수면제의 적절한 처방 및 유해성 관리

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강 의 순 서

- 불면증의 정의와 분류
- 불면증의 비약물 요법
- 불면증의 약물 요법
- 정 리

Insomnia
Patient's complaints

- 잠들기 어렵다.
- 새벽에 너무 일찍 깬다.
- 자주 깨서 잠을 유지하기 어렵다.
- 자는데도 아침에 피로가 회복되지 않는다.

Insomnia Dx Criteria

1. Patient-reports

- Difficulty initiating/maintaining sleep, or waking up too early
- Chronically non-restorative sleep (poor in quality)

2. The above sleep difficulty

- Despite adequate opportunity & circumstances

Insomina Dx Criteria

3. Daytime impairment (at least 1)

- Fatigue or malaise
- Attention, concentration, or memory impairment
- Social or vocational dysfunction, or poor school performance
- Mood disturbances or irritability
- Daytime sleepiness
- Motivation, energy, or initiative reduction
- Proneness for errors, or accidents at work or while driving
- Tension, headaches, or GI symptoms in response to sleep loss
- Concerns or worries about sleep

Sleep History

Temporal aspects

- Times at which the patient goes to bed, attempts to sleep, wakes up, & gets out of bed

Quantitative aspects

- Sleep latency; No. & duration of awakenings; wakefulness after sleep onset (WASO); total sleep time

Qualitative aspects

- Subjective sleep quality, satisfaction

Sleep History

Behavioral & Envirnmental factors

- Nonsleep activities in bed (phone, TV); environment (temperature, light, sound); bed partners & pets; perceived causes of awakening

Symptoms of other sleep disorders

- OSA; RLS; Parasomnias (unusual sleep behavior); circadian rhythm disorders (unusual sleep timing)

Daytime causes & consequences of disturbed sleep

- Napping; exercise; work & activities; social & family stressors; use of caffeine, alcohol, & tobacco

Medical & Psychiatric History

Medical disorders

- Neurologic (stroke, migraine); pulmonary (Asthma, COPD); Chronic pain (arthritis, FM); endocrine (thyroid dysfunction); GERD; cardiovascular (CHF)

Psychiatric disorders

- Depression; MDI; anxiety disorders; substance use disorders

Medications

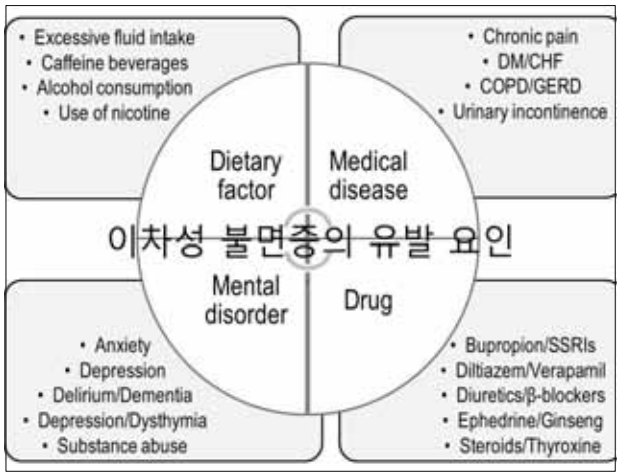
- Antidepressants; other sedatives; antihypertensives; steroids; decongestant & antihistamines; adrenergic agonists

불 면 증

일차성	이차성
• Psychophysiological	• 다른 수면 장애
• Paradoxical	• 내과 질환
• Adjustment	• 정신과 질환
• Poor sleep hygiene	• 신경과 질환
• Idiopathic	• 약물/중독성 물질/알코올

일차성 불면증

- Psychophysiological
  - 여러 스트레스에 의해 시작
  - 환자 스스로 악화시켜 만성화
- Paradoxical
  - 실제로 잠을 자는데 환자는 거의 못 잔다고 생각
- Adjustment
  - 스트레스에 의한 일시적 불면증
- Poor sleep hygiene
  - 불량한 수면 위생에 의한 불면증
- Idiopathic
  - 어릴 적부터 높은 각성 상태로 2~3시간 밖에 못 잠



