Insomnia and Menopause

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Insomnia & Menopause

- Epidemiology
- Mechanism
- Cognitive Behavioral Treatment
- Hormone Therapy
- Other Treatment

Epidemiology

Mechanism

Cognitive Behavioral Treatment

Hormone Thearpy

Other Treatment

Epidemiology

- Definition: ≥ 3 / wk for 3 months
- 46-48% of menopausal women
- Main predictive factor: premenopausal sleep condition

Introduction

Definition

- Insomnia

  persistent difficulty of falling asleep and maintaining sleep results in daytime impairment

- Chronic insomnia

  at least 3 nights a week for 3 consecutive months

Adverse impacts

- Daytime symptoms

  fatigue, sleepiness, mood disturbances, memory functions and attention alterations, accidents

- Cardiovascular diseases

  hypertension, cerebrovascular diseases, diabetes, increased risk of mortality

- *American Academy of Sleep Medicine; 2014*
- *Sleep Med Clin 2017;12:167–77*

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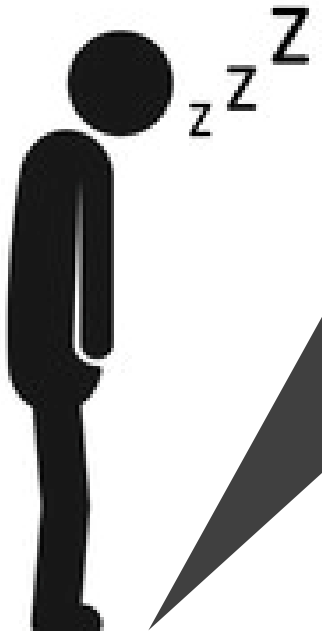
Incidence of insomnia



Main predictive factors:

premenopausal sleep condition

Most frequently reported:

disorder of sleep maintenance

ppulation-based study in

s. 38% premenopausal

Sleep disorder during menopause: insomnia, obstructive sleep apnea (16-20%), restless leg syndrome (20-24%)

