

불면증의 약물 치료 : 진정수면제

Drug Treatment of Insomnia : Sedative-Hypnotics

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■ ABSTRACT

A growing number of people are concerned about their sleep. There are many people with chronic sleep disorders. Sedative-hypnotics including benzodiazepine and non-benzodiazepine have been widely used in chronic insomniacs. It is widely accepted that current hypnotics are efficient in alleviating subjective symptoms of insomnia. Non-benzodiazepine hypnotics include zolpidem, zopiclone, and melatonin. These novel non-benzodiazepine hypnotics that have efficacy comparable to benzodiazepines were developed with more understanding of benzodiazepine receptor pharmacology. Their unique pharmacologic profiles may offer few significant advantages in terms of adverse effects of benzodiazepines. However, most of hypnotics including non-benzodiazepine have some of dependence, tolerance, impaired daytime function and rebound insomnia. Currently, it is accepted that combination therapy with pharmacologic and behavioral intervention is the most effective for chronic insomniacs. **Sleep Medicine and Psychophysiology 1999 ; 6(1) : 5-18**

Key words: Sedative · Hypnotics · Benzodiazepine · Non-benzodiazepine Hypnotics · Insomnia.

서 론

(1).
(poor self-esteem)
(2).
WHO (collaborative study)(3)
(psychological problems)
5,438 가 26.8%가
(diffi - (centre) 가
Nagasaki 8.3% Rio de Janeiro 42.
9% (transient)
85% (4),
(5,6).
(2,7).

1

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가 (sleep state misperception) - (sleep - wake schedule disorder)

(Int -

International Classification of Sleep Disorders)(8)
(psychophysiological insomnia)

본 론

25~50% 가
(9).
가
4%가
(10). 1995

Gallup (11)
37%가
(over - the - counter drug)
22%가 . Pillitteri
(12) 1 가
6.4% , 11.4%
23.4%

가 (13),
(prescribing guidelines)
2 4 (10, 14 -
17). 가

Mellinger (10)
85%가
5%
(18).

가
가
가
가

1. 역 사
1860 (chloral hydrate)가
(Bromides) 1870 , (paraldehyde)
1880 , 1900 (barbiturates)가
가
가
가

가 가 . ,
가 1950
(meprobamate) pro -
panediol carbamates가
가 .
1961 (chlordiazepoxide)가
(benzodiazepines, BZDs)

가 ,
flurazepam, temazepam triazolam
(dependency) (tolerance)
(initiating sleep)

1980 1990 cyclo - pyrrolone zo -
piclone imidazopyridine zolpidem

2. 수면 기능 및 기전
1) 수면 기능
(19,20),
(restorative
effect) 가 가 .
(tissue repair)(21,22), - (thermo - regulation)(23),
(immune function)(24 - 26),
(regulation of noradrenergic receptor
sensitivity)(27) (maintenance of memory)
(28)

2) 신경전달물질(neurotransmitters)과 신경조절물질(neuromodulators)

(1) BZD - GABA_A (receptor complex) GABA_A 가 GABA_A (ch-loride ion channel)

(subunit)

(1).