Other Tools & Tests

Sleep-wake diary

- Prospective record of sleep-wake timing, quantity, & quality; may identify patterns that are useful targets for behavioral treatment

Wrist actigraphy

- Measure & store movement data for up to 28 days; rest-activity patterns correlate with sleep-wakefulness

Polysomnography (sleep study)

- Not recommended for routine assessment of insomnia but appropriate to evaluate suspected sleep apnea or parasomnias

Cognitive-Behavioral Interventions for Insomnia

- Sleep hygiene education
- Stimulus control therapy
- Sleep restriction therapy
- Relaxation training
- Cognitive therapy
- Cognitive-behavioral therapy for insomnia
- Brief behavioral treatment of insomnia

수면 위생

취침과 기상 시각을 일정하게 한다.

- 늦게 자더라도 같은 시각에 일어난다.

낮잠은 피한다.

- 정말로 졸리는 경우, 10~15분 정도로 제한한다.

매일 규칙적으로 운동한다.

- 잠자리에 들기 2~3시간 전에는 마치는 것이 좋다.

샤워나 목욕으로 체온을 올린다.

- 잠자리에 들기 2시간 이내에 약 30분간 온수로 한다.

수면 위생

수면을 방해하는 물질을 삼간다.

- 담배, 술/카페인 음료 등을 피우지도 먹지도 않는다.

시계는 보이지 않는 곳에 둔다.

- 밤에 일어나더라도 시계를 보지 않는다.

침실은 어둡고, 조용하고, 공기 순환이 잘 되도록 한다.

- 편안한 실내 온도를 유지하도록 한다.

15분 이상 잠이 오지 않으면, 누워 있지 말고 일어난다.

- 단순 반복 작업을 하면서 잠이 올 때까지 기다린다.

자극 조절 교육

1. 잠이 올 때에만 잠자리에 든다.
   잠자리에 누운 후 15~20분 이내에 잠에 들지 않으면,
2. 침실을 나가서 독서, TV 시청 등 다른 활동을 하다가
   잠이 오면 다시 침실로 들어간다.
3. 잠에 들 때까지 2번을 여러 번 반복한다.
4. 잠에 늦게 들더라도 아침 기상 시각은 일정하게 한다.
5. 밤에 잠을 잘 자지 못했더라도 낮잠을 가급적 자지 않는다.

수면 제한 요법

8시간 누워 있으나, 실제 잔 시간은 5.5시간

- 수면 효율 = 68.7%
- 누워 있는 시간을 5.5시간으로 제한하고,
  매일 수면 일기를 작성하도록 한다.
- 1주 후, 수면 효율이 90% 이상이면,
  누워 있는 시간을 15분 늘린다.
- 1주 후, 수면 효율이 90% 이상이면, 15분씩 늘린다.
  하지만, 85% 미만으로 떨어지면, 잠자리 시간을 다시 줄인다.
- 이와 같은 방법으로 가장 적절한 수면 시간에 도달하게 한다.

Characteristics of the ideal sedative-hypnotic

Has rapid onset of action

Prevents nocturnal & early-morning awakenings

Maintains normal sleep architecture

Produce no daytime sedation or adverse effects

Lacks active metabolites of parent compound
(ie, has defined duration of action, fewer residual effects)

Has no drug-drug interaction

Characteristics of the ideal sedative-hypnotic

Is metabolized through a mechanism
other than the hepatic CYP 450 system

Has no potential
for abuse/tolerance/rebound insomnia after discontinuation

Is safe in overdose

Has fixed dosing with no need
to reduce the optimal dose in elderly patients

Address the physiologic condition underlying insomnia

불면증의 약물치료

- Benzodiazepine Receptor Agonists (BzRAs)
- Melatonin Receptor Agonists (MRAs)
- Anti-depressants (ADs)
- Anti-psychotics (APs)

