



Insomnia and Health



What is sleep?

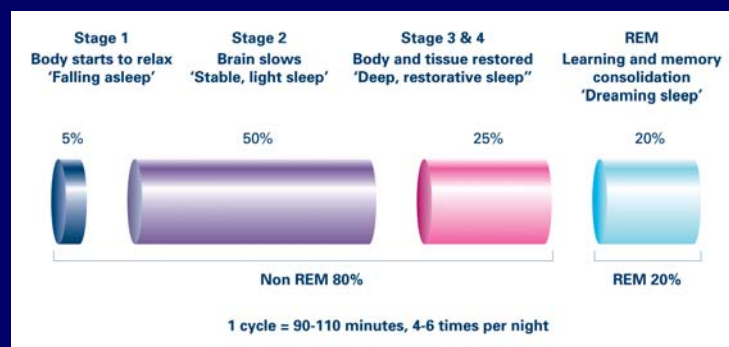


The normal sleep cycle

- ◆ Types of Sleep:
 - REM (rapid eye movement)
 - 20-25% of sleep
 - NREM (non-rapid eye movement)
 - Subdivided into stages 1-4
 - 75-80% of sleep
- ◆ On a typical night, 3-6 cycles of alternating NREM and REM occur

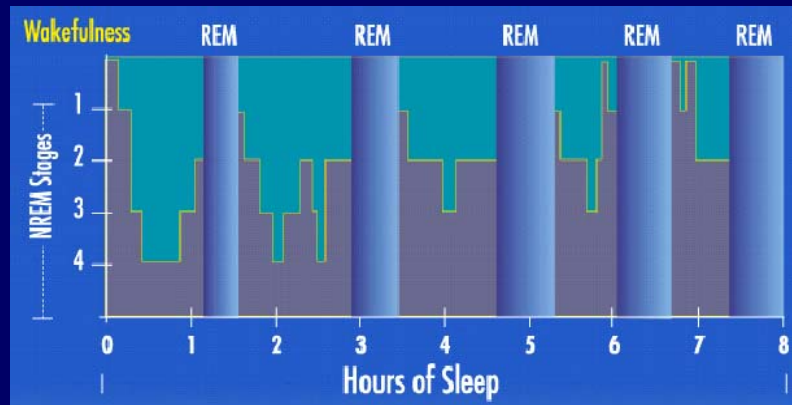
1. Lavie P, et al. Sleep Disorders: Diagnosis, management and treatment. A handbook for clinicians. London: Martin Dunitz Ltd (a member of the Taylor & Francis Group); 2002:1-18

The normal sleep cycle



1. Adapted from Lavie, P et al. Sleep Disorders: Diagnosis, management and treatment. A handbook for clinicians. London: Martin Dunitz Ltd (a member of the Taylor & Francis Group); 2002:1-18
2. Phillips BA & Gelula RL (eds). 2006. Sleep-Wake cycle: its physiology and impact on health. National Sleep Foundation. www.sleepfoundation.org

The normal sleep cycle



The importance of REM and non-REM sleep

- ◆ Both REM and non-REM are essential to normal sleep¹:
- ◆ REM
 - Stimulation of brain growth
 - Consolidation of memory
- ◆ NREM
 - Growth hormone secretion
 - Repair and restoration of physiological systems

1. Erman MK. *J Clin Psychiatry* 2001; 62 (suppl 10):9-17

Sleep needs and architecture vary with age

Sleep duration and architecture changes across the life span

	Sleep hours	Stage 1-2 (%)	Stage 3-4 (%)	REM (%)
Infants	13-16	10-30	30-40	40-50
Children	8-12	40-60	20-30	20-30
Adults	6-9	45-60	15-25	15-25
Elderly	5-8	50-80	5-15	5-25

1. Kennedy GA, et al. How to Treat – Insomnia – Part 1. Australian Doctor. 2004.
Available at: http://www.australiandoctor.com.au/html/pdf/AD_HTT_037_44_APR02_04.pdf.
[Accessed: 15/11/07]

How is sleep regulated

- ◆ Homeostatic sleep drive and circadian rhythms work together to regulate sleep
- ◆ Homeostatic sleep drive
 - During the day the homeostatic sleep drive builds up and dissipates during sleep
- ◆ The circadian rhythm runs on a ~24 hr cycle of physiological activity
 - The circadian rhythm is driven by light which in turn regulates release of melatonin
 - Bright light on the retina activates the circadian pacemaker in the suprachiasmatic nucleus that in turn down regulates melatonin release from the pineal gland
 - Melatonin entrains the circadian rhythm to the light-dark cycle and is also mildly hypnotic and increases the propensity for sleep

1. Lack LC, et al. *Cell Mol Life Sci* 2007; 64:1205-15

What is insomnia?

What is insomnia?



1. Buysse D. Definition, diagnosis, classification and etiology of chronic insomnia. In: National Institutes of Health, NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults; 2005 June 13-15; Bethesda, USA. Bethesda, MD: National Institutes of Health, 2005

Next day symptoms

- ◆ At least one of the following forms of daytime impairment may be reported:
 - Fatigue/malaise
 - Attention, concentration, memory impairment
 - Social/vocational dysfunction or poor school performance
 - Mood disturbance/irritability
 - Motivation/energy reduction
 - Errors/accidents
 - Tension headaches/gastrointestinal symptoms
 - Concerns or worries about sleep

1. Buysse D. Definition, diagnosis, classification and etiology of chronic insomnia.
In: National Institutes of Health, NIH State-of-the-Science Conference on Manifestations
and Management of Chronic Insomnia in Adults; 2005 June 13-15. Bethesda, USA.
Bethesda, MD: National Institutes of Health, 2005

Classification of insomnia

- ◆ Primary insomnia^{1,2}
 - Sleep difficulty for ≥ 1 month
 - Independent for another sleep or mental disorder
 - A clinically significant impairment of functioning
 - Not due to substance or general medical condition
 - 25-30% of insomnia cases³
- ◆ Comorbid insomnia^{1,2} (Secondary insomnia)
 - Insomnia associated with
 - A mental disorder
 - A medical condition
 - Substance-induced sleep disorder, insomnia type
 - Up to 75% of cases in general practice³

1. American Psychiatric Association. Diagnostic and statistical Manual of mental disorders 4th ed text rev(DSM-IV TR)

2. NIH State-of the Science Conference Statement J Clin Sleep Med. 2005;1:412-421

3. Leger D, et al. *Curr Med Res & Opin* 2005;21:1785-92

2005 NIH Consensus Conference

recommended that the term “**comorbid insomnia**” replace “secondary” insomnia.

◆ NIH 2005 Consensus statement

- “Most cases of insomnia are comorbid with other condition.”
- “... there is concern that the term secondary insomnia may promote undertreatment. Therefore, we propose that the term ‘comorbid insomnia’ may be more appropriate.”
- “‘Primary insomnia’ implies that no other case of sleep disturbance has been identified.”

Who is at most risk of insomnia?