2). BZD - GABA_A subunit subunit

(allosteric conformation) GABA(gamma - aminobutyric acid) subunit GABA_A 가 가

GABA GABA_A 가

GABA

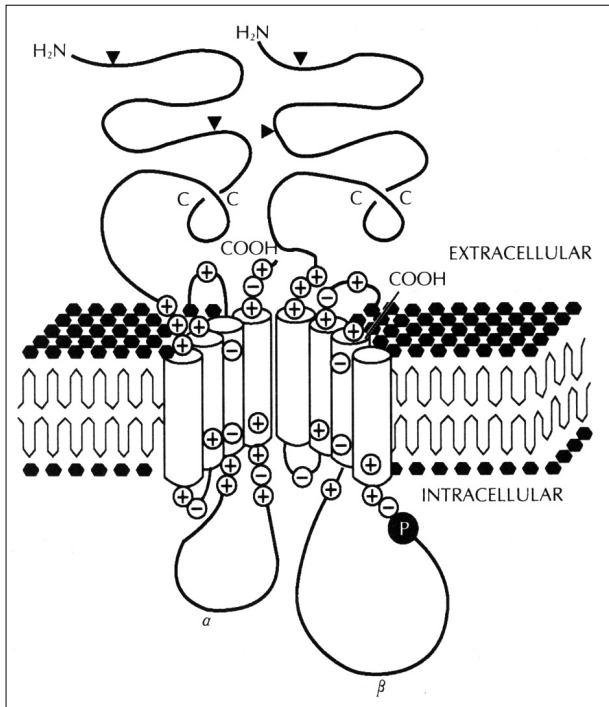


Fig. 1. Diagrammatic model of the complex GABA_A receptor, showing two subunits(α and β) lining a central ion channel. Native receptors contain two copies of the α and β subunits and may also contain a third subunit, γ (From Schofield PR et al. 1987).

GABA_A 가 GABA

(cross tolerance) 3가

GABA가 가

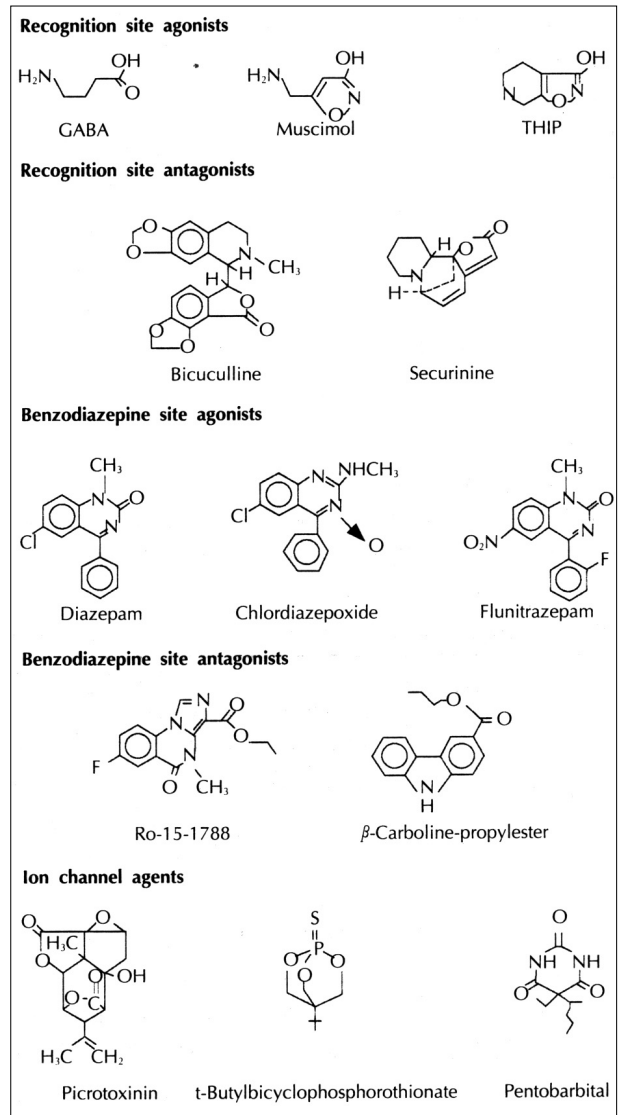


Fig. 2. The structures of the prototypical ligands for each of the binding domains of the complex GABA_A receptor.

3. 이상적인 진정수면제의 조건

GABA (hyperpolarization) (firing rate) 7 15 20 가 , 5 가 , (locus coeruleus) (monoamine - containing neurons) (29). BZD (inverse agonist) (: beta - carbolines) GABA_A (30).

3 4. 바비류레이트 가 FDA BZD 1(omega 1) , BZD 2(omega 2) , pentobarbital, secobarbital, amobarbital secobarbital amobarbital , BZD 3(omega 3) (peripheral receptor) BZD - GABA_A (, hexobarbital) , quazepam, halazepam (, pentobarbital) (, phenobarbital) 가 (2) BZD - GABA_A pentobarbital GABA - 1

Table 1. Neurotransmitters and neuromodulators that may regulate sleep-wake states