BzRAs Benzodiazepines

Drugs	Usual Bedtime Dose, mg	Dose in the Elderly, mg	Onset of Action, hr	Duration of Action, hr
Estazolam	1~2	0.5~1	1~2	6~10
Flurazepam	15~30	Avoid	1~2	10~20
Quazepam	7.5~15	Avoid	1~2	10~20
Temazepam	15~30	7.5~15	1~2	6~10
Triazolam	0.125~0.25	0.125	0.25~0.5	2~5

BzRAs Benzodiazepines

Drugs	Clinically Significant Metabolites	Half-life Mean (Range), hr	Metabolism	Food Effect
Estazolam	No	15(10~24)	CYP2D6/3A4	No
Flurazepam	Yes	75 (40~150)	CYP2D6/3A4	No
Quazepam	Yes	40 (25~79)	CYP2D6/3A4	No
Temazepam	No	8.8 (3.5~18.4)	Glucuronidation	No
Triazolam	No	2.5 (1.5~5.5)	CYP3A4	No

BzRAs Benzodiazepines

- Flurazepam – **Avoid in the elderly!**
  - 달마둠 15 mg
- Temazepam
  - 복합 아루사루민 : 4 T po tid (식간/취침시)
    - Scopolia extract 5 mg, Sucralfate 200 mg, Temazepam 1.2 mg
  - 수크라민/잔트락에스/잔티팜: 2 T po tid (식간/취침시)
    - Scopolia extract 10 mg, Sucralfate 400 mg, Temazepam 2.4 mg
- Triazolam
  - 할시온/트리졸/졸민 : 0.125 mg/0.25 mg; 트리람 0.25 mg

No Approved Benzodiazepines

Drugs	T_{max}, hr	Elimin. half-life, hr	Usual Hypnotic Dose, mg	Comments
Alprazolam	0.6~1.4	6~20	0.25~0.5	Often noted for significant withdrawal
Lorazepam	0.7~1	10~20	0.25~1	Metabolized by conjugation (no CYP drug interactions)
Clonazepam	1~2.5	20~40	0.5~3	Often used for restless leg syndrome

BzRAs Non-Benzodiazepines

Drugs	Usual Bedtime Dose, mg	Dose in the Elderly, mg	Onset of Action, hr	Duration of Action, hr
Eszopiclone	2~3	1~2	0.5~1	5~8
Zaleplon	5~10	5	0.25~0.5	2~4
Zolpidem	5~10	2.5~5	0.25~0.5	3~8
Zolpidem CR	6.25~12.5	6.25	0.25~0.5	3~8

BzRAs Non-Benzodiazepines

Drugs	Clinically Significant Metabolites	Half-life Mean (Range), hr	Metabolism	Food Effect
Eszopiclone	No	6 (5~7)	CYP3A4/2E1	Yes
Zaleplon	No	1 (0.9~1.1)	Aldehyde oxidase /CYP3A4	Yes
Zolpidem	No	2.5 (1.4~4.5)	CYP3A4	Yes
Zolpidem CR	No	2.8 (1.6~4.1)	CYP3A4	Yes

Zolpidem

- Zolpidem 10 mg
  - 스틸녹스, 졸피드, 졸피람, ...
  - 졸뎀 속붕정 (Zoldem OD)
- Zolpidem-CR 6.25 mg/12.5 mg
  - 스틸녹스-CR 6.25 mg/12.5 mg

Adverse effects of BzRA hypnotics

- Morning sedation
  - **Residual effects**
    : the experience of impaired function in the morning after using a hypnotic.
- Antero-grade amnesia
- Impaired balance → Falls & hip fractures ↑
- Complex sleep-related behaviors
  - **Sleep** eating/walking/**driving**; sexual or violent behavior

Additional concerns regarding BzRAs

- Rebound insomnia
  - worsened sleep for 1~ 2 nights after discontinuation relative to baseline
  - during abrupt discontinuation
- Withdrawal
  - new symptoms other than the initial one after discontinuation
- Dependence
  - Individuals with no substance use history
    : therapy-seeking behavior rather than drug-seeking behavior
  - Individuals with a history of alcohol or other sedative abuse
    : abuse can occur with BZ & non-BZ hypnotics.