- ◆ Insomnia affects up to 30-40% of the population of Western Societies²
- ◆ More commonly affects:
 - Women
 - Elderly
 - People living alone (i.e. divorced or widowed)
 - Shift workers with disturbed sleep patterns
 - Travelers adjusting to new time zones
 - Individuals suffering work related/emotional stress

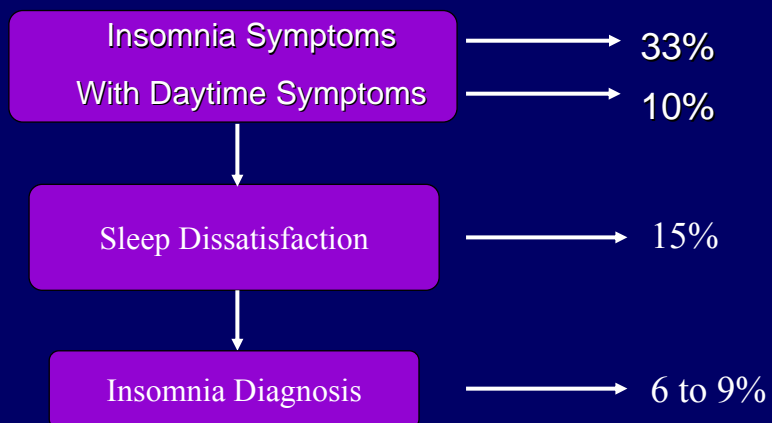
1. Access Economics Pty Limited for sleep health Australia. Wake up Australia: The value of healthy sleep. October 2004

2. Ohayon MM. *Sleep Med Rev* 2002;6:97-111

Prevalence/epidemiology of insomnia



Prevalence of Insomnia



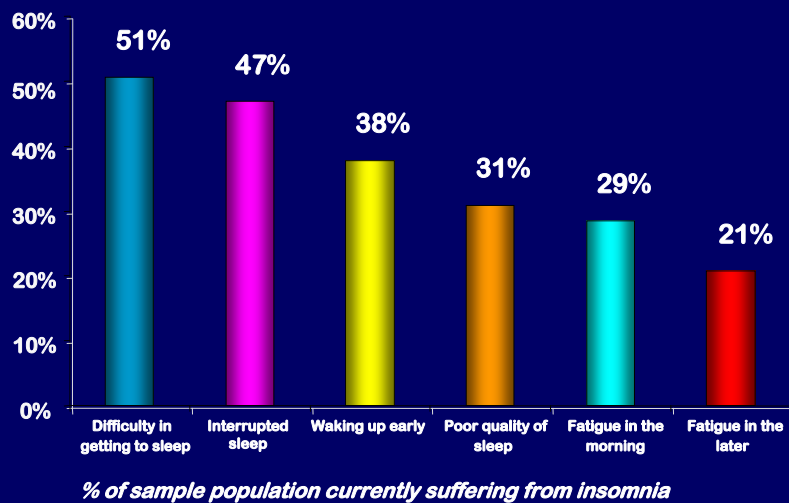
Ohayon MM. *Sleep Med Rev.* 2002;6:97-111.

The Prevalence of Chronic Insomnia

- ◆ Approximately 30% of the general population experience insomnia at least occasionally, and about 10% suffer from chronic insomnia. ¹⁾
 - In general populations : 8.5~24.3%
 - In clinical populations : 27.8~43.0%
 - In outpatients of general practice:19.8~53.7%
- ◆ Remission rate after 4-month follow up: 13.1%

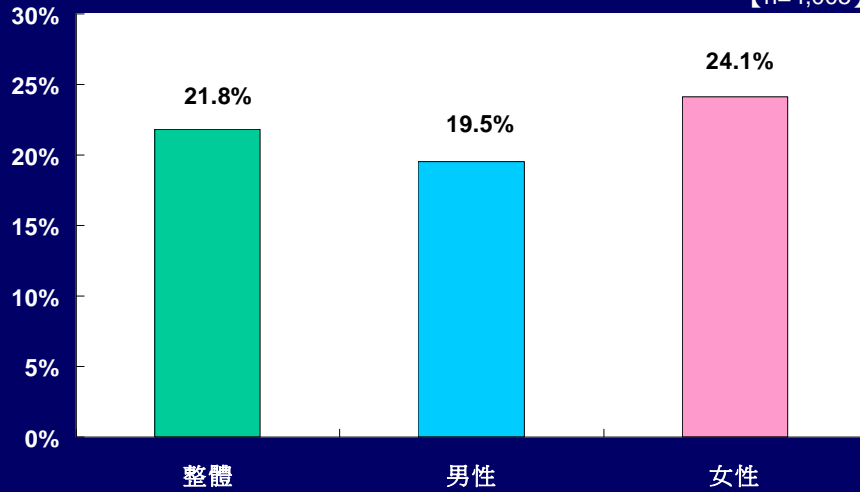
National Institutes of Health. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults /Evidence report/Agency for health Research and Quality 2005, June 13-15, 2005. Sleep. 2005;28:1049-1057.

Symptoms reported by Consumers (Consumer Omnibus Phase, n = 1515)



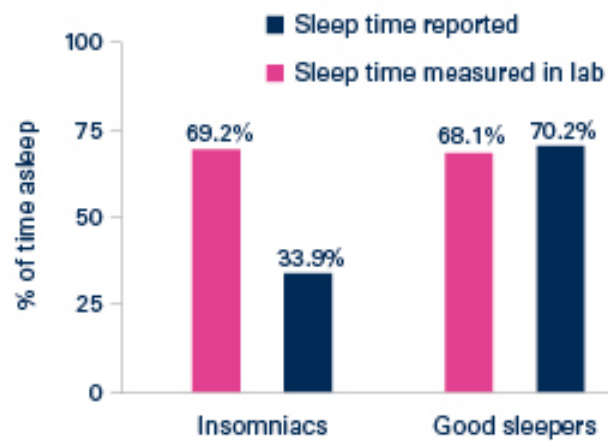
台灣慢性失眠盛行率

【n=4,005】



2009年12月睡眠醫學學會電訪結果

Optimal sleep hours – perception and reality



1. Mercer JD, et al. *Sleep* 2002;25:559-66

Burden and Costs of Insomnia

- ◆ Quality of life
 - ◆ Psychiatric and medical comorbidity
 - ◆ Functional impairment
 - ◆ Work absenteeism
 - ◆ Health care utilization/cost
-

Impact of daily sleep on Health

Under strict experimental conditions, short-term restriction of sleep results in:

- Hypertension
 - Activation of the sympathetic nervous system
 - Impairment of glucose control
 - Increased inflammation
-

Alvarez GG et al. *Prog Cardiovasc Nurs.* 2004

Types of insomnia

Pattern	Duration	Causative groupings
Transient	A few days	Acute illness, social stress, jet lag, work shift changes
Short-term	A few weeks < 30 days	Grief, stress, substance or medicinal exposures
Chronic	Long-term > 30 days	Medical illness, pain conditions, psychiatric illness
Primary sleep disorders	Long-term	Sleep apneas, restless legs syndrome

1. Lippmann S, et al. *South Med J* 2001;94:866-73

Causes of insomnia

◆ Causes of Acute Insomnia

- Situational stress
 - Work, family, money
- Environmental
 - Climate, noise
- Death or illness of loved one

◆ Causes of Chronic Insomnia

- Medical
 - Including: cancer, chronic pain, nocturia, stroke
- Psychiatric disorders
 - Including: depression, bipolar disorder, schizophrenia
- Medications
 - Including: antidepressants, antiepileptics, beta blockers, steroids
- Primary sleep disorder
 - Periodic limb movements, sleep apnoea, restless leg syndrome
- Sleep disorder
 - Jetlag, shift work, sleep cycle disorder
- Substance abuse

1. Ramakrishnan K, et al. *Am Acad Fam Physician* 2007;76:517-26

Common Comorbid Medical Disorders...