Substance	Possible roles in regulation of sleep-wakefulness
Serotonin	L-tryptophan has hypnotic effects, increases delta sleep. Serotonergic neurons in DRN cease firing in REM sleep and may inhibit cholinergic neurons in LDT-PPT, PGO waves, and REM sleep
Norepinephrine	Noradrenergic neurons in LC cease firing in REM sleep and may inhibit REM sleep. Arousal
Acetylcholine	Cholinergic neurons in dorsal tegmentum orchestrate REM sleep, and together with basal forebrain inhibit cortical EEG synchronization through influence on thalamus
Dopamine	Mediates alerting effects of amphetamine and cocaine and sedating effects of antipsychotics. Sleepiness of narcolepsy may be related to decreased dopamine turnover
Adenosine	Appears to promote sleep. Alerting effects of caffeine may be mediated by blockade of adenosine receptors
Interleukins and other immune modulators	Interleukins promote slow-wave sleep in animals, and immune modulators may be increased in plasma at sleep onset in normal controls. NREM sleep measures may correlate with natural killer cell activity in humans
Prostaglandins	PDG2 and PGE2 increase sleep and wakefulness, respectively, in animals
Endogenous sleep factors	Putative hypnotoxins include delta-sleep-inducing substance peptide(DSIP), uridine, arginine vasotocin, muramyl peptides, and others

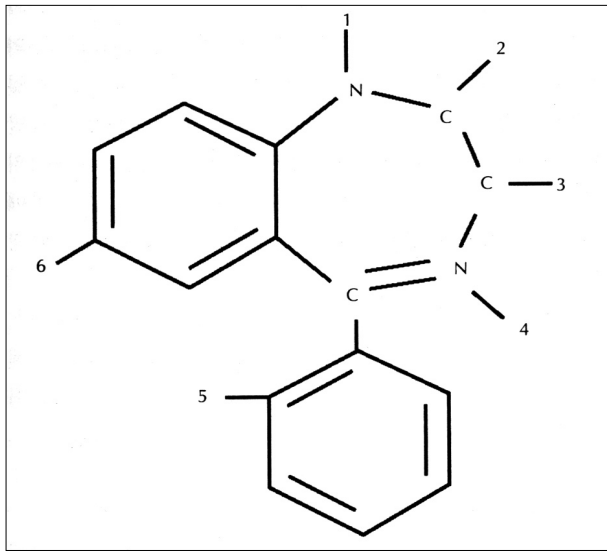


Fig. 3. Structure of core benzodiazepine.

5. BZD

2 benzene 7
diazepine
(aryl) (substitution) 가

가 (3). 2 - keto BZD(chlordiazepoxide, diazepam, clorazepate, prazepam, halazepam, flurazepam), 3 - hydroxy BZD(oxazepam, lorazepam, temazepam), triazolo BZD(alprazolam, triazolam), imidazo BZD(midazolam) 2 - thione BZD(quazepam)

(pharmacokinetics)
(absorption), (distribution), (metabolism) solubility)
(excretion) . (pharmacokinetic half - life) (dynamic effect)

clorazepate desmethyldiazepam
1~3 (enterohepatic re-circulation) 6~10 2
1.5
. Chlordiazepoxide diazepam
2 - keto 가
2 - keto diazepam, clorazepate, prazepam, halazepam, flurazepam 2 - thione BZD quazepam desmethyldiazepam
oxazepam glucuronidation

desmethyldiazepam 가
2 - keto, 2 - thione BZD (half - life time)
가 30~100 (longest - acting)
(steady plasma level) 2 ,
7~10 가 (toxicity)
가 . 3 - hydroxy BZD
glucuronidation (active metabolite)
(short - acting) 10~30
. triazolo BZD hydroxylation glu-curonidation
(shortest - acting) alprazolam 10~15
triazolam 2~3 . imidazo BZD 가 (injectable form)
(medical procedure)
가 . glucuronide hepatic microsome , oxazepam, lorazepam, temazepam
가
가
가
(lipid solubility) (pharmacokinetic half - life) (pharmacodynamic effect) 가
(affinity) (lipid solubility) , lorazepam diazepam
가 (31), diazepam(high lipid solubility) lorazepam(moderate lipid solubility)
가
가 48 diazepam 8

lorazepam 가 (32).
 midazolam 가
 1
 가 5~24
 가 (>>24)
 가
 가 (tolerance), (abstinence syndromes), (sedation) (impaired psychomotor performance)
 1

(33).
 가
 5
 가
 (34).
 (tapering)
 가
 (paradoxical reactions)
 가
 (low - voltage fast activity)가 가 (28).