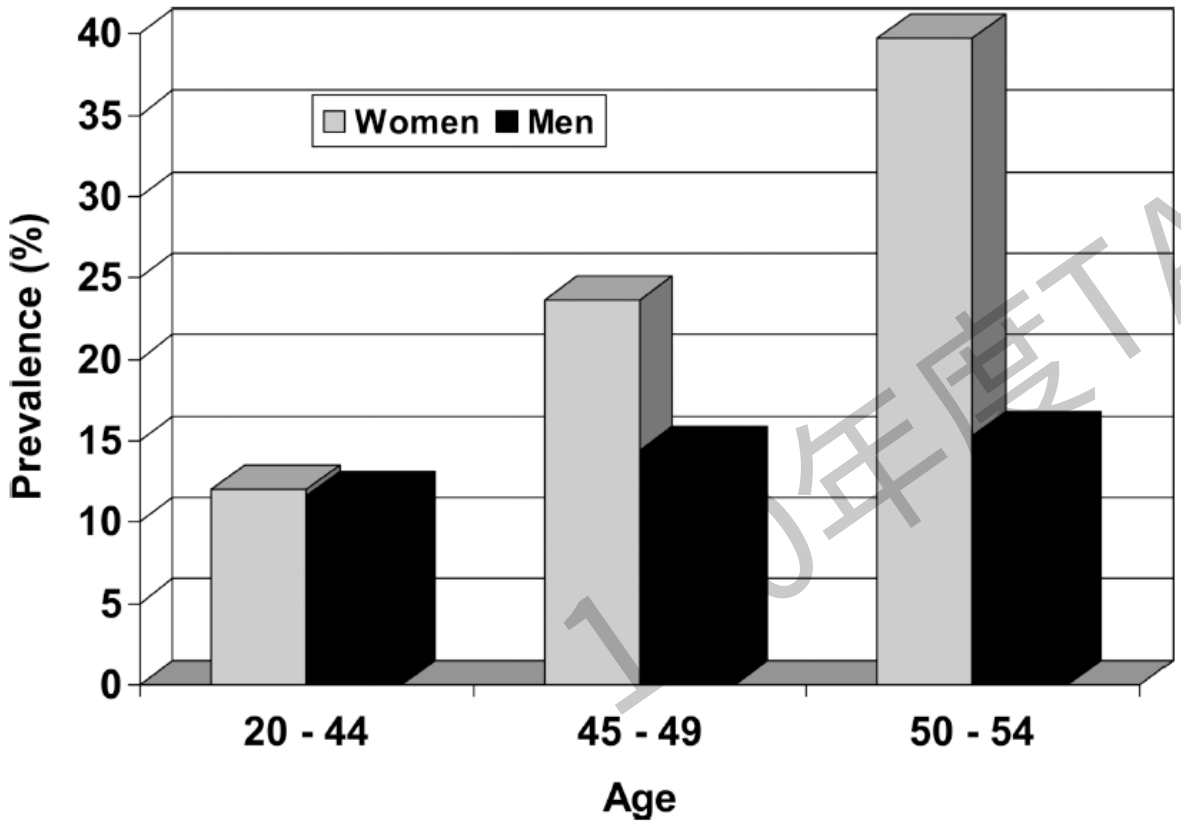
Sleep Med 2006;7:123–30

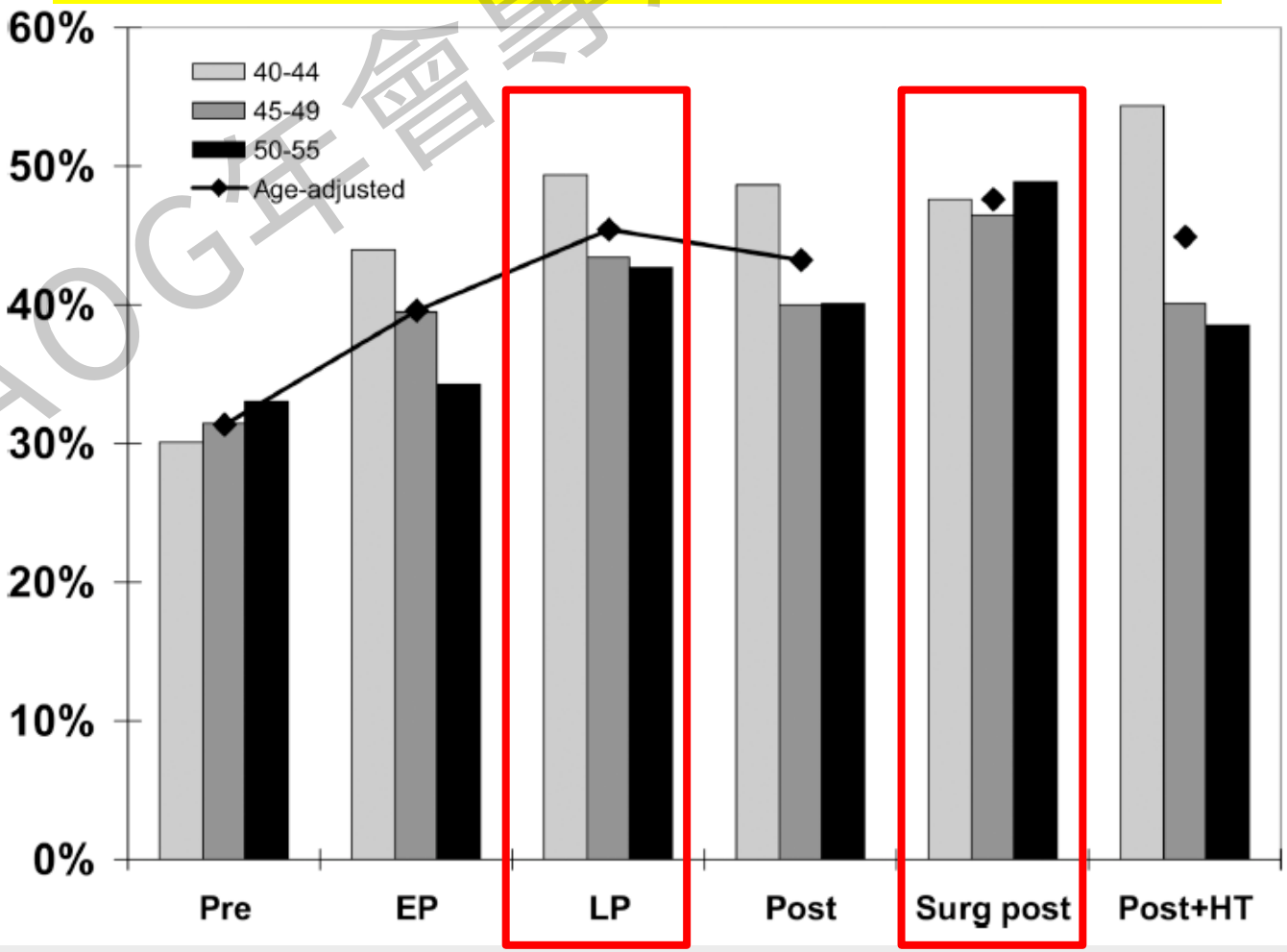
Climacteric 2013;16:214–19

Obstet Gynecol Clin North Am 2011;38:567–86

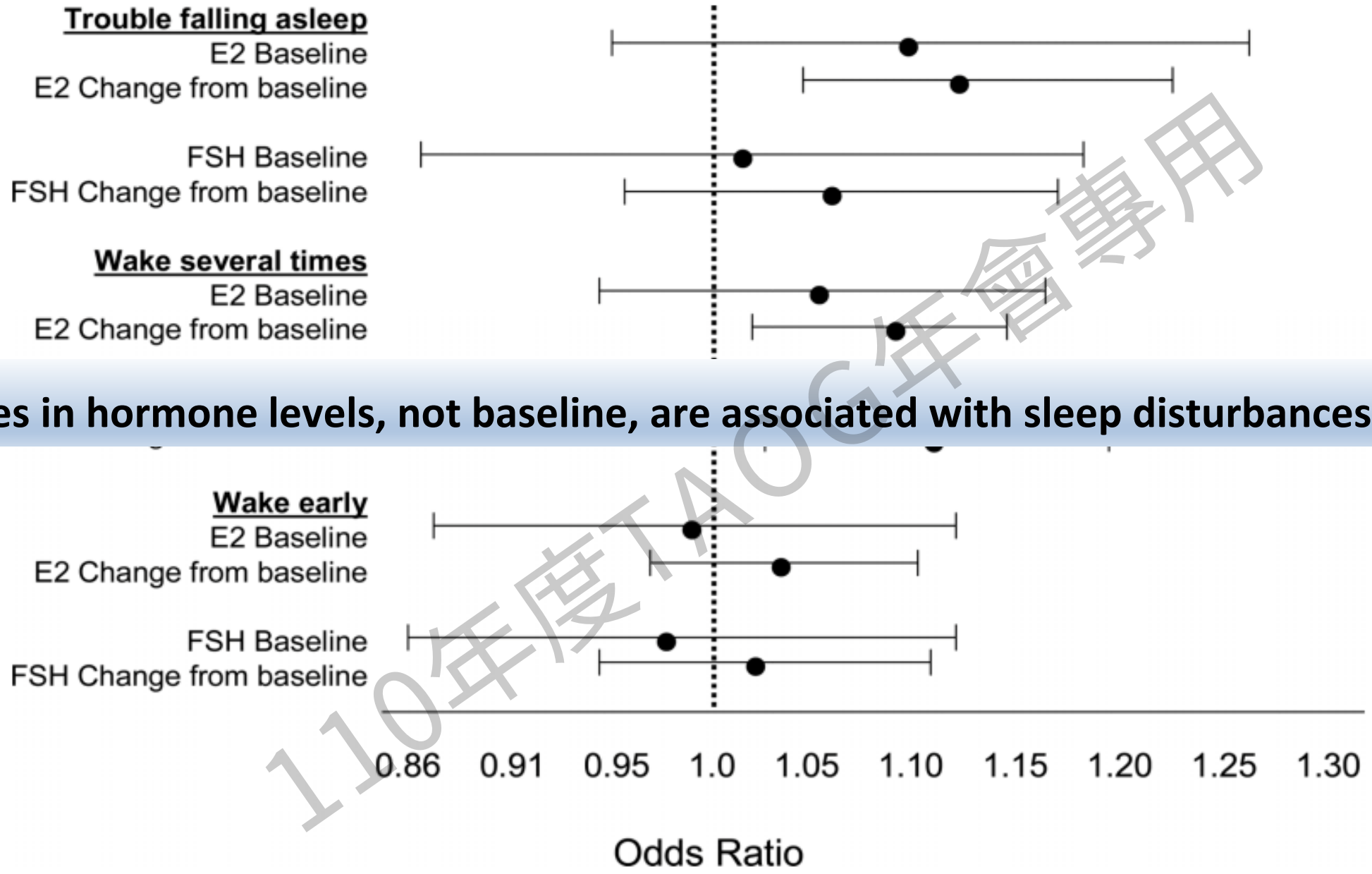
Women diverse from men at critical age: 45

Perimenopausal transition at younger age: higher prevalence



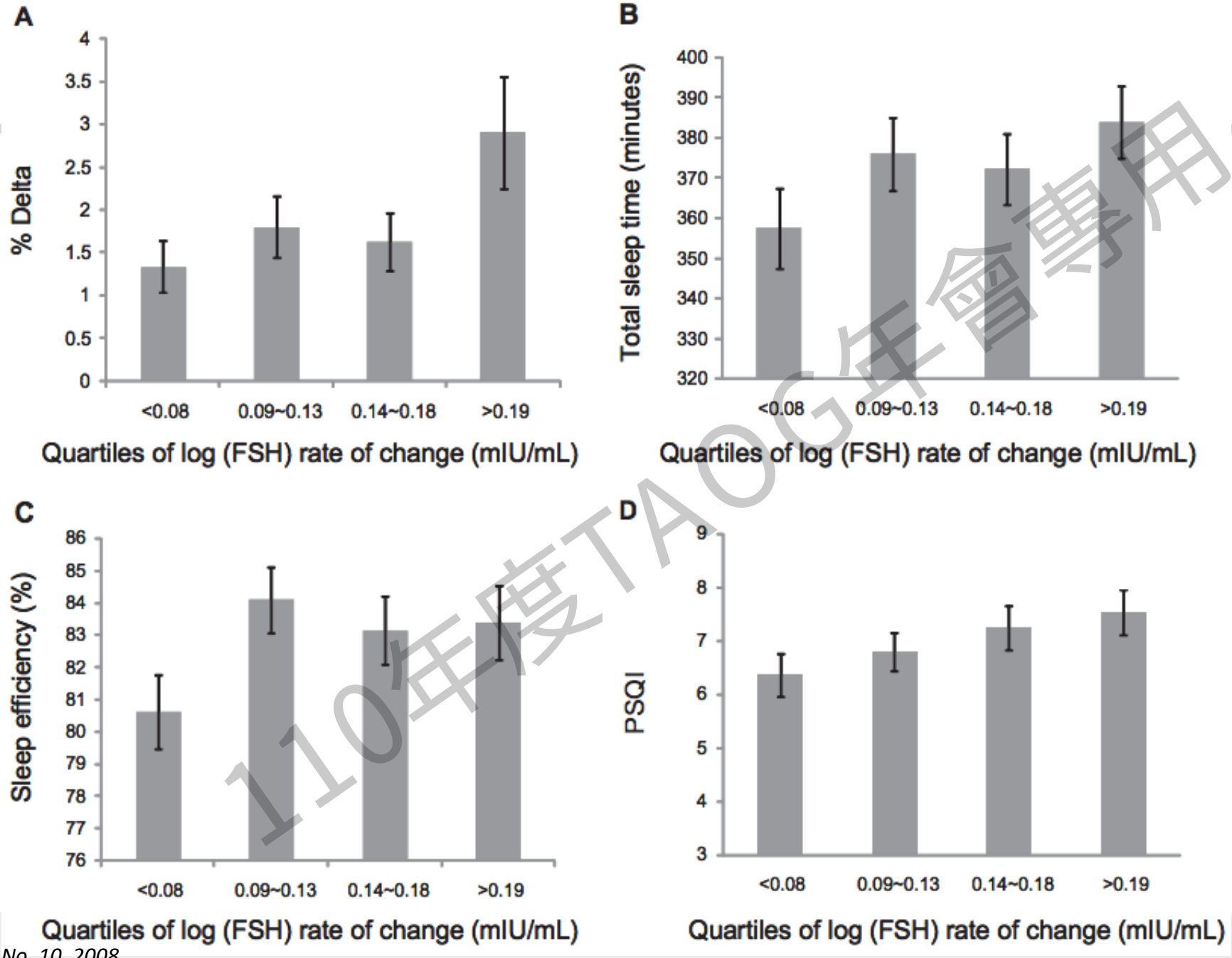


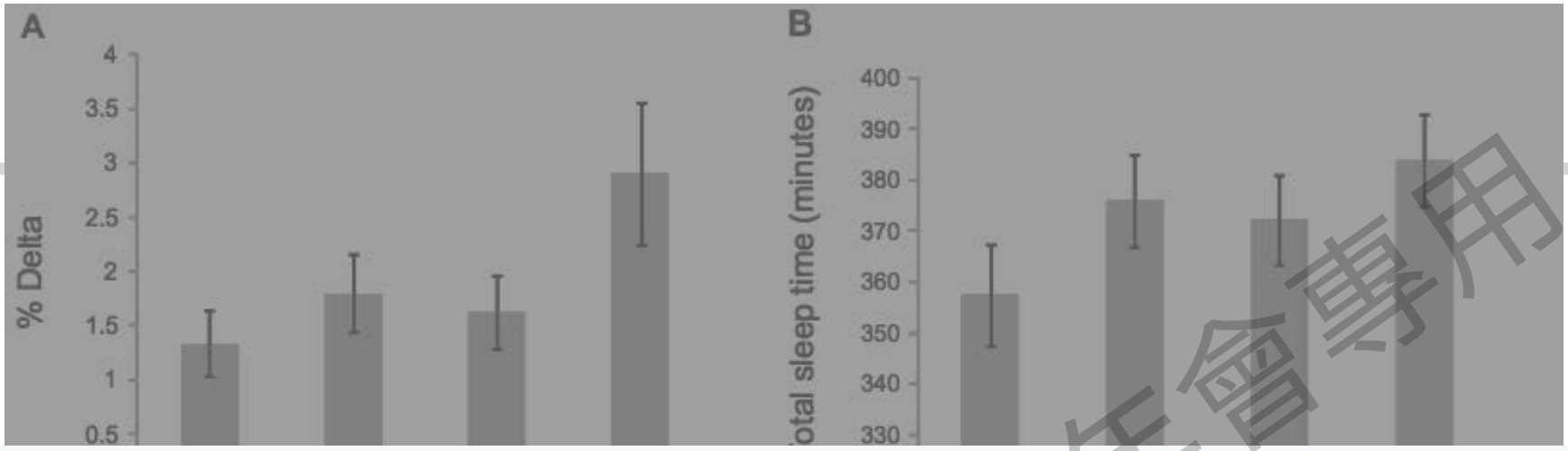
Obstet Gynecol Clin North Am . 2011 September ; 38(3): 567–586.