MRAs

Drugs	Usual Bedtime Dose, mg	Dose in the Elderly, mg	Onset of Action, hr	Duration of Action, hr
Ramelteon	8	8	0.25~0.5	6~8
Melatonin * No FDA approved	0.5~3		0.3~1	

MRAs

Drugs	Clinically Significant Metabolites	Half-life Mean (Range), hr	Metabolism	Food Effect
Ramelteon	Yes	2 (1~2.6)	CYP1A2 * Avoid using with CYP1A2 inhibitors (eg, fluvoxamine)	No
Melatonin		(0.6~1)		

Sedating ADs

Drugs	T_{max}, hr	Half life, hr	Mechanism	Usual Hypnotic Dose, mg	FDA-Approved
Doxepin	3.5 (1.5~4)	15 (10~30)	LD: H1 ANT HD: 5HT2, α1, M1 ANT; NE, 5HT RI	3~6 10~100	Insomnia Depression
Amitriptyline	2~5	30 (5~45)	5HT2, α1, M1 ANT; NE, 5HT RI	10~100	Depression
Trazodone	1~2	9 (7~15)	5HT2, α1, H1 ANT; 5HT RI	25~150	Depression
Mirtazapine	2 (1~3)	30 (20~40)	5HT2-3, α1-2, H1, M1 ANT; 5HT RI	7.5~30	Depression

Sedating APs

Drugs	T_{max}, hr	Half life, hr	Mechanism	Usual Hypnotic Dose, mg	FDA-Approved
Olanzapine * Hypotension, wt gain, akathisia, dizziness	4~6	4~8	5HT2, D1-4, α1, H1, M1-5 ANT	2.5~20	Schizophrenia Bipolar disorder
Quetiapine * Dry mouth, constipation, wt gain, asthenia, headache	1~2	10	5HT1-2, D1-2, α1-2, H1, ANT	25~50	Schizophrenia Bipolar disorder

Others commonly used as hypnotics

Anti-histamine drugs

- H1, M1 antagonist
- Diphenhydramine, doxylamine, hydroxyzine
- Adverse effects : cognitive impairment, urinary retention

Anti-convulsant drugs

- Gabapentin (hypnotic dose :100~900 mg) : PHN, DPN
- Pregabalin (hypnotic dose : 50~300 mg) : DPN, PHN, FM
- Adverse effects : dizziness, dry mouth, fatigue, ataxia, ...

Summary - 1

Insomnia : diagnosis

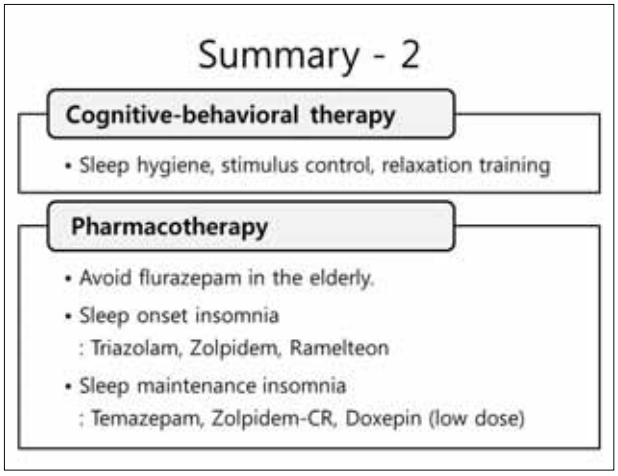
- Not only sleep difficulty, but also a daytime impairment or distress.

Insomnia : subtypes

- Primary << Secondary

Insomnia : treatment

- Cognitive-Behavioral Therapy + Pharmacotherapy


Summary - 2
Cognitive-behavioral therapy
• Sleep hygiene, stimulus control, relaxation training
Pharmacotherapy
• Avoid flurazepam in the elderly.
• Sleep onset insomnia
: Triazolam, Zolpidem, Ramelteon
• Sleep maintenance insomnia
: Temazepam, Zolpidem-CR, Doxepin (low dose)