(29).
 4
 temazepam
 가
 density)가 가
 2
 (29). flurazepam,
 (REM
 6. Zopiclone
 Zopiclone 1987

. zopiclone
 가 cy -

clopyrralone . zopiclone
 가 . zopiclone
 5 8
 7.5 mg(3.75 mg)
 가 ,
 . 1995 20
 , zopiclone
 .
 zopiclone

7. Zolpidem
 imidazopyridine zolpidem
 가 (35). zolpidem
 quazepam GABA_A
 (GABA_A receptor complex)
 1(type 1 BZD receptor)
 (36), quazepam
 1.5~2
 2.5~3 , conjugation
 . zolpidem
 가
 zolpidem
 가
 . Roth

(37) zolpidem
 , zolpidem 7.5 mg 10 mg
 가
 , Palminteri Narbonne(38) zolpidem
 20mg
 zolpidem , , , ,
 5 10mg
 . Zol -
 pidem
 (39), 24 (rebound effe -

cts)
 (40). Besset (41) zolpidem 8
 가 2 , REM

65 mg 가 . 65 mg 가 . 10 mg 가 . 15~20 mg 가 .

9. 수면제가 수면다원검사에 끼치는 효과(polysomnographic effect of hypnotics)

(macrostructure) 가

8. 기타 진정수면제

cycle ethers(: paraldehyde), carbamates(: meprobamate, ethinamate, carisoprodol), piperidinediones (: glutethimide, methyprylon) tertiary carbinols (: ethchlorvynol) 4

가

가 (44).

가 (anticholinergic effects) 가 (spectral analysis)

. Ppyrilamine maleate (Compoz) (mic-rostructure) non-REM

L - tryptophan serotonin (cyclic alternating pattern : CAP) SSRIs (47). CAP 가 가 가 (eosinophilia - myalgia syndrome) 4 (42).

melatonin

. melatonin 가 가 (dietary supplement)

10. 원인별 수면제 사용법

melatonin FDA (transient), (short - term) . Haimov (1995) melatonin (chronic) 가 .

tonin . Dement (acute stress), (jet - lag) Pelayo(35) (initiation) (fast - release) melatonin (time - zone changes) , (situational stress), (sustained - release) melatonin (maintenance) ,

melatonin , melatonin 4 (35).

(replacement therapy)