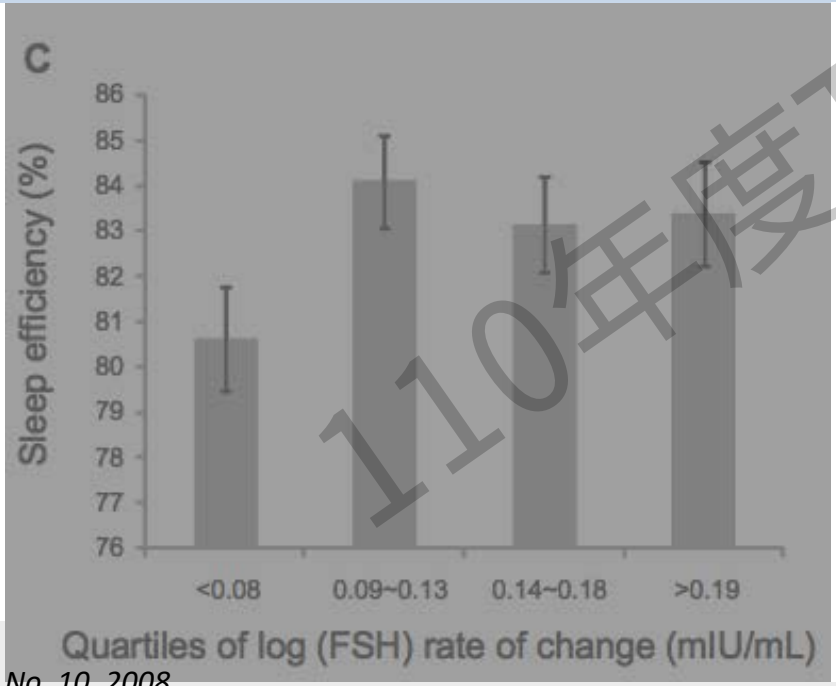
Changes in hormone levels, not baseline, are associated with sleep disturbances

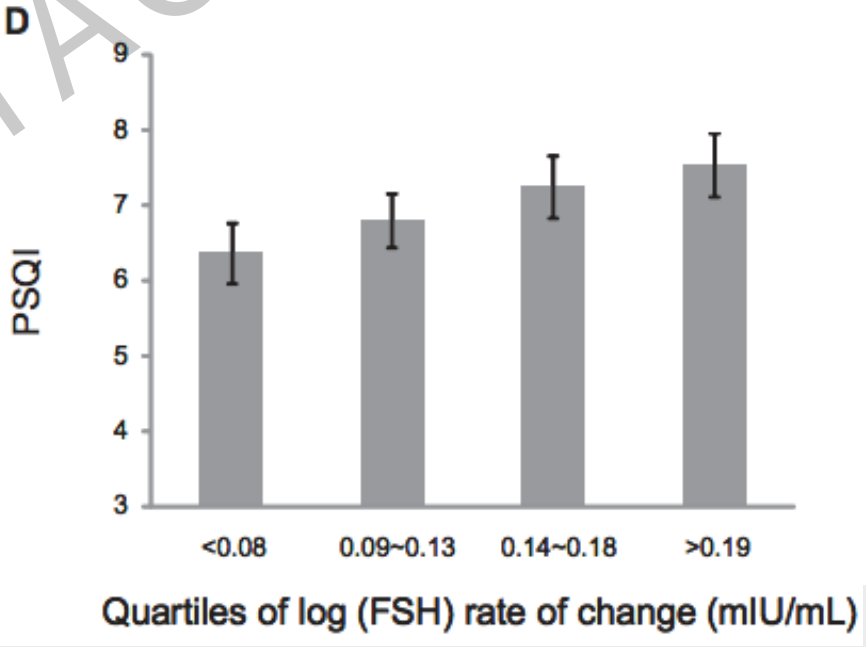
Sleep. 2008; 31:979–990





The faster FSH change, the worse sleep quality





SLEEP, Vol. 31, No. 10, 2008

Epidemiology

Mechanism

Cognitive Behavioral Treatment

Hormone Thearpy

Other Treatment

Mechanism

- Hormonal changes: progesterone, estrogen, androgen
- Hot flushes
- Mood disorders: increased risk of major depressive episode in menopausal women
- Circadian modification: melatonin

Hormonal Changes

Progesterone

- Stimulating benzodiazepine receptors
- Anxiolytic and sedative

Favoring non-rapid Eye movement sleep

Estrogen

- Sleep latency
- Number of awakenings

Decreased

- Regulate the time of lowest body temperature during the night

Androgen: DHEA-S with nocturnal awakening

- *Front Neuroendocrinol 2017;47:134–53*
- *J Clin Endocrinol Metab 2016;101:3968–77*

Hot Flushes

- 80% of menopausal women
- Discordant data:
- 29% of menopausal women with HF→ insomnia *J Sleep Res 2007;16:24–32*
- 80% of HF interfered with sleep *Fertil Steril 2014;102:1708–15.e1*

high body core temperature prior to and during sleep (even without VMS)

→ **poor sleep efficiency & high LH levels**

Moderate-to-severe HFs

→ **higher risk of frequent nocturnal awakenings**

Number of HFs at night ↑

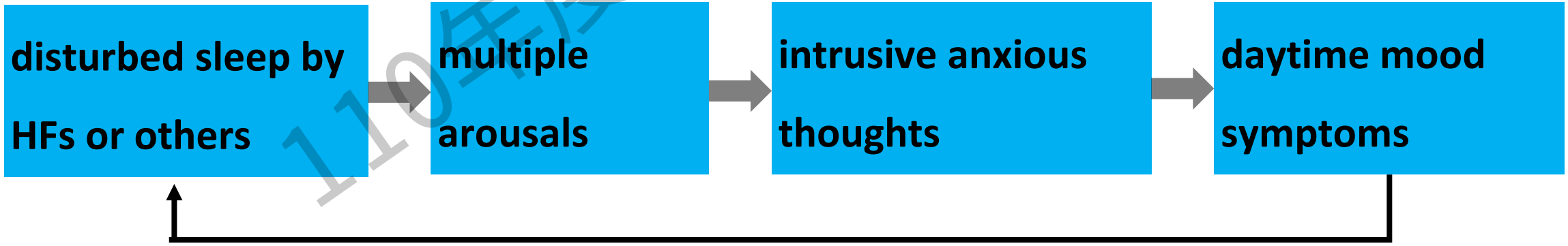
→ **Worsening of sleep disturbance indices**

J Clin Sleep Med 2016;12:1003–9

Obstet Gynecol Clin North Am 2011;38:567–86

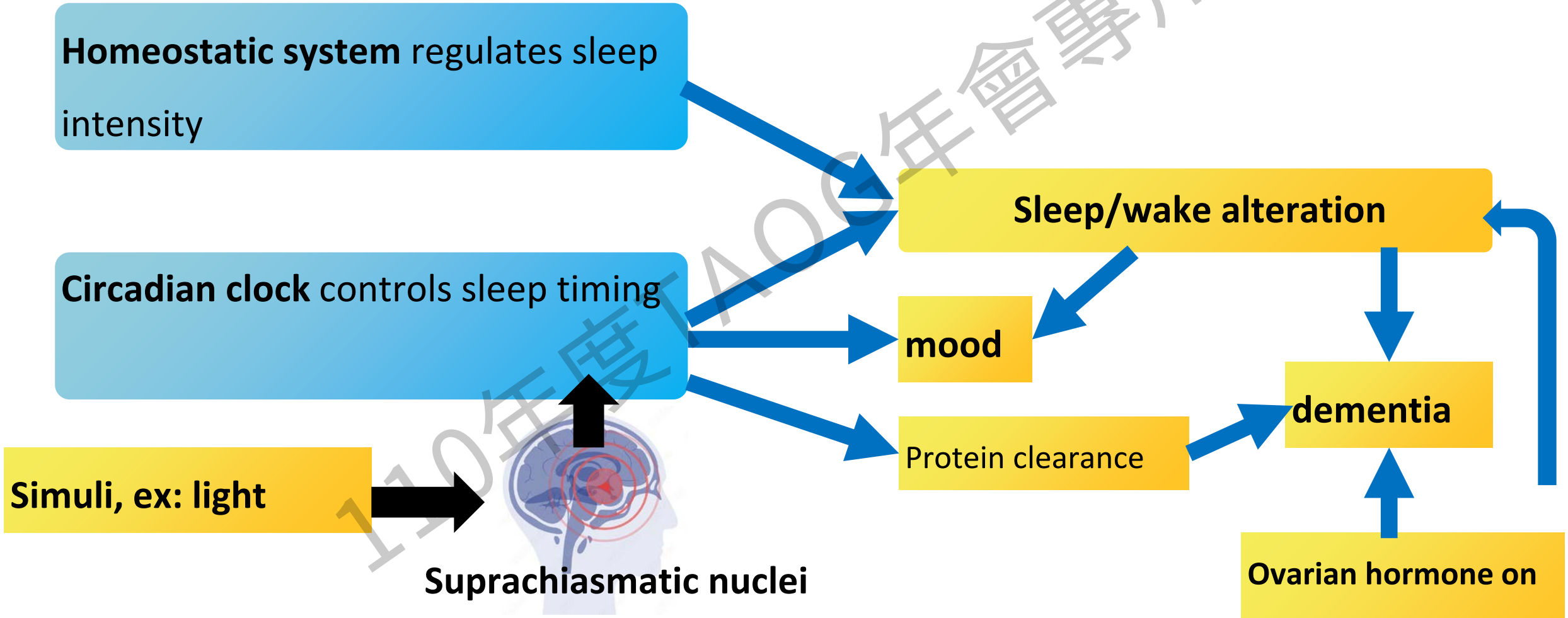
Mood Disorders

- Depression: a risk factor for poor sleep
- Menopausal women: increased risk of major depressive episode, especially when HFs are present
- Domino effect theory:



Menopause 2008;15:841–7

Circadian Modification



Curr Neuropharmacol 2017;15:434–43

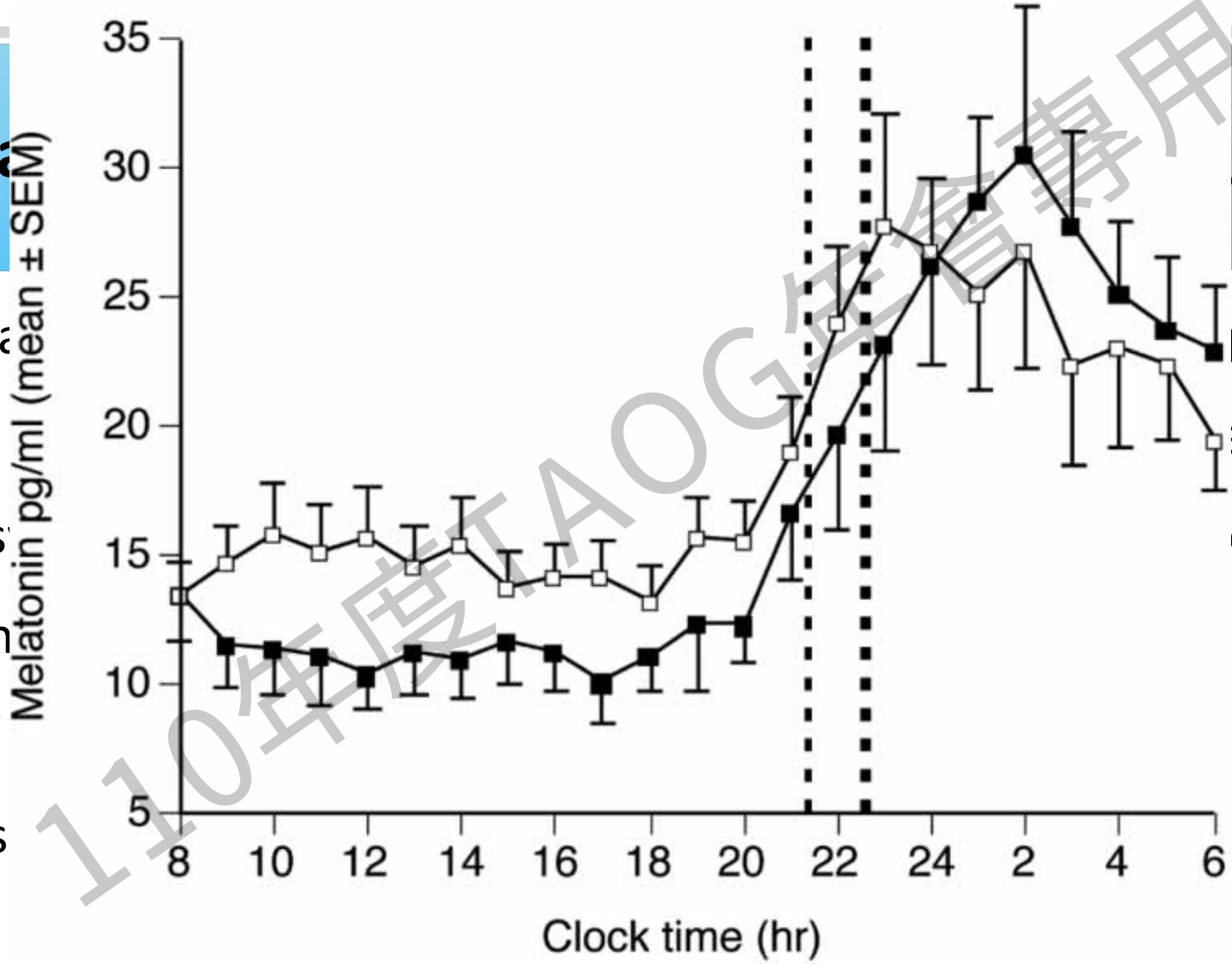
Menopause 2014; 21:493–500

Circadian Modification

Mela

ging

- From pineal gla gulation: more level
- Soporific and s early awakening circadian rhyth ctive hormone
- Modulation of carcinogenesis



Curr Neuropharmacol 2017;15:434–43

Chronobiol Int 2005;22:859–72

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Epidemiology

Mechanism

Cognitive Behavioral Treatment

Hormone Thearpy

Other Treatment

Cognitive Behavioral Treatment

- Multicomponent treatment targeting cognitive and behavioral factors
- Efficacy proven from controlled trials

Management of insomnia during menopause

Menopausal transition

Before sleep difficulty

High risk:

Primary prevention—

Ex: education on stress management

Secondary prevention—

Ex: modify sleep-related behaviors

After sleep difficulty

Sleep history assessment or questionaires

- Timing of sleep difficulties in relation to menopausal symptoms
- Changes in bleeding patterns
- Symptoms suggestive for SA or RLS

Management of insomnia during menopause

Sleep history assessment or questionaires

- Timing of sleep difficulties in relation to menopausal symptoms
- Changes in bleeding patterns
- Symptoms suggestive for SA or RLS

→ **Primary insomnia** → **Therapy**

→ **Supposed other sleep disorder or non-responder**

- Consider polysomnography

→ **Treat other sleep disorder**

Maturitas 2019;129:30–9

Maturitas 2019;128:1–3

Cognitive Behavioral Treatment

The firtst-line treatment for chronic insomnia of any age

Targeting cognitive and behavioral factors contributing to insomnia

Well known efficacy from multiple controlled trials

Cognitive Behavioral Treatment

JAMA Internal Medicine

JAMA Intern Med. 2016;176(7):913-920

Telephone-Based Cognitive Behavioral Therapy for Insomnia in Perimenopausal and Postmenopausal Women With Vasomotor Symptoms

A MsFLASH Randomized Clinical Trial

106 perimenopausal or postmenopausal women

aged 40 to 65 years

Moderate insomnia (insomnia severity index [ISI] ≥12)

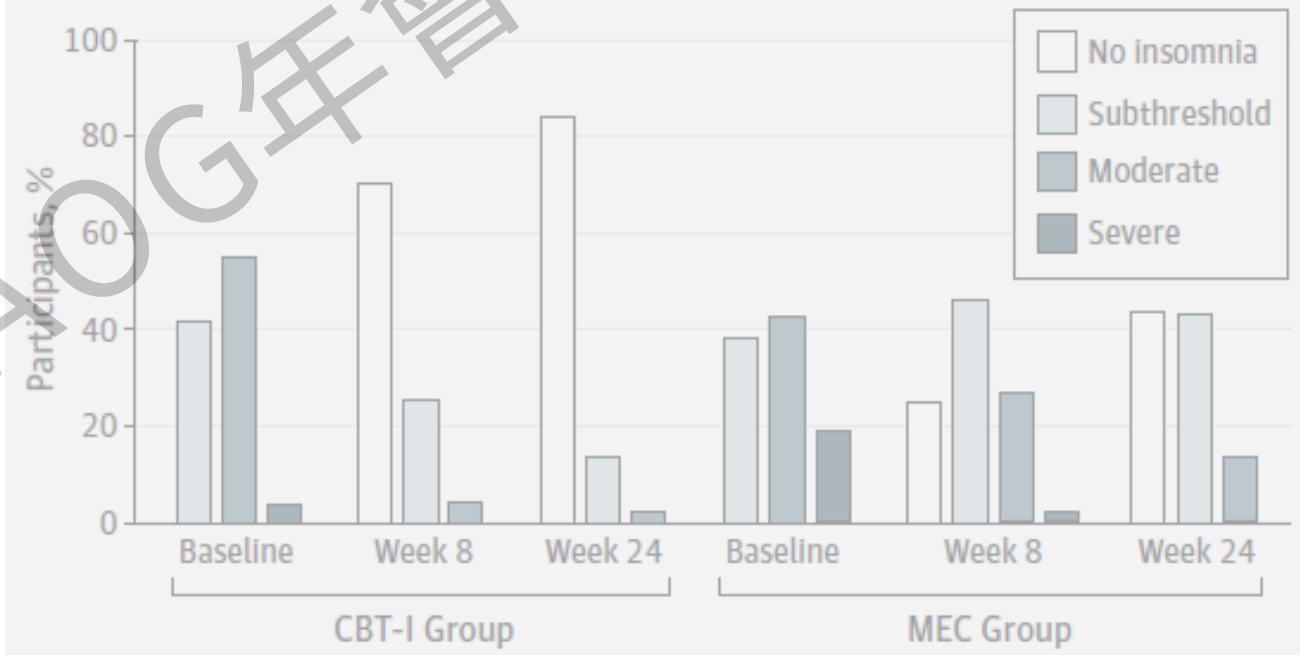
CBT-I vs. MEC for 8 weeks

Cognitive Behavioral Treatment

Session	CBT-I	MEC
1	Sleep changes during menopause Rationale for behavioral approach Sleep scheduling and bed restriction	Introduction to menopause: what to expect Sleep hygiene strategies
2	Review of behavioral sleep plan Stimulus control instructions	Hot flashes: self-management techniques
3	Review of behavioral sleep plan Sleep stages and cycles across the age span	Pharmacologic supplements and natural remedies
4	Review of behavioral sleep plan Changing beliefs and attitudes about sleep	Benefits of exercise in menopause
5	Review of behavioral sleep plan Constructive worry Sleep hygiene recommendations	Postmenopausal health concerns and nutrition
6	Review of behavioral sleep plan Maintenance and relapse prevention plan	Sexuality, urinary, and vaginal tract health
Treatment components	Education Sleep monitoring Sleep scheduling and goal setting Behavioral homework and problem solving	Education Sleep monitoring Support

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; MEC, menopause education control.