System	Examples
Neurological	Stroke, dementia, Parkinson's, seizures, headache, TBI, neuropathy, pain, neuromuscular
Cardiovascular	Angina, CHF, dyspnea, dysrhythmias
Pulmonary	COPD, emphysema, asthma, laryngospasm
Digestive	Reflux, ulcer, colitis, irritable bowel syndrome
Genitourinary	Incontinence, benign prostatic hypertrophy, nocturia, enuresis, interstitial cystitis
Endocrine	Hypothyroidism, hyperthyroidism, diabetes
Musculoskeletal	Arthritis, fibromyalgia, Sjogren's, kyphosis
Reproductive	Pregnancy, menopause, menstrual variations

Common Comorbid Psychiatric Disorders

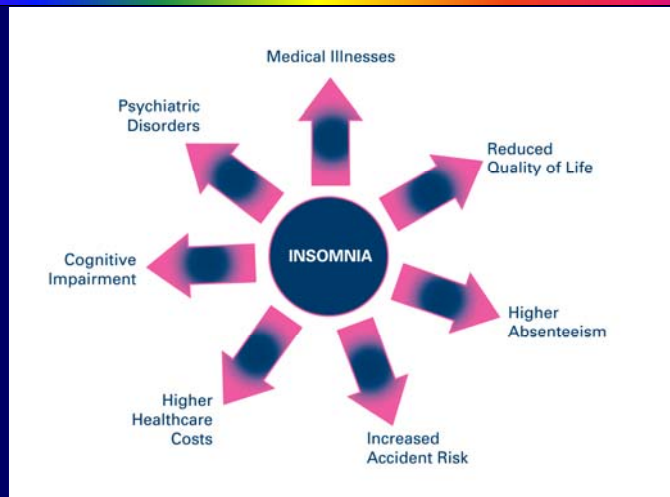
Category	Examples
Mood disorders	Major depressive, bipolar mood, dysthymia
Anxiety disorders	Generalized anxiety, panic, post-traumatic stress, OCD
Psychotic disorders	Schizophrenia, schizoaffective
Amnestic disorders	Alzheimer's, other dementias
Seen in childhood	Attention deficit disorder
Other disorders and symptoms	Adjustment, personality, bereavement, stress

Common Contributing Medications and Substances

Category	Examples
Antidepressants	SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine), venlafaxine, duloxetine, MAOIs
Stimulants	Caffeine, methylphenidate, amphetamine derivatives, ephedrine, cocaine
Decongestants	Pseudoephedrine, phenylephrine, phenylpropanolamine
Narcotic analgesics	Oxycodone, codeine, propoxyphene
Cardiovascular	Beta blockers, alpha receptor agonists/antagonists, diuretics, lipid-lowering agents
Pulmonary	Theophylline, albuterol
Alcohol	

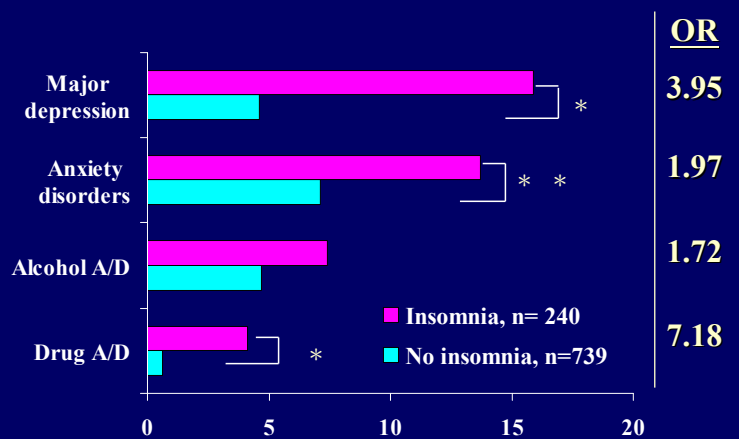
Consequences and impact of insomnia

Consequences and impact of insomnia



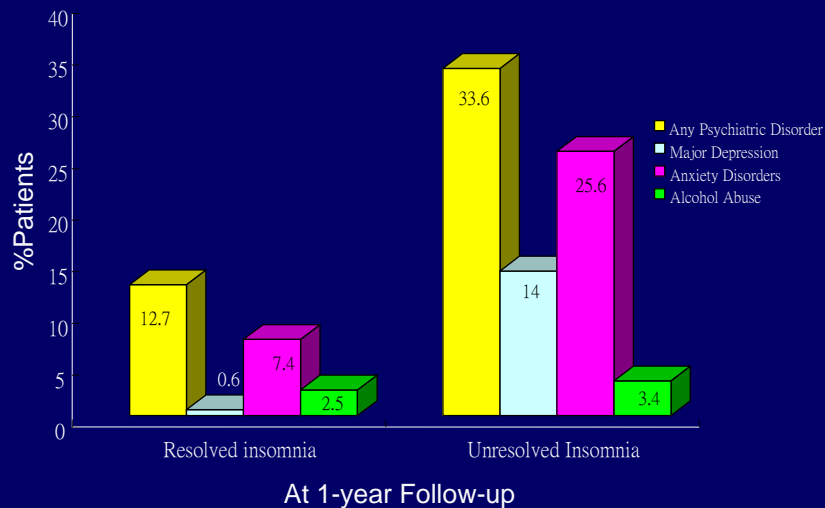
1. Benca RM, et al. *Clin Psychiatry* 2001;62(Suppl 10):33-38

Incidence and Odds Ratios of New Psychiatric Disorders by Prior History of Insomnia (3.5 years)



Breslau et al. *Biol Psychiatry*. 1996;39:411-418.