가 melatonin 가 가 (43). 가

melatonin

가

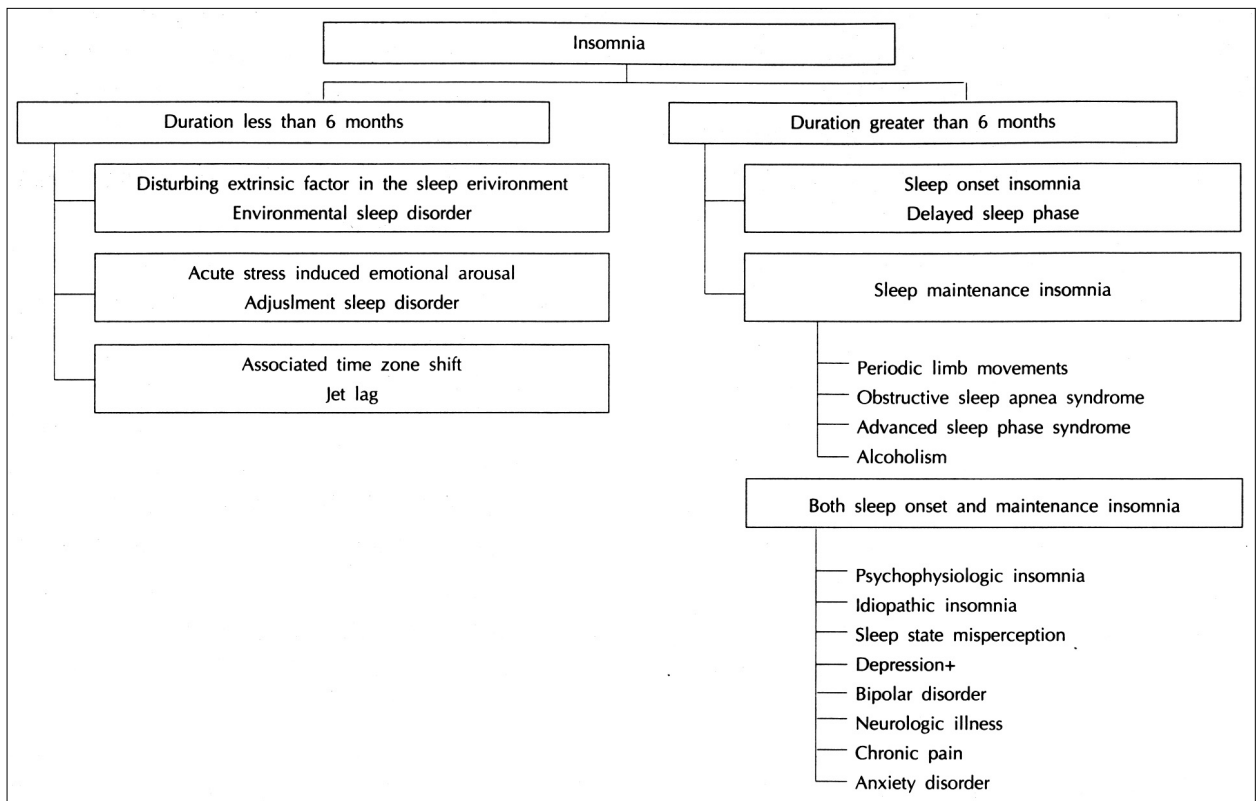


Fig. 4. Decision tree for common forms of insomnia(from De-ment WC, Pelayo R 1997).

1 3 , 1~2
 , 2
 , 3 가
 , 4 (acute epi-
 , 5 sodes of excitement),
 가
 (sleep - wake schedule disorder) , 6
 가
 (parasomnia) , 7 1 2
 (primary insomnia) , 1) 일과성 및 단기성 불면증(transient and short-term in-
 8 somnia)
 dyssomnia NOS (National Institute of (1) - (environment - related tra-
 1984 Mental Health : NIMH) (Consensus Confe- nsient insomnia)
 (5). (unfamiliar sleep environment)
 가
 (short - acting agent) (first night effect)
 가 (nonconductive sleep environment)

Table 2. Common hypnotics used in the US

Common hypnotics	Dosage(mg)	Estimated cost for brand name pills	Pharmacology T1/2(hours)
Zolpidem (Ambien®)	10	\$52.40	1.7 ± 0.1
Triazolam (Halcion®)	0.125(elderly) 0.250(adults)	\$25.90(0.25mg)	2.6 ± 0.7
Temazepam (Restoril®)	15(elderly) 30 - 60(adults)	\$27.75(30mg)	8.4 ± 0.6
Diazepam (Valium®)	2.5 - 5(elderly) 5 - 10(adults)	\$22.10(5mg)	32.0 ± 11.0
Flurazepam (Dalmane®)	15(elderly) 15 - 30(adults)	\$23.15(30mg)	40 - 100
Estazolam (ProSom®)	0.5 - 1(elderly) 1(adults)	\$34.60(1mg)	Active metabolites 17.1 ± 1.3
Lorazepam (Ativan®)	1 - 2(elderly)	\$29.60(2mg)	

(from Dement WC & Pelayo R 1997)