Figure 2. Percentage of Insomnia Severity Index Total Scores Categorized by Insomnia Category at Baseline and 8- and 24-Week Follow-up



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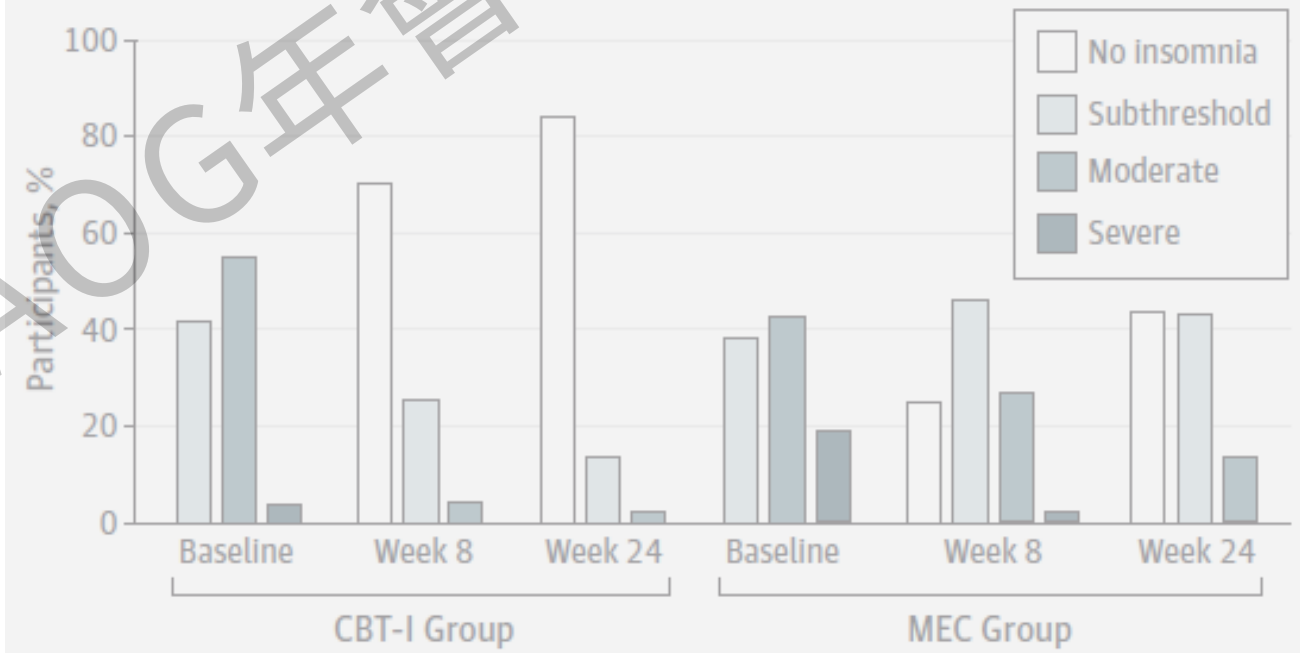

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Initial restriction window according to baseline screening/ ≥5.5 hours

Extended by 15 minutes per week (if 85% sleep efficacy)

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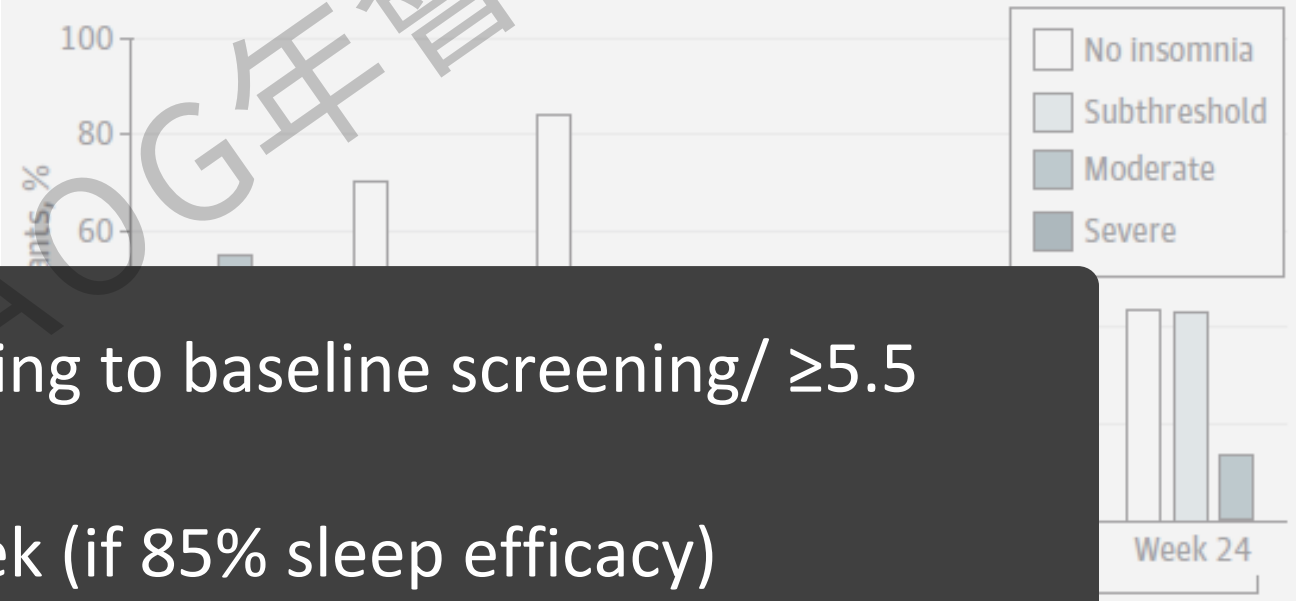

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Reducing time spent in bed on nonsleep activities

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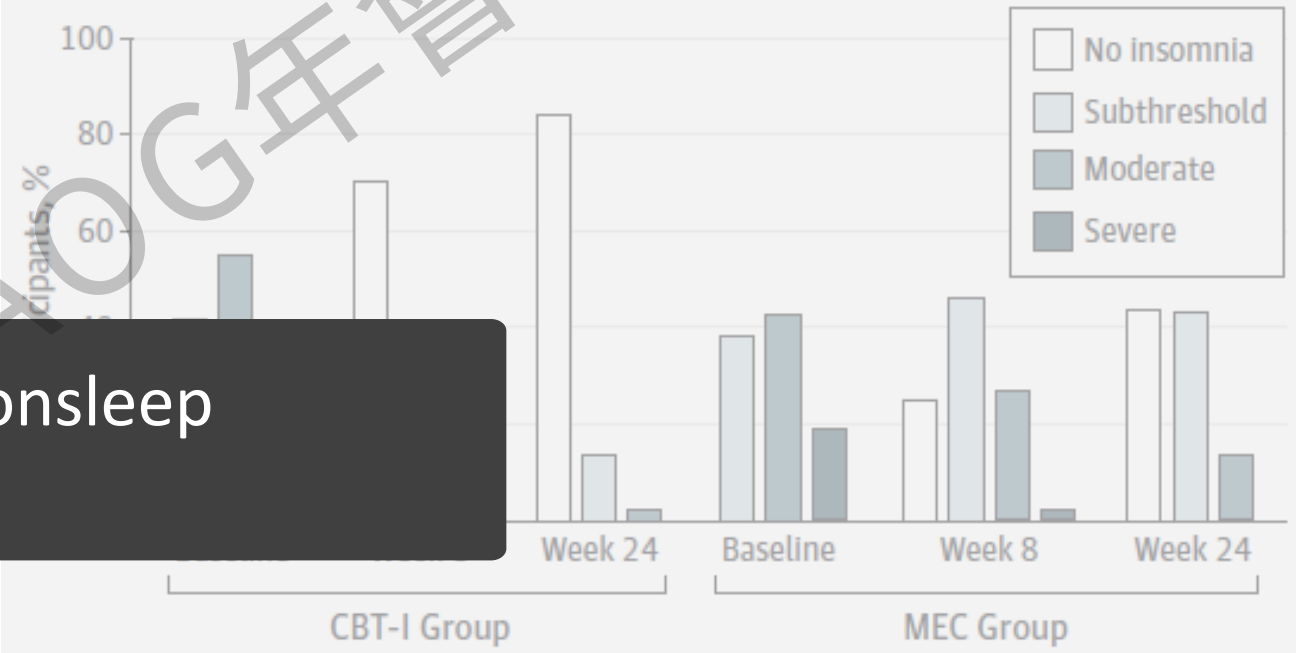

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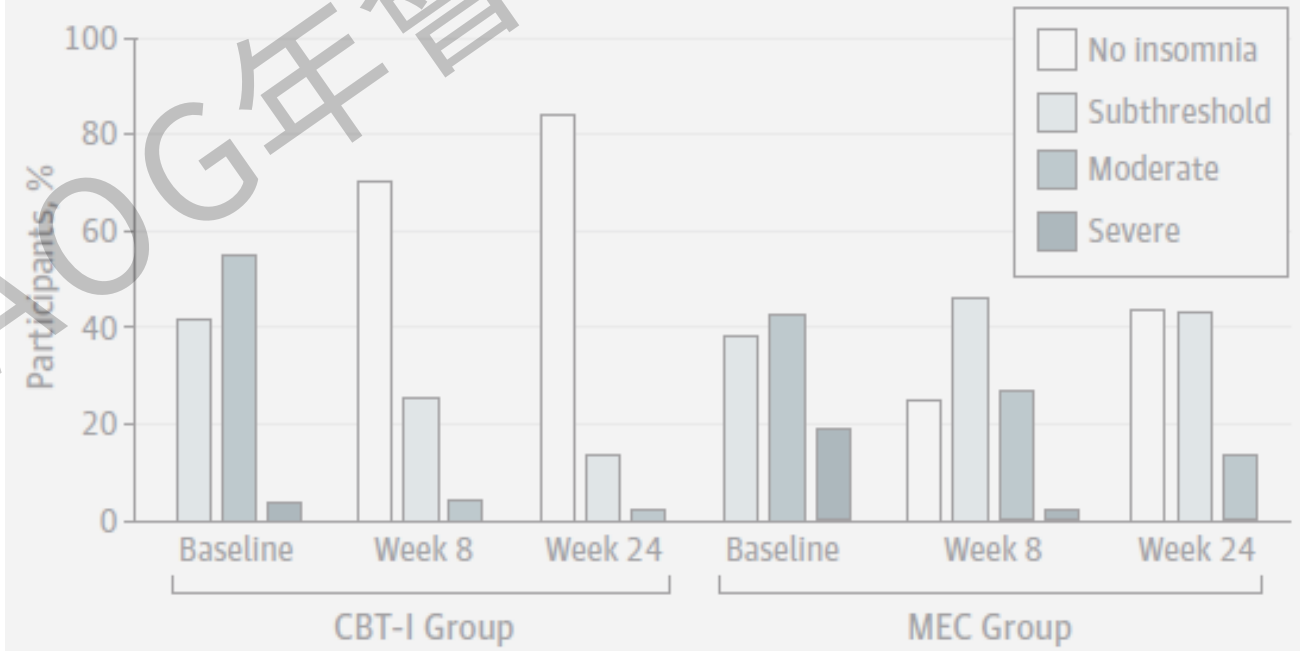