Persistent insomnia is a risk factor for future psychiatric disorder



Adapted from Ford DE and Kamerow DB, 1989

Insomnia is recognized as a chronic disorder

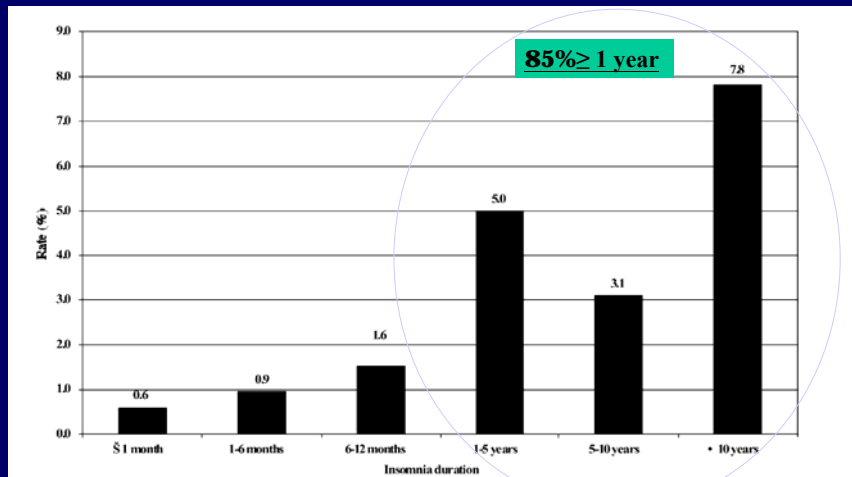
Persistent insomnia is associated with an increased risk for certain medical disorders and psychiatric illnesses

- ◆ Sleep disturbance had persisted for at least 6 months in 90% of those reporting insomnia. ¹⁾
- ◆ At the 2-year follow-up, the sleep disturbance persisted in 83% of the patients reporting severe baseline insomnia and 59% of those with mild baseline insomnia. ²⁾

1. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res.* 2003;37:9-15

2. Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med.* 1998;158:1090-1107

Insomnia is a Chronic Condition

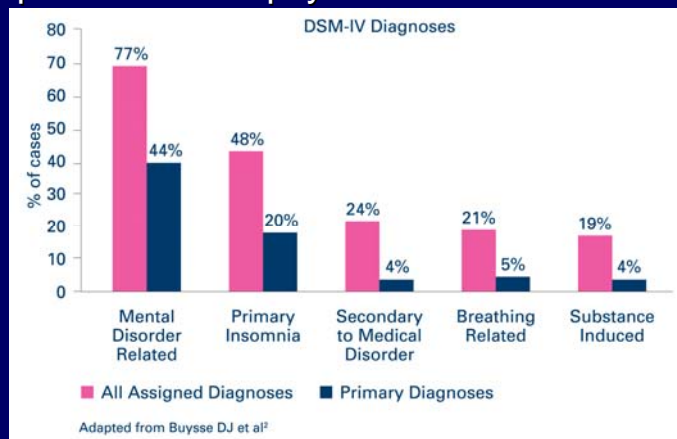


Ohayon MM, Roth T(2003). Journal of Psychiatric Research.37:9-15.

Insomnia and psychiatric illness

Insomnia and psychiatric disorders

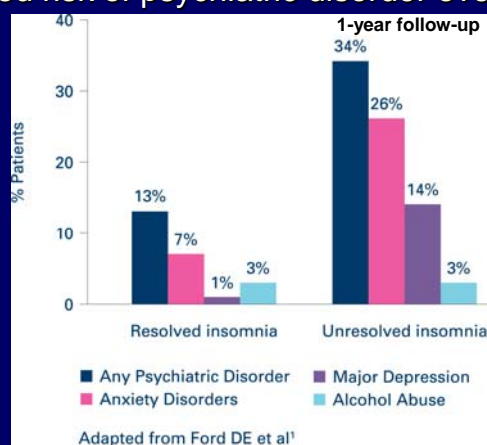
- ◆ Insomnia is a common co-morbidity in patients with a psychiatric disorder^{1,2}



1. Neubauer DN. *Prim Psychiatry* 2006;13:1-16
 2. Buysse DJ, et al. *Sleep* 1994;17:630-37

Insomnia and psychiatric illness

- ◆ Unresolved insomnia may be associated in an increased risk of psychiatric disorder over time¹



1. Ford DE, et al. *JAMA* 1989;262:1479-84

Insomnia and psychiatric illness

- ◆ Patients with psychiatric disorders report a wide range of sleep-related problems¹

Sleep-related disturbances associated with psychiatric disorders	
Psychiatric disorder	Sleep-related disturbances
Alzheimer's disease	Reversal of day-night sleep patterns
Depression	Insomnia; hypersomnia; dream disorders
Generalised anxiety and panic disorders	Nocturnal panic attacks
Mania	Insomnia
Post-traumatic stress disorder	Insomnia; restless sleep; nightmares
Schizophrenia	Insomnia; hypersomnia; nightmares; sleep fragmentation; reversal of day-night sleep patterns

1. Kennedy CA and Solin P. How to Treat – Insomnia – Part 1. Australian Doctor. 2004.
Available at: http://www.australiandoctor.com.au/html/pdf/AD_HTT_037_44_APR02_04.pdf
[Accessed: 05/0708]

Insomnia and psychiatric illness

Insomnia can precede the onset of psychiatric illness in the general population¹

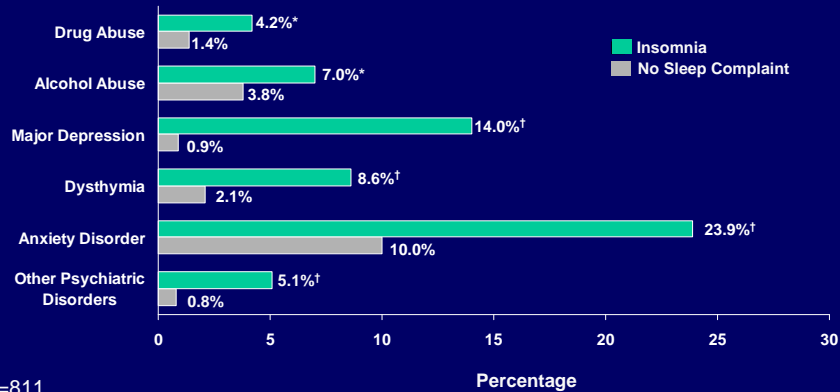
Adjusted odds ratio for developing new onset major depression (95% CI)	Resolved Insomnia	Unresolved Insomnia
Major Depression	1.6	39.8***
Anxiety Disorders	1.5	6.3***
Alcohol Abuse	1.4	2.4*
Any Psychiatric Disorder	1.6	4.0**

*** P <0.001 compared to respondents not reporting insomnia
** P <0.01 compared to respondents not reporting insomnia
* P <0.05 compared to respondents not reporting insomnia

