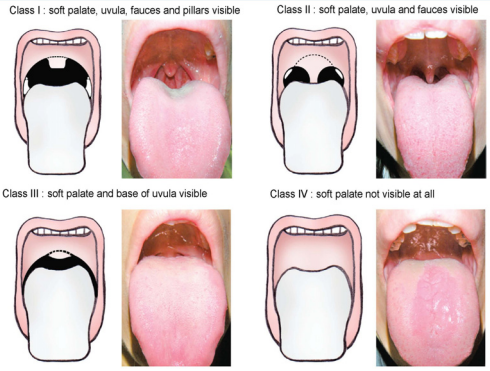
		Age	Prevalence of AHI>5		Prevalence of AHI>15	
			Men	Women	Men	Women
Wisconsin	626	30-60	24 (19-28)	9 (6-12)	9 (6-11)	4 (2-7)
Penn	1741	20-99	17 (15-20)		7 (6-9)	2 (2-3)
Spain	400	30-70	26 (20-32)	28 (20-35)	14 (10-18)	7 (3-11)

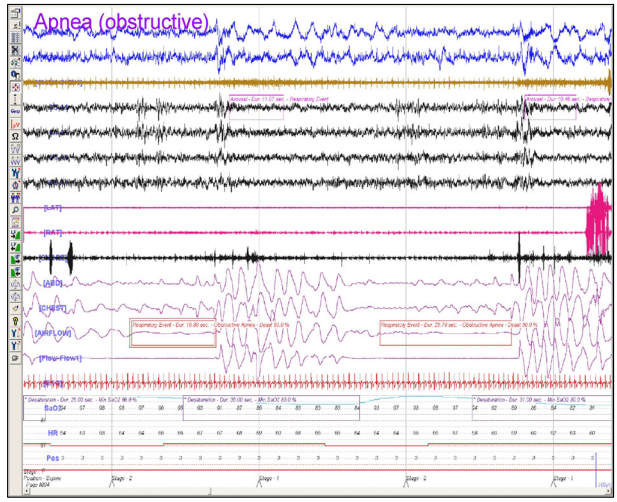
Young T, Am J Respir Crit Care Med (2002)

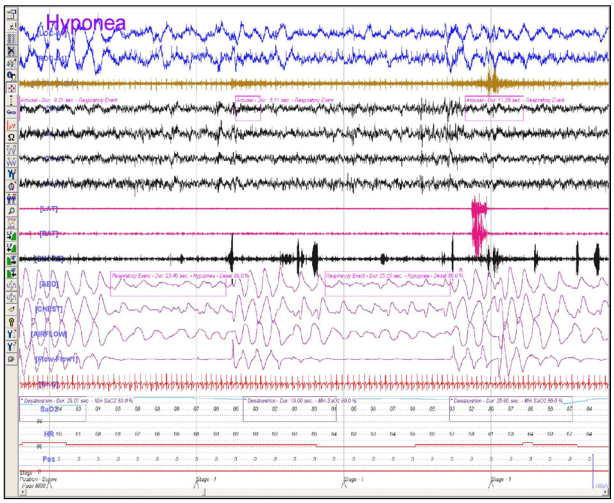
Diagnosis of OSA

- Past History
- Family
- Polysomnography

Modified Mallampati classification







Diagnosis of OSA in PSG

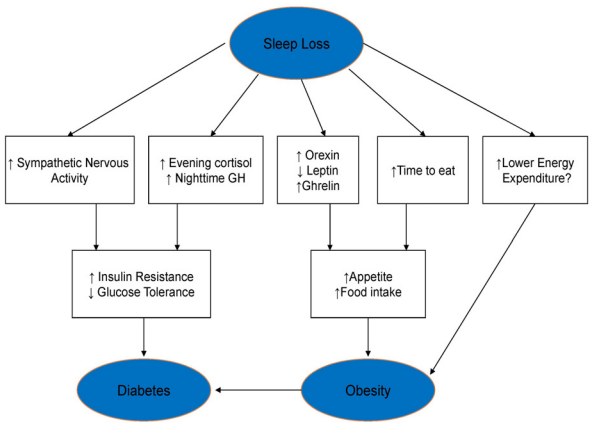
- Apnea index (AI) + Hypopnea index (HI): AHI
- Rough guideline for severity
  - normal : AHI < 5/hr
  - mild: AHI < 15/hr, moderate : 15-30/hr, severe: > 30/hr
- Desaturation: decrease in SaO2 of 4% or more