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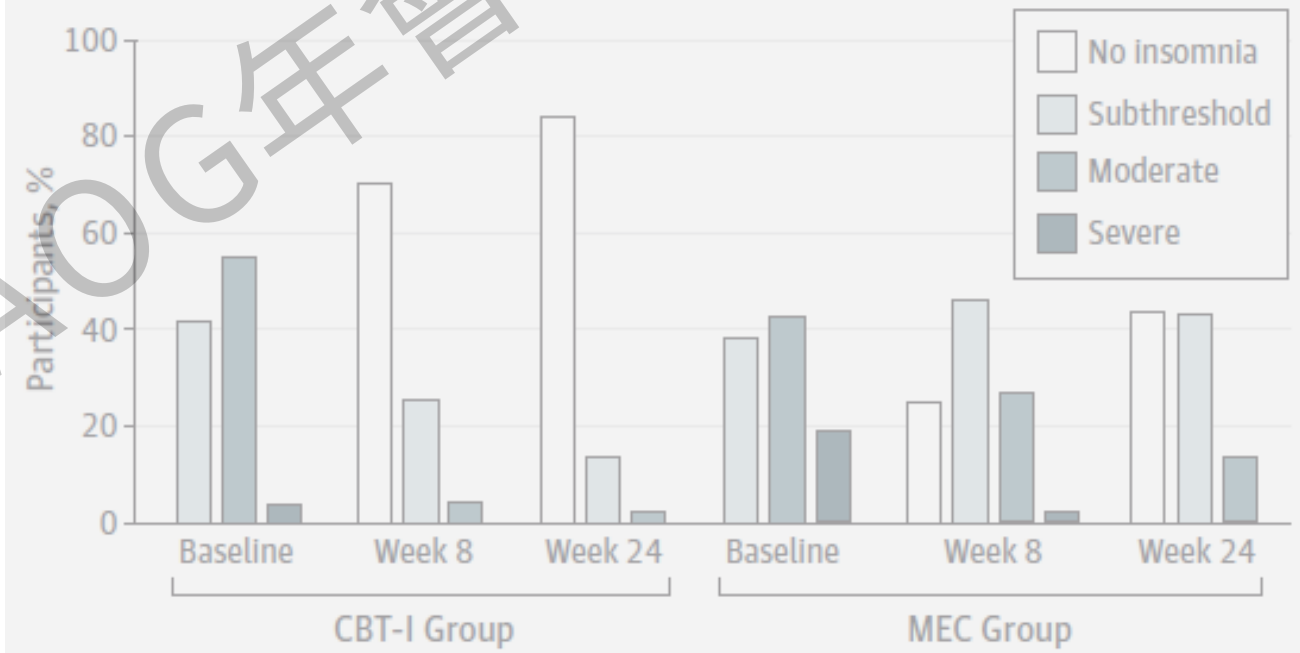

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Sleep hygiene: improving bedtime routines and identifying negative behavioral and environmental factors

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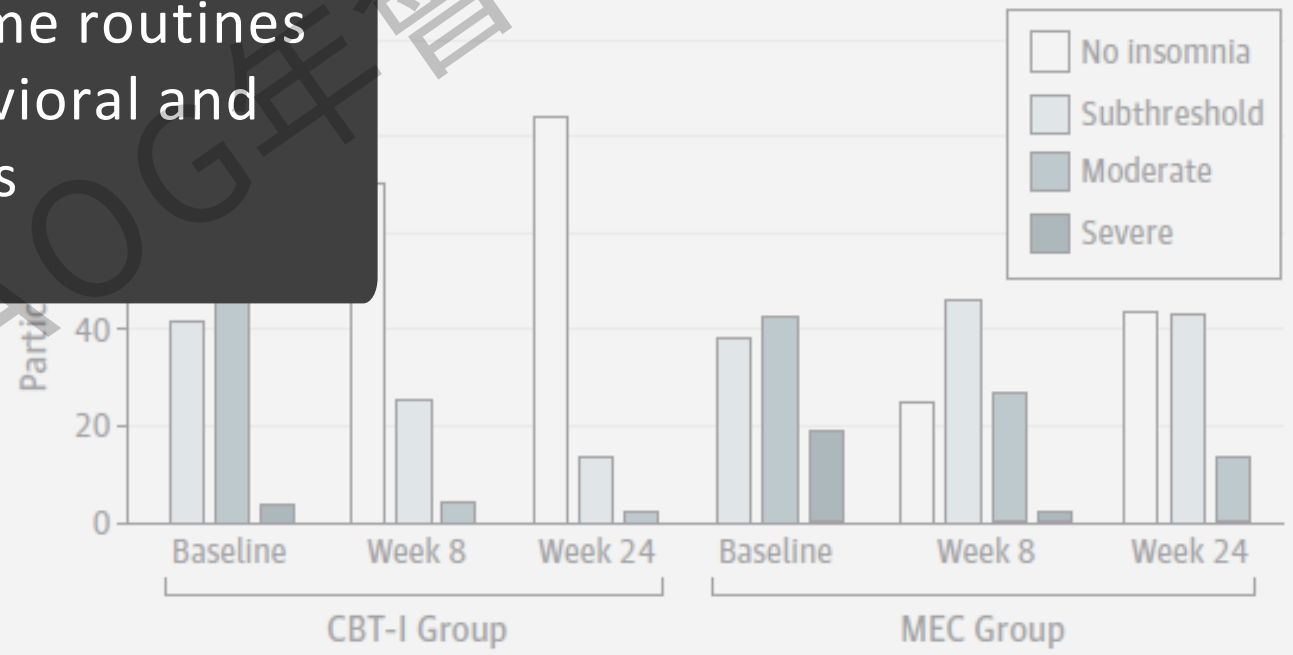

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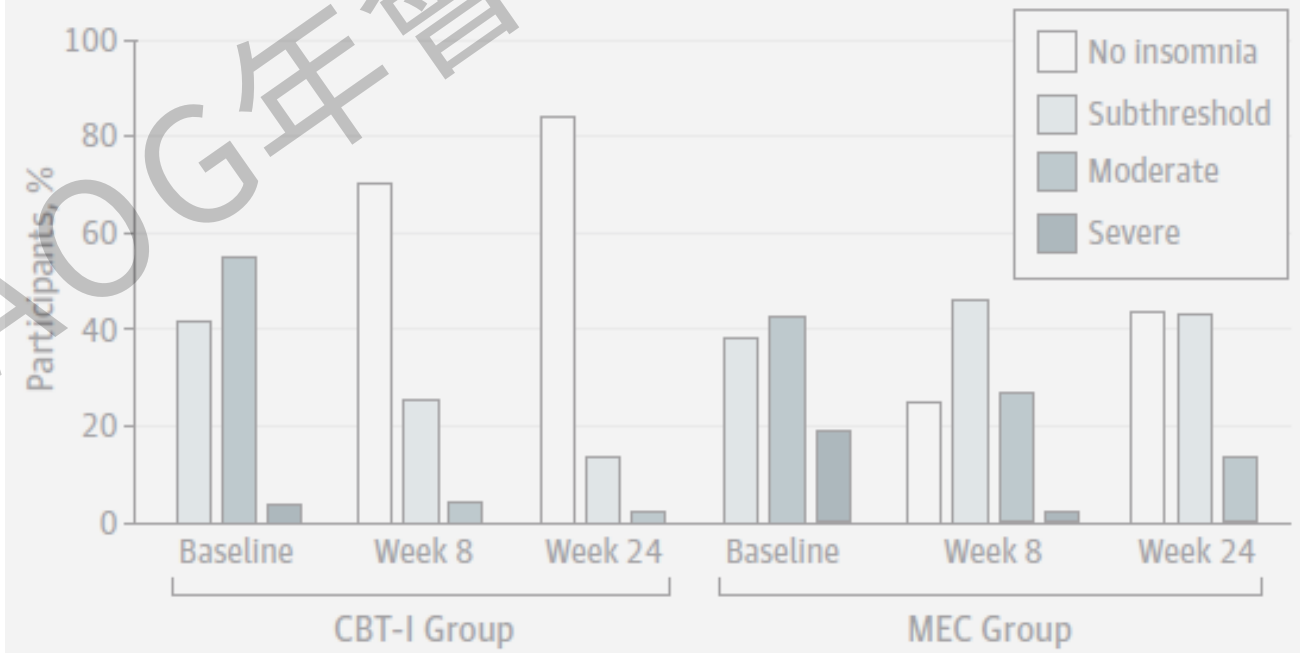