1. Ford DE, et al. *JAMA* 1989;262:1479-84

Prevalence of Comorbid Psychiatric Disorders Among Patients With Insomnia

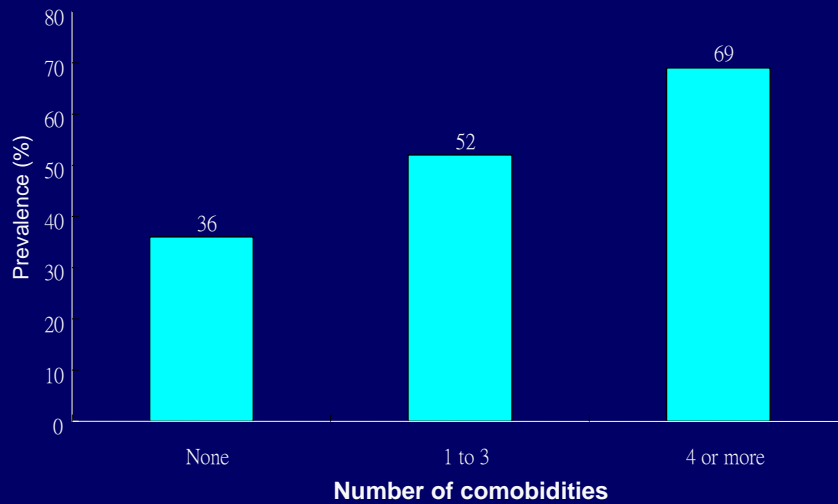
Significantly More Respondents With Insomnia Had ≥ 1 Psychiatric Disorder vs Those With No Sleep Complaints



Ford DE, Kamerow DB. *JAMA*. 1989;262:1479-1484.

Insomnia and medical disease

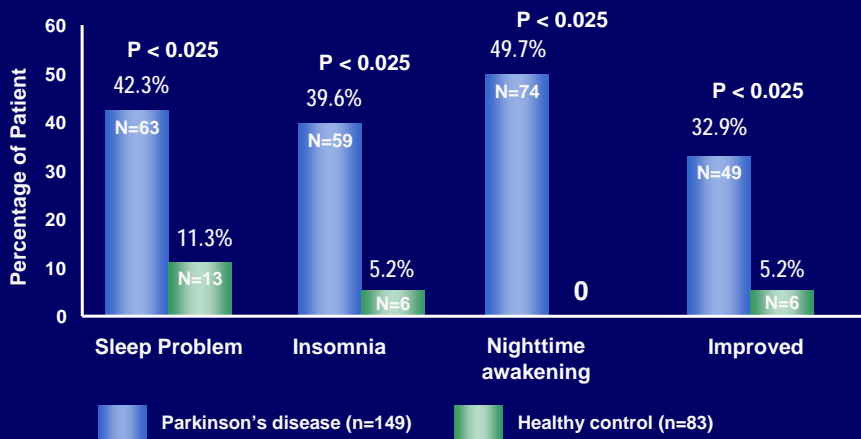
Prevalence of sleep problem with comorbid illness



Foley D et al. *J Psychosom Res.* 2004; 56: 497-502

Sleep Disorders in Parkinson's Disease

Hospital-based study



Kumar S et al. *Mov Disord.* 2002

Parkinson's Disease

Levodopa-induced arousal

- ◆ Patients with sleep disturbances were on higher doses of levodopa compared to patients without sleep disturbances (549mg vs. 352mg; $p < 0.000$)
- ◆ Levodopa suppressed rapid eye movement

Kumar S et al. *Mov Disord.* 2002

Prevalence of DSM-IV Insomnia in Presence or Absence of Specific Medical Disorders

Medical Condition	Prevalence of Insomnia if Disease Present (%)	Prevalence of Insomnia if Disease Absent (%)	Adjusted Odds Ratio	P
Heart Disease	14.8	10.3	1.59	0.049*
Hypertension	15	9.1	1.97	0.000*
Diabetes	16.4	9.4	1.67	0.021*
Thyroid	11.2	10.6	0.94	0.692
Arthritis	16.6	8.7	2.20	0.000*
Migraines	22.0	8.4	2.84	0.000*
Asthma	15.0	10.1	1.40	0.040*
COPD	24.7	9.9	2.94	0.000*
Menstrual problems	24.3	9.9	2.41	0.000*

*Statistically significant

Adjusted odds ratio refers to the odds of developing insomnia in presence of that particular disorder, adjusted for age and gender

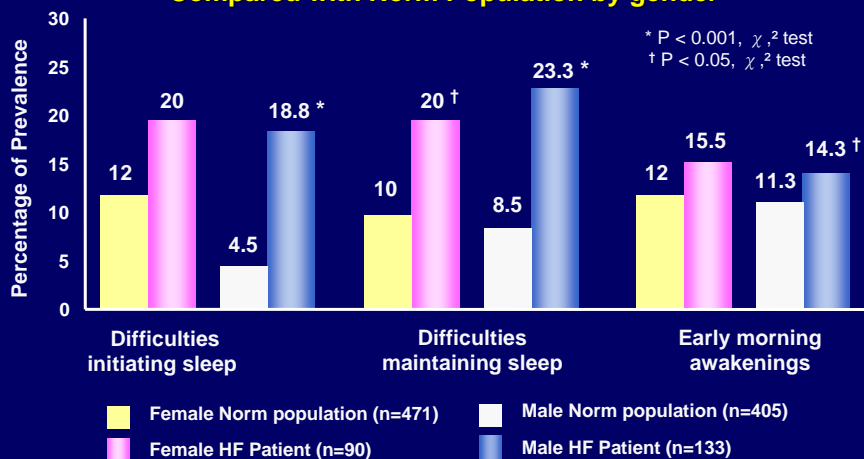
Insomnia : Cardiovascular Disorders

- ◆ Insomnia is a risk factor associated with a first myocardial infarction
- ◆ Sleep maintenance problem predicted coronary artery disease mortality
- ◆ Workers with either sleep onset or sleep maintenance insomnia had increased incidence of new hypertension (40.1% and 42.3% respectively, compared with 30.7% in the control)

Appels A, et al. Behav Med. 2000;26:86-89; van Diest R, Appels WP. Psychosom Med. 1994;56:28-35; Mallon L, et al. J Intern Med. 2002;251:207-216; Suka M, et al. J Occup Health. 2003;45:344-350.

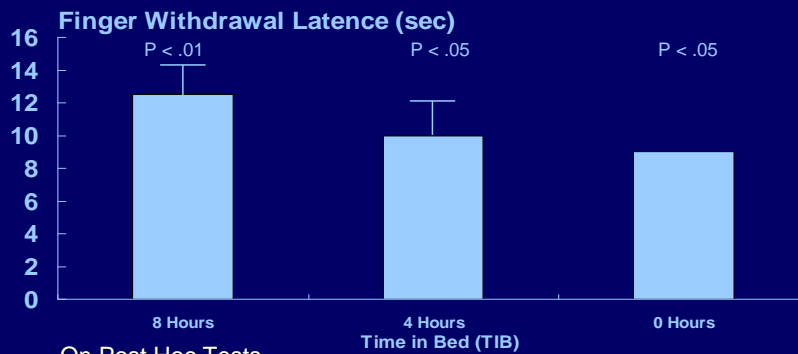
Prevalence of Sleeping Difficulties with Chronic Heart Failure

Compared with Norm Population by gender



Brostrm A et al. *J Cardiovasc Nurs.* 2004

Sleep Loss and Pain Sensitivity



On Post Hoc Tests

- ❖ The 4-h TIB condition differed from the 8-h TIB condition
- ❖ The 0-h TIB condition differed from the 4-h and 8-h TIB condition

Roehrs T, et al. *Sleep*. 2006;29:145-151.