* note that nadir in SaO_2 commonly follows apnea (hypopnea) termination by approximately 10-30 sec (at finger)

- The number of desaturations below 85%, the mean and minimum saturations

Sleep Apnea-Hypopnea Syndrome

- Excessive daytime sleepiness
- Snoring
- Obesity is a risk
  - Only 50% are obese, means 50% NOT obese
- Poor cognition/memory
- Social/sexual/psychologic problems



Schematic of the putative pathways leading from sleep loss to diabetes and obesity risk.

Knutson AN, Ann N Y Acad Sci. (2008)

Cardiovascular Disease

- The association with hypertension is ***striking***
- Increased risk for Heart Attack
- Increased risk for Stroke
- Increased incidence of Sudden Death
- Many cardiac rhythm disturbances

Treatment

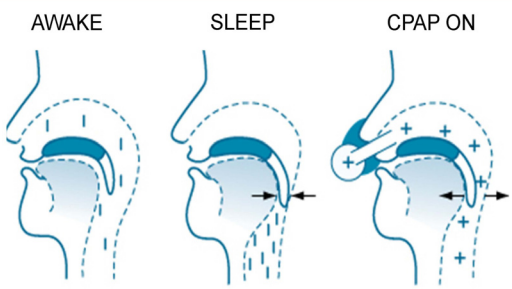
- Medical Treatment
  - Lose weight if obese
  - Eliminate alcohol, sedatives
  - Improved sleep hygiene
  - Smoking Cessation
- Continuous Positive Airway Pressure (CPAP)
- Upper airway surgery
- Dental orthotic or mandibular positioning devices

Note: Treatment recommendations are individualized for each patient: No "one size fits all"

Continuous Positive Airway Pressure (CPAP)



95% effective – usually first line treatment for severe disease



Surgical treatment

Nasal Surgery
1. Nasal septoplasty
2. Inferior turbinectomy
3. Adenoidectomy
4. Nasal tumor or polyp excision
5. Nasal valve reconstruction

Palatal Surgery
1. Uvulopalatopharyngoplasty
2. Uvulopalatal flap
3. Tonsillectomy
4. Transpalatal advancement pharyngoplasty
5. Laser-assisted uvulopalatoplasty
6. Palatal radiofrequency

Hypopharyngeal Surgery
1. Maxillomandibular osteotomy and advancement
2. Mandibular osteotomy with genioglossus advancement
3. Hyoid myotomy and suspension
4. Tongue base radiofrequency
5. Partial glossectomy
6. Lingual tonsillectomy
7. Repose tongue suspension

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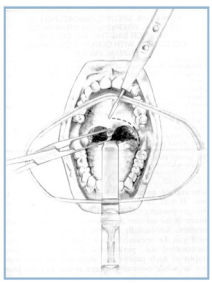
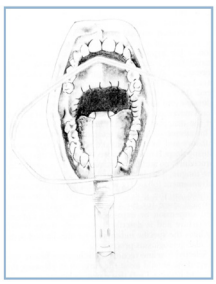
7. Repose tongue suspension

Uvulopalatopharyngoplasty (UPPP)

- Severity of disease is poor outcome predictor
- 80% initial success decreased to 46% success rate at 12mon

Dental devices

- Mandibular advancement device
- Tongue retaining device


General guidelines

UARS / mild OSA	Moderate OSA	Severe OSA
체중조절	CPAP	CPAP
자세치료	구강장치	기관지절개술
Treat nasal congestion	UPPP, GAHM	GAHM, MMO
구강장치	체중조절 - 보조적	구강장치
UPPP for OSA, UARS	자세치료 - 보조적	체중조절 - 보조적
LAUP for snoring		
CPAP		

UARS = upper airway syndrome, UPPP = Uvulopalatopharyngoplasty, LAUP = Laser-assisted uvulopalatoplasty , GAHM = Genioglossus advancement Hyoid myotomy, MMO = maxillary mandibular osteotomy, positive air pressure = CPAP or bilevel pressure