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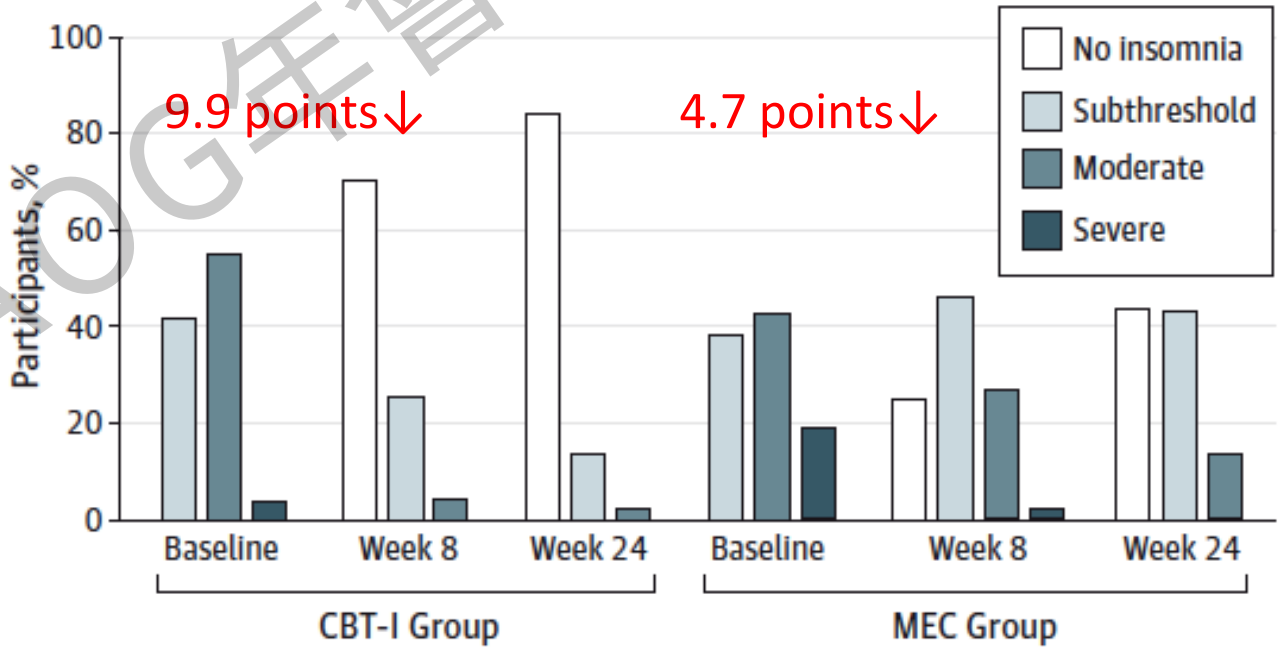

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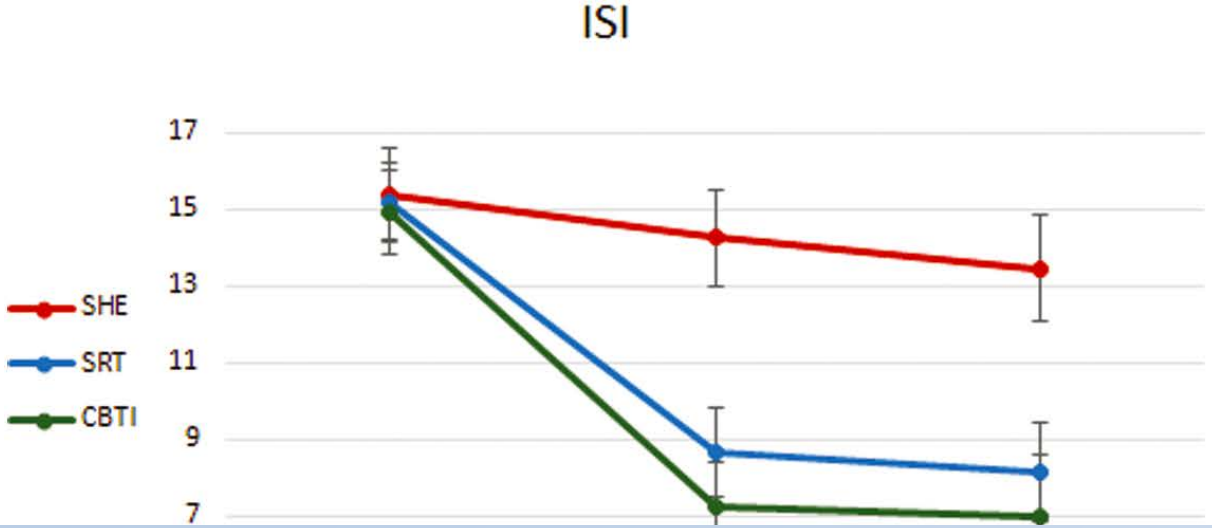
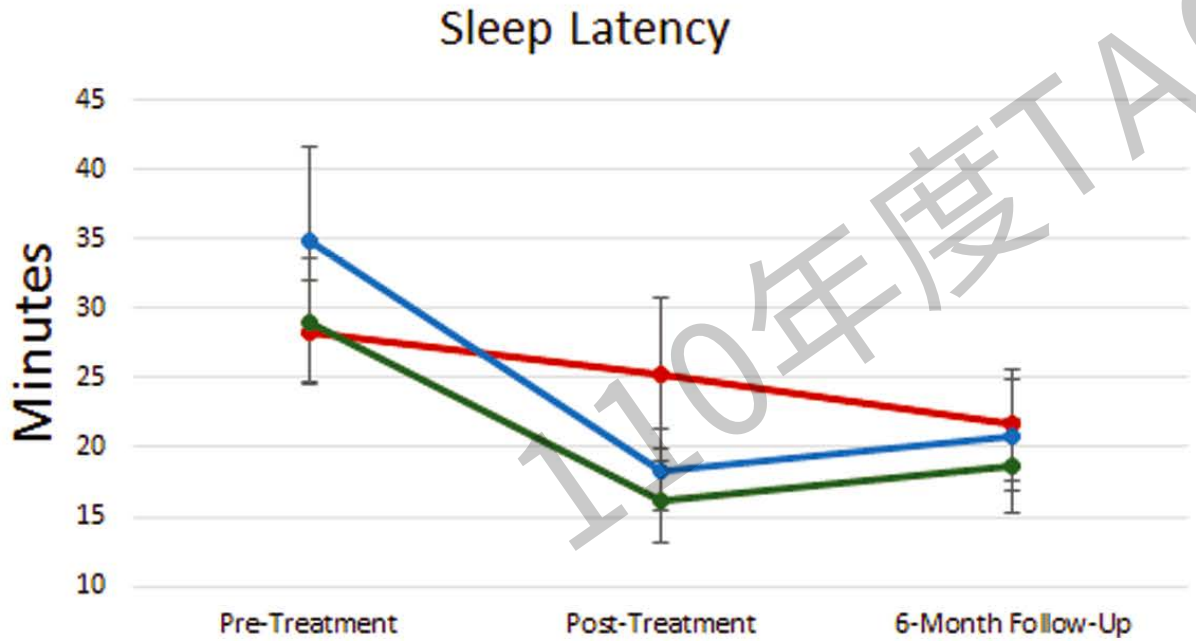
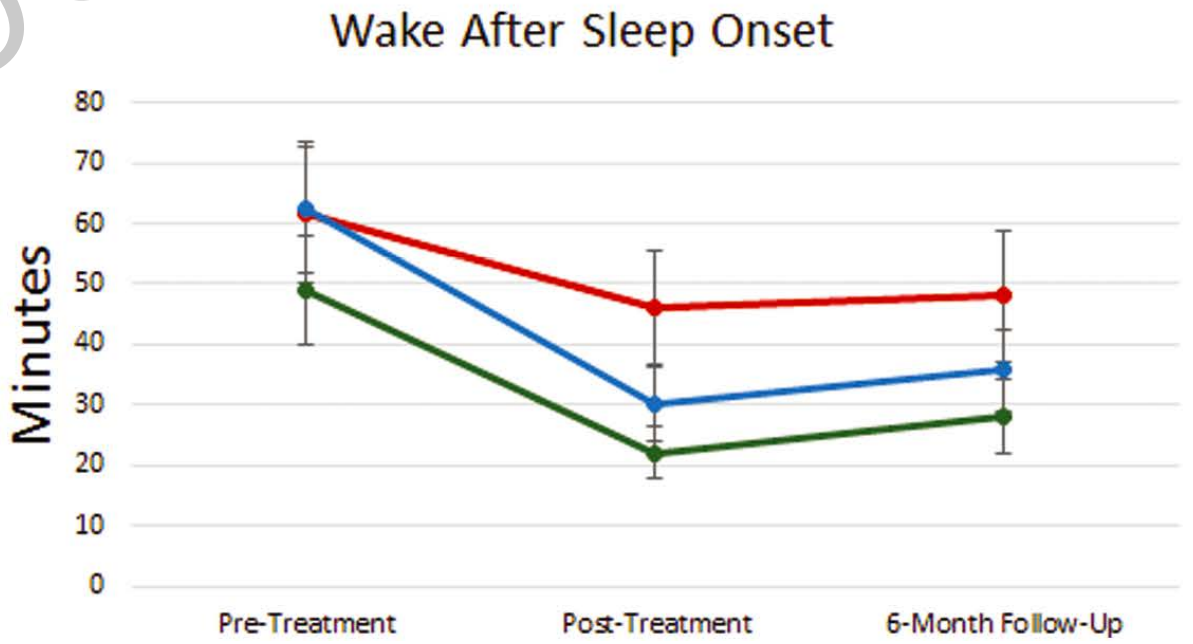