Insomnia and cancer

- ◆ Cancer patients undergoing chemotherapy are nearly 3 times more likely to suffer from insomnia than the general population, a new study shows.
- ◆ Insomnia is the most common residual symptom of depression, yet treating depression doesn't necessarily take care of the insomnia. Likewise, we shouldn't expect it in other diseases, including serious medical disease," he concluded

SLEEP 2008: 22nd Annual Meeting of the Associated Professional Sleep Societies (APSS). Abstract 0698. Presented June 10, 2008.

Sleep Loss and Aging

	Sleep Loss	Aging
Glucose tolerance	↓	↓
Insulin sensitivity	↓	↓
C-reactive protein	↑	↑
Cardiac sympathetic activity	↑	↑
Plasma epinephrine	↑	↑
Evening cortisol levels	↑	↑
Plasma TSH	↓	↓
Plasma leptin	↓	↓



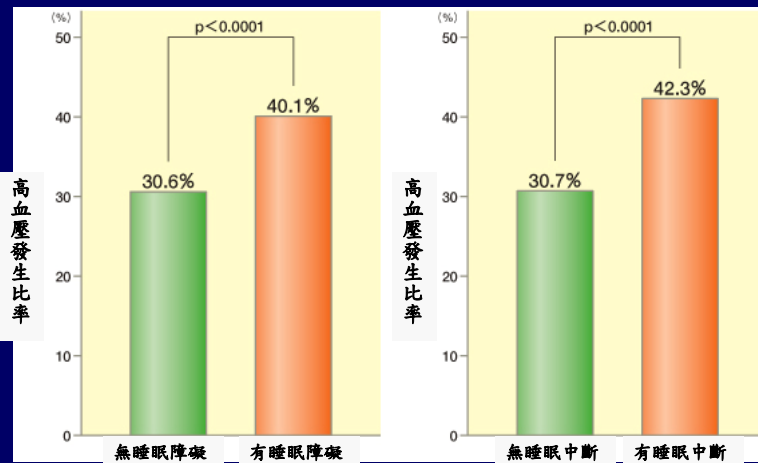
Sleep Complaints in Diabetes

- ◆ Adult Type II DM patients vs. Control in Canada
 - Diabetics had higher rates of insomnia vs. control (50% vs. 31.3%, $p=0.04$)
 - Difficulty maintaining sleep ~ in 40.0% of diabetic insomniacs
 - Sleep onset insomnia ~ in 17.1% of diabetic insomnia patients
 - Combination of sleep onset and maintenance difficulties ~ in 42.9% of diabetic insomnia patients
 - Diabetics used more hypnotics vs. control (25.9% vs. 6%, $p=0.02$)



Skomro RP et al. *Sleep Med.* 2001

失眠與發生高血壓之比率



【對象】中年男性勞動者 (40~55歲)

睡眠障礙調查群組4,794位 睡眠中斷調查群組4,443位

【方法】1994年的健康檢查後直到1998年持續的精確追蹤調查。討論有無睡眠障礙時發生高血壓的比率。

※入睡障礙OR=1.96、95%CI 1.42-2.70 睡眠中斷OR=1.86、95%CI 1.43-2.45

Suka M. et al : J. Occup. Health 45 : 344-350, 自2003修改

GI disease and sleep

- ◆ Duodenal ulcer
- ◆ Gastroesophageal Reflux(GER)
 - 60% of heartburn suffer admit to be awakened from sleep with heartburn
 - 40% reported nocturnal heartburn frequently results in diminished daytime performance and sleepiness
- ◆ Functional bowel disorder
 - Prevalence of reported sleep complaints:25%~30%
 - Common complaints: multiple arousal from sleep, unrefreshing sleep
 - Over 57% of patients reported: abdominal pain awakened them from sleep

Source: Sleep medicine

Sleep Disorders in Continuous Ambulatory Peritoneal Dialysis (CAPD)

A questionnaire survey in Chinese Patients

	With sleep disorder (n=110)	Without sleep disorder (n=69)	p-Value
Sleep disorder severity	6	1	0.0001
Actual duration of sleep (hrs)	4.6 ± 2.2	7.3 ± 1.4	0.0001
Difficulty falling asleep	74.5%	16.0%	0.001
Awakening during sleep	68.8%	29.0%	0.001
Early morning waking	68.0%	31.9%	0.001
Difficulty returning to sleep after awakening	66.0%	11.6%	0.001
Restless leg	64.5%	27.5%	0.001
Insomnia before dialysis	35%	21.7%	0.068

Lui SL et al. *Perit Dial Int.* 2002

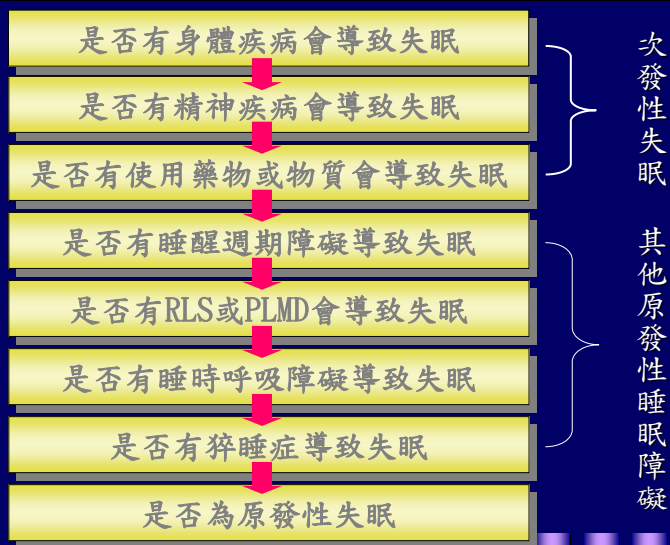
Management of insomnia

Evaluation of insomnia

- ◆ History and examination:
 - Medical, social histories and physical examination to exclude other illness
 - Psychosocial issues particularly important to identify and address
 - Sleep history
 - History must span entire day
 - Interview partner/caregiver
- ◆ Sleep diary:
 - Bedtime, rise time, naps, sleep-onset latency, night-time awakenings, mood
- ◆ Polysomnography, actigraphy, neuroimaging

1. Ramakrishnan K, et al. *Am Fam Physician* 2007;76:517-26

慢性失眠的鑑別診斷



睡眠醫學學會失眠問診指引 2007

失眠自我評量表 (中文版雅典失眠量表, CAIS)