Table 3. Effects of hypnotic drugs on sleep structures and others

Hypnotic drugs	Healthy volunteer		Insomniacs		Others
	Increase	Decrease	Increase	Decrease	
Flurazepam (T _{1/2} : >40 h)	SPT S2 spindle power delta power	SWS S4	TST SE	REM-S SWS	- No evidence of rebound insomnia - MSLT
Flunirazepam (T _{1/2} : 25 h)	TST SE S2 REM-L spindle power	SL REM-S	SWS(during first 2hr in short term use)		- rebound insomnia after long term use
Temazepam (T _{1/2} : 9.5 - 12.4 h)	S2	SL WASO S1 S4 delta powersd	SPT S2	SL SWS	- No signs of rebound insomnia in elderly - MSLT
Triazolam (T _{1/2} : 1.5 - 5.5 h)	TST SE S2 spindle power delta power	SL WASO SWS	SPT S2 spindle power	WASO delta power	- No MSLT - Evidence of rebound insomnia
Zopiclone (T _{1/2} : 3.6 - 6 h)	SPT S2	WASO SL S1 REM-S	TST REM-L spindle power SWS(some case)	WASO SL CAP rate	- No evidence of rebound insomnia
Zolpidem (T _{1/2} : 1.5 - 2.4 h)	SE	SL	SPT SWS S2	SL WASO CAP rate	- Unremarkable macrostructural change in healthy - No MSLT - No evidence of rebound insomnia

SPT: sleep period time ; TST: total sleep time ; SE: sleep efficiency ; SL: sleep latency ; WASO: wake after sleep onset ; S1: stage 1 sleep ; S2: stage 2 sleep ; S3: stage 3 sleep ; S4: stage 4 sleep ; SWS: slow wave sleep ; REM-L: REM latency ; REM-S ; REM sleep ; CAP: cyclic alternating pattern

(2) - (stress - related tra -
nsient insomnia)

가 가

가

가

가 . 가 . (4) - (drug - related transient insomnia)

가 .

가 . 1~2 . 가, 가,

가 . 가 .

가 . 가 . (behavioral dependency)

가 . 가 .

2~3 . 1~2 .

가 . (reassurance), (support) (education) . (ed - 가 .

3 . , (beta - blocker) 가

가 .

(3) - (sleep schedule - related transient insomnia) 2) 일차성 불면증(primary insomnia) (primary) DSM

가. (jet lag) . , 1 .

가 . 가 . 가 . (8) (psychophysiological insomnia), (sleep state misperception), (circadian rhythm) , (idiopathic insomnia) .

3 . 가 .

(1) (psychophysiological insomnia) " " ("behavioral" insomnia) 가

(shift work) . , 1 . 가 , 가

가, . 가 . (chronotherapy) , 가 .

가 (innate 가
hyperarousal) amitriptyline 10 mg hs
가 trazodone 200 mg

가 TV 가 가 가 가
(3) (sleep state misperception)
가

가 5%

1 가 가 가 가
가 가 가 가
가 15% 가 가 가
가 가 가

가

(2) (idiopathic insomnia) 3) 수면다원검사상의 특징적 소견과 관련된 불면증

(1)
(reticular activating system) solitary tract nuclei, raphe nuclei, medial forebrain area (C-PAP), (uvulopalatopharyngoplasty, UPPP)
"pu- 가 가
sh-pull system

(2) (atypical polysomnographic findings ; alpha - delta sleep pattern)

가 가 가
가 (nonrestorative sleep)
가 (first - night effect)가 (hypersomnolence)
가 7.5~11 Hz 가
(alpha - delta pattern).

alpha intrusion (sleep apnea, periodic move-

ment of the legs) 가

가 . 가 가 . PLMS

(fibrositis, rheumatoid arthritis, posttrau- 가 . (nonrestorative
matic or other pain disorder) , sleep) . 12%

6% PLMS가 . 40 가

PLMS가

, 가 fibrositis

amitryptiline cyclobenzaprine .

5~120 0.5~5

. 8 40

(3) (restless legs and
periodic limb movements in sleep) clonazepam 0.5~2 mg
(restless legs syndrome : RLS) , temazepam .
(calves) baclofen, levodopa . 가

(periodic limb movements during sleep : PLMS) ,

. RLS PLMS

. RLS가

(sensory manifestation) PLMS **결 론**

(motor manifestation) .

PLMS nocturnal my- 가

oclonus, sleep - related myoclonus (48), 가

, myoclonus가 (Babinski re- 가

flex) . RLS 가

PLMS가 .

가

(dopaminergic activity) 가

. , folate, ferritin 가 , (47).

RLS 1993 Gallup (48)

10 7 (69%)

. RLS , 32%

가 가 .

PLMS 20~40 가

(self - efficacy)

중심 단어 :

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