Cognitive-behavioral therapy is effective in menopause-related insomnia





Sleep 2019;42:42

Epidemiology

Mechanism

Cognitive Behavioral Treatment

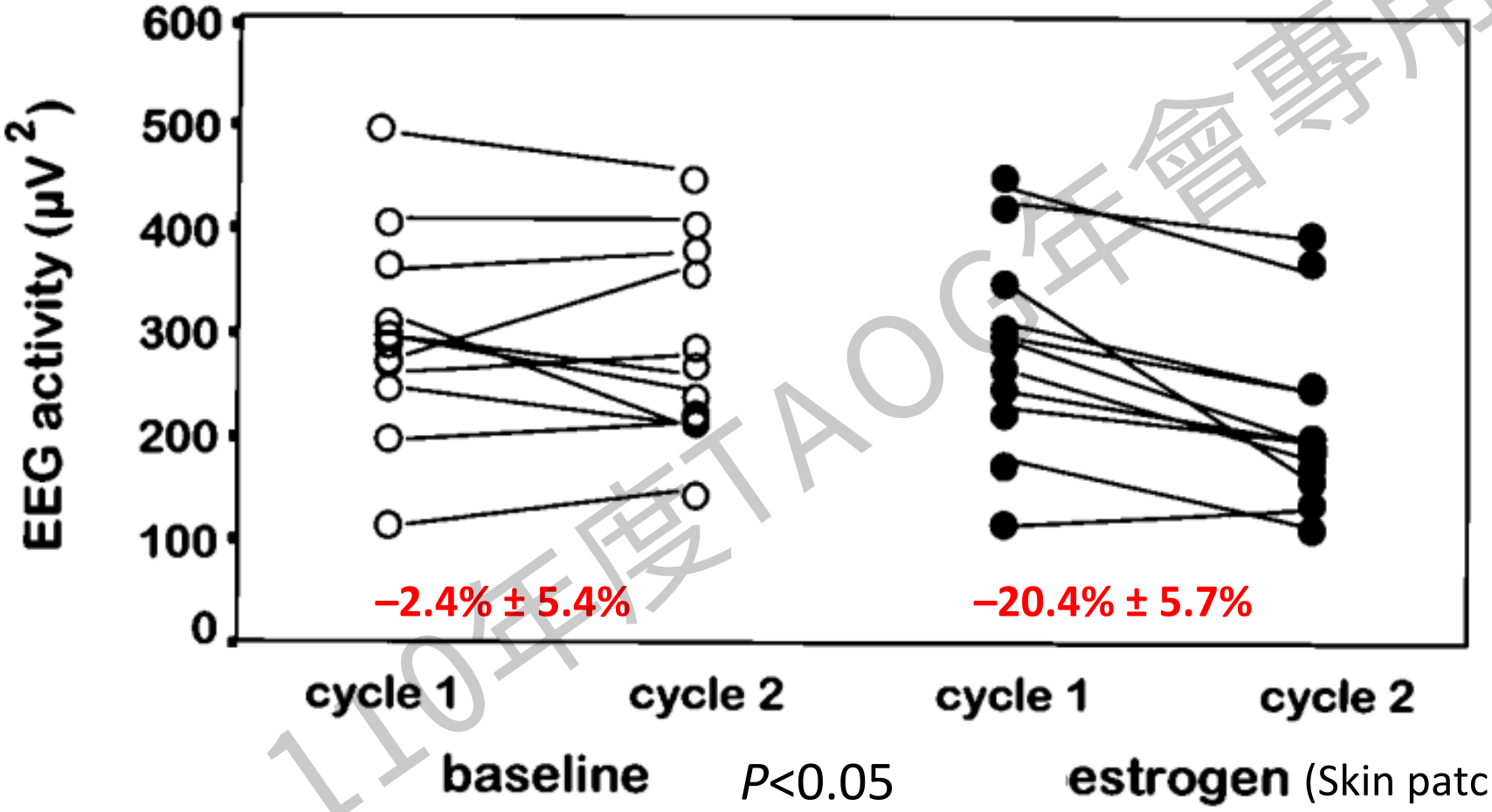
Hormone Thearpy

Other Treatment

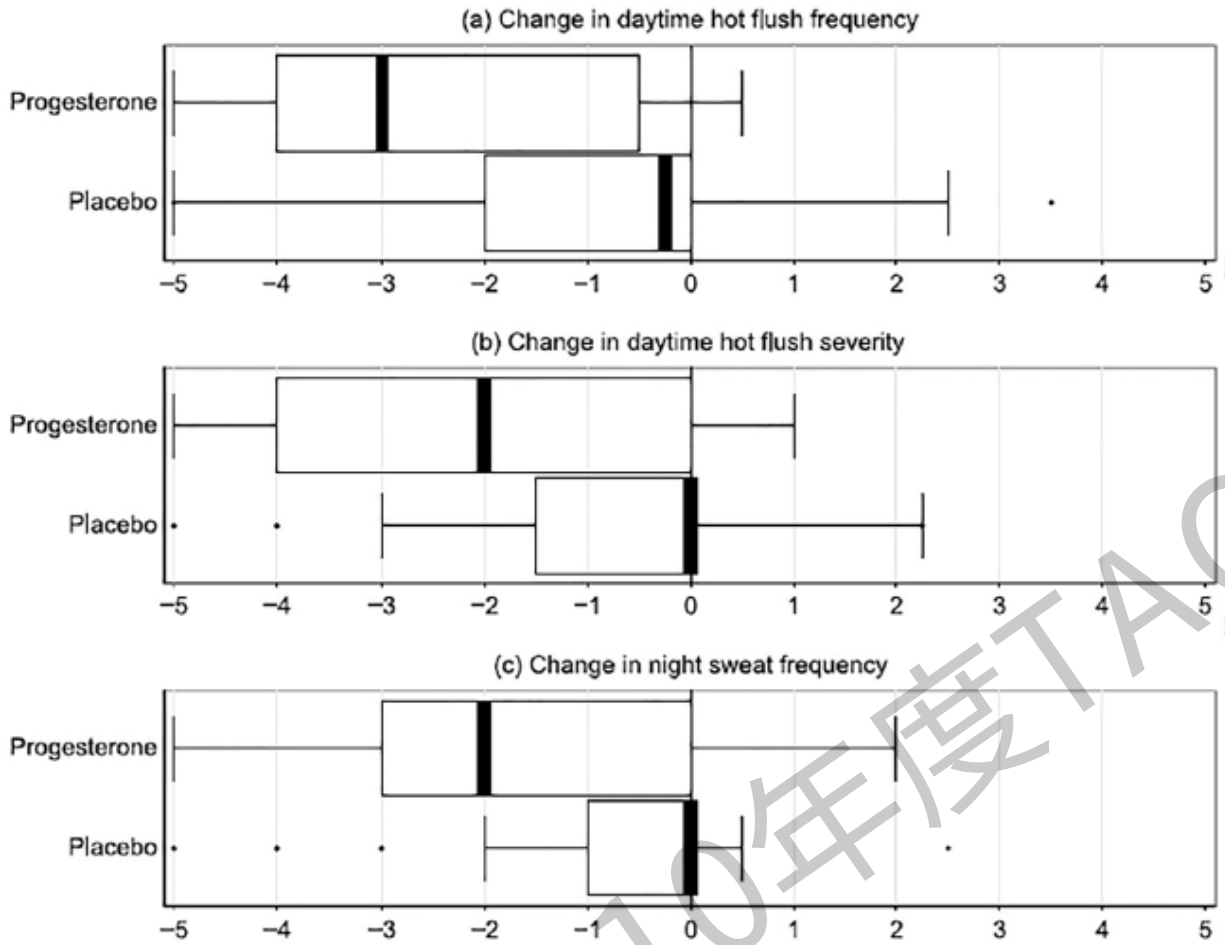
Hormone Thearpy

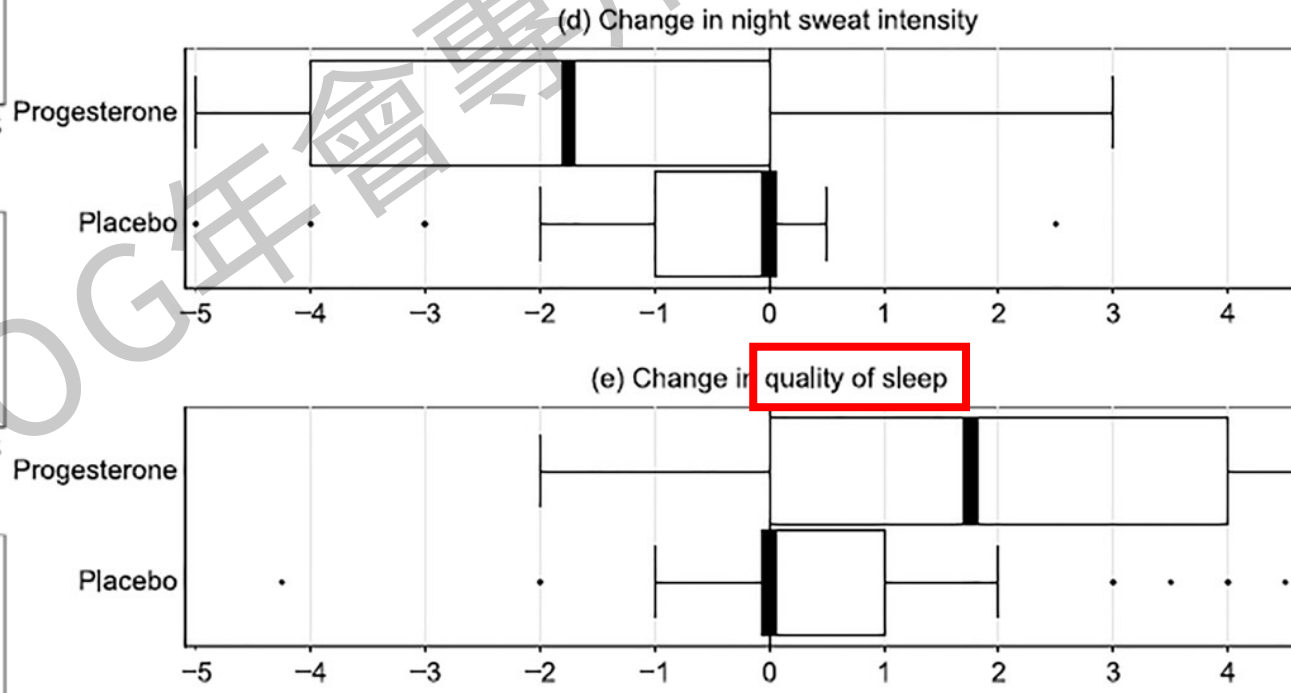
- Only in patients with VMS
- Estrogen: antidepressant, body thermoregulation
- Progesterone: sedative, anxiolytic, especially oral micronized progesterone

Delta EEG activity decrease from first to second non-rapid-eye-movement period during ERT