- ◆ 說明：這一份量表是爲了協助你評估自己的睡眠困擾程度，過去一個月以來，你如果每星期至少有三天的睡眠困擾，便可加以估算：

入睡時間	0 沒問題	1 略為延遲	2 中度延遲	3 嚴重延遲
睡眠中斷	0 沒問題	1 問題不大	2 問題明顯	3 嚴重中斷
過早清醒	0 沒問題	1 有點提前	2 明顯早醒	3 嚴重早醒
總睡眠時間	0 已足夠	1 有點不足	2 中度不足	3 嚴重不足
整體睡眠品質	0 很滿意	1 有點不佳	2 明顯欠佳	3 極不滿意
白天的美好感*	0 還不錯	1 有點下降	2 中度影響	3 嚴重下降
白天身心功能**	0 還正常	1 有點下降	2 中度影響	3 嚴重下降
白天嗜睡程度	0 沒有嗜睡	1 輕度嗜睡	2 中度嗜睡	3 嚴重嗜睡

* 美好感意指心情、情緒狀態

** 包括體力、注意力、記憶力等

[說明] 總分達8分以上者，為「失眠症」之高危險群，建議儘速尋求醫療人員協助。

問卷版權爲國立陽明大學社區醫學研究中心 周碧蓉教授所有，使用請註明出處
Chiang HL, Chen HC et al. (2009) Taiwanese Journal of Psychiatry, 23: 43-52.

Management of Insomnia

- ◆ Treat the cause of insomnia
- ◆ Treat acute insomnia at once to prevent chronification (“early treatment”)
- ◆ Use strategy for **long-term treatment** of chronic insomniacs:
 - Drug with low risk for abuse and addiction
 - **Behavioural treatment**
 - “as needed” hypnotic treatment

Non-pharmacological treatment of insomnia

- ◆ Relaxation training
 - Breathing exercises & muscle relaxation
- ◆ Stimulus control
 - Controlling amount of time patient in bed/awake
- ◆ Sleep restriction therapy
 - Partial sleep deprivation with a gradual increase in amount of time in bed
- ◆ Cognitive therapy
 - Can include distraction and imagery techniques, cognitive restructuring
- ◆ Other therapy
 - Exercise, give up caffeine from late afternoon, avoid alcohol

1. Smith MT, et al. *Clin Cornerstone* 2003;5:28-37

Pharmacological treatment

NIH State of the Science Conference: panel conclusions

- ◆ Benzodiazepine receptor agonists
- ◆ **Non-benzodiazepine receptor agonists**
 - Approved for the treatment of insomnia
 - Demonstrated efficacy in acute management of chronic insomnia
 - Lower frequency and severity of adverse events vs approved benzodiazepines
- ◆ Antidepressants used to treat insomnia
 - Not approved for the treatment of insomnia
 - Lack clinical study and evaluation; no established dose-response relationship
 - Potential for significant adverse effects
- ◆ OTC and alternative preparations (i.e. melatonin, valerian)
 - No demonstrated efficacy, no long-term safety data
 - Significant concerns about the risks of OTC medications

1. NIH State of the Science Conference Statement. *J Clin Sleep Med* 2005;1:412-21

Characteristics of the ideal hypnotic

- ◆ Induce sleep within 30 minutes
- ◆ Maintain a normal sleep pattern for 6-8 hours without suppression of rapid eye movement
- ◆ Sustained minimally effective plasma levels
- ◆ Would avoid tolerance or dependence
- ◆ No withdrawal symptoms

1. Neubauer DN. *Primary Psychiatry* 2006;13(8 Suppl 4):1-16

Antidepressants

- ◆ 缺乏針對非憂鬱症失眠病患的療效研究
- ◆ 可能引起日間殘餘症狀
- ◆ 需考量其他副作用
- ◆ 使用上需會診專科意見

台灣睡眠醫學學會 失眠問診指引

Antihistamine

- ◆ 缺乏針對失眠的療效研究
- ◆ 可能引起明顯的日間殘餘症狀
- ◆ 容易產生依賴

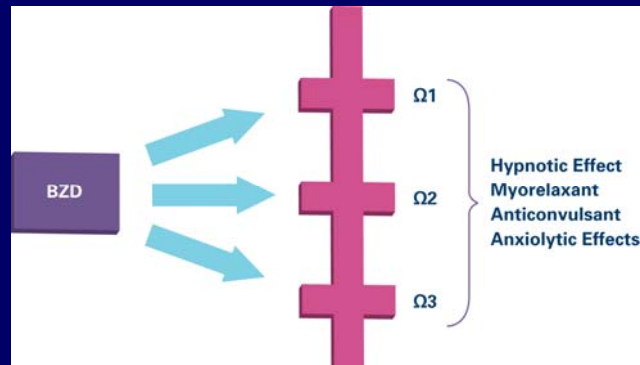
台灣睡眠醫學學會 失眠問診指引

國內有失眠症適應症之安眠藥

藥品學名	管制	常見商品名	上市劑量	建議劑量	作用	半衰期
非苯二氮平類藥物						
Zolpidem	第四級	Stilnox (使蒂諾斯)	10 mg	5-10 mg	短效	1.5-2.4小時
Zolpidem	第四級	Stilnox CR (使蒂諾斯 長效錠)	6.25mg	6.25mg- 12.5mg	短效	2.6小時
Zopiclone	第四級	Imovane (宜眠安)	7.5 mg	3.75-7.5 mg	短效	5-6小時
Zaleplon	第四級		10 mg	5-10 mg	短效	1.0小時
苯二氮平類藥物						
Estazolam	第四級	Eurodin (悠樂丁)	2 mg	1-2 mg	中效	8-24小時
Triazolam	第三級	Halcion (酣樂欣)	0.25 mg	0.125-0.25 mg	短效	2-3小時
Flunitrazepam	第三級	Rohypnol (羅眠樂)	1 mg	0.5-1 mg	中效	10-20小時
Brotizolam	第三級	Lendormin (戀多眠)	0.25mg	0.25-0.5 mg	中短效	7小時
Nitrazepam	第四級	Mogadon (眠確奮)	5mg	5-10 mg	中效	18-38小時
Midazolam	第四級	Dormicum (導眠靜)	7.5mg	7.5-15mg	短效	1.5-2.5小時
Nimetazepam	第三級	Erimin (愈利眠)	5mg	5mg	中效	26小時
Flurazepam	第四級	Dalmadorm (當眠多)	15, 30 mg	15-30 mg	長效	40-100小時

Benzodiazepine mode of action

- ◆ Facilitation of GABA neurotransmission via non-selective binding to the Ω_1 , Ω_2 and Ω_3 subunits of GABA_A receptor



1. Darcourt G, et al. *J Psychopharmacol* 1999;13:81-93

Non-benzodiazepine Hypnotics

- ◆ 長期使用的安全性較高
- ◆ 較少影響睡眠的生理結構
- ◆ 較少白天殘餘症狀
- ◆ 較低之依賴與濫用比率

台灣睡眠醫學學會 失眠問診指引

Comparison of hypnotic treatments

	Sleep Latency	Total Sleep Time	REM Sleep %	Hangover Effects	Rebound Insomnia
BZD*	↓	↑	↓	+ / ++	++ / +++
Zopiclone	↓	↑	↔	++	++
Zolpidem	↓	↑	↔	+	↔

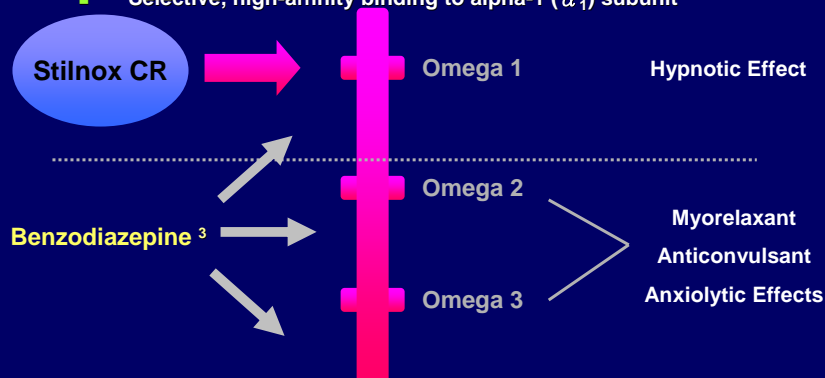
↔ = no change or no effect, ↓ = decrease ↑ = increase
 + = mild effect, ++ = moderate effect, +++ = marked effect
 * BZD included intermediate acting (6-24 hrs).

1. Wagner J et al. *Ann Pharmacother* 1998;32:680-8

Stilnox CR Mode of Action

◆ Mechanism of action (zolpidem)^{1,2}

- Modulation of GABA_A receptor
- Selective, high-affinity binding to alpha-1 (α_1) subunit



1. Stilnox CR approved Product Information

2. Stilnox Product Information

3. Graham et al. *Sleep* 1996 Vol 19 (8) S43-S45

Stilnox CR has a unique Formulation

- ◆ Stilnox CR 6.25 mg contains zolpidem tartrate
 - The same chemical entity found in Stilnox

Coated 2-Layer Tablet

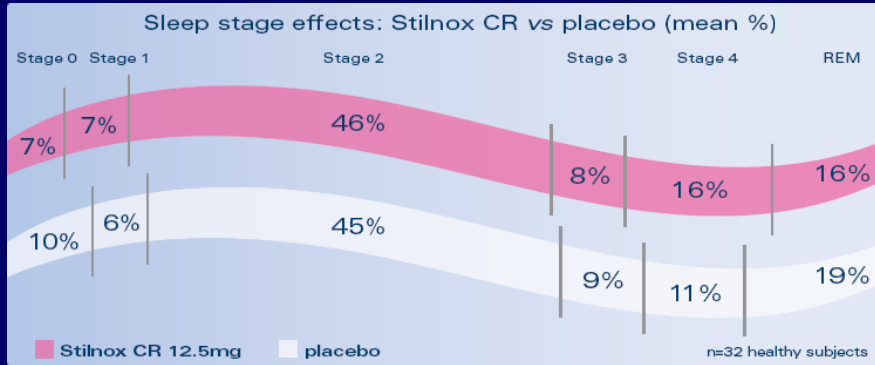


Stilnox CR approved Product Information.

Stilnox CR Pharmacokinetic properties

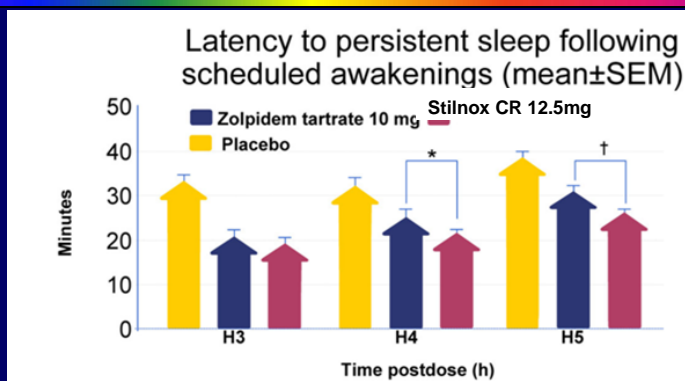
- ◆ Rapid absorption ; Bioavailability: 70 %
- ◆ C_{max} : 134 ng/mL
- ◆ T_{max} : 1.5小時
- ◆ elimination half-life : 2.8hours (Adult:1.62-4.05 hours)
- ◆ Protein binding: 92.5 ± 0.1 %(conc. 40-790 ng/mL)
- ◆ All metabolites are pharmacologically inactive and are eliminated in the urine (65%) and in the faeces (37%)
 - 變成無活性的代謝物，主要是由腎臟排除
 - Partial CYP 3A metabolism :CYP 3A4 (61%) , CYP2C9 (22%) 、CYP1A2 (14%) 、CYP2D6 (2.5%) 、CYP2C19 (0.5%)
 - Lower drug interactions

Stilnox CR Preserves Natural Sleep Architecture^{1,2}



1. Stilnox CR approved Product Information
 2. Data on file

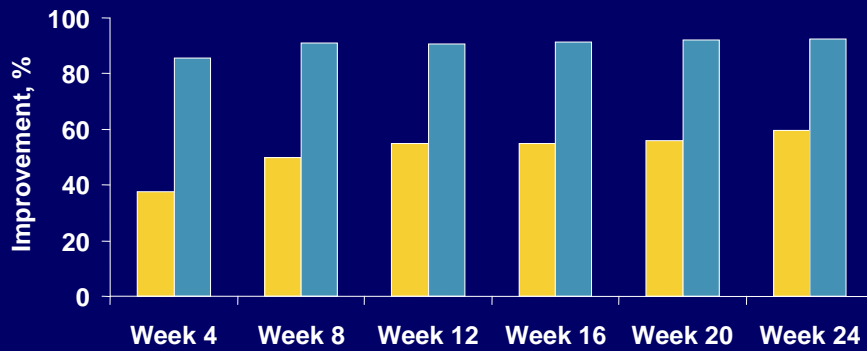
Stilnox CR Efficacy ~ Subjects returned to sleep faster ~



N=54.
 *P=.0373 vs zolpidem tartrate.
 †P=.0096 vs zolpidem tartrate.
 Effects of AMBIEN CR (12.5 mg) and zolpidem (10 mg) on LPS in a phase 1 crossover trial using a scheduled awakening model of sleep disturbance in normal subjects.
 Hindmarch I, et al. *Sleep*. 2005;28(abstract suppl):A245-A246.
 Data on file. Sanofi-aventis.

Zolpidem MR: long-term intermittent dosing

Patient Global Impression of Treatment Aid to Sleep
Taken "as needed" 3 to 7 nights per week*



*p<0.0001
for each visit

■ Placebo (N=349) ■ Zolpidem ER 12.5 mg (N=667)

Erman et al; Int J Neuropsychopharmacol 2006;9(suppl 1);S256.

◆ Thank you for your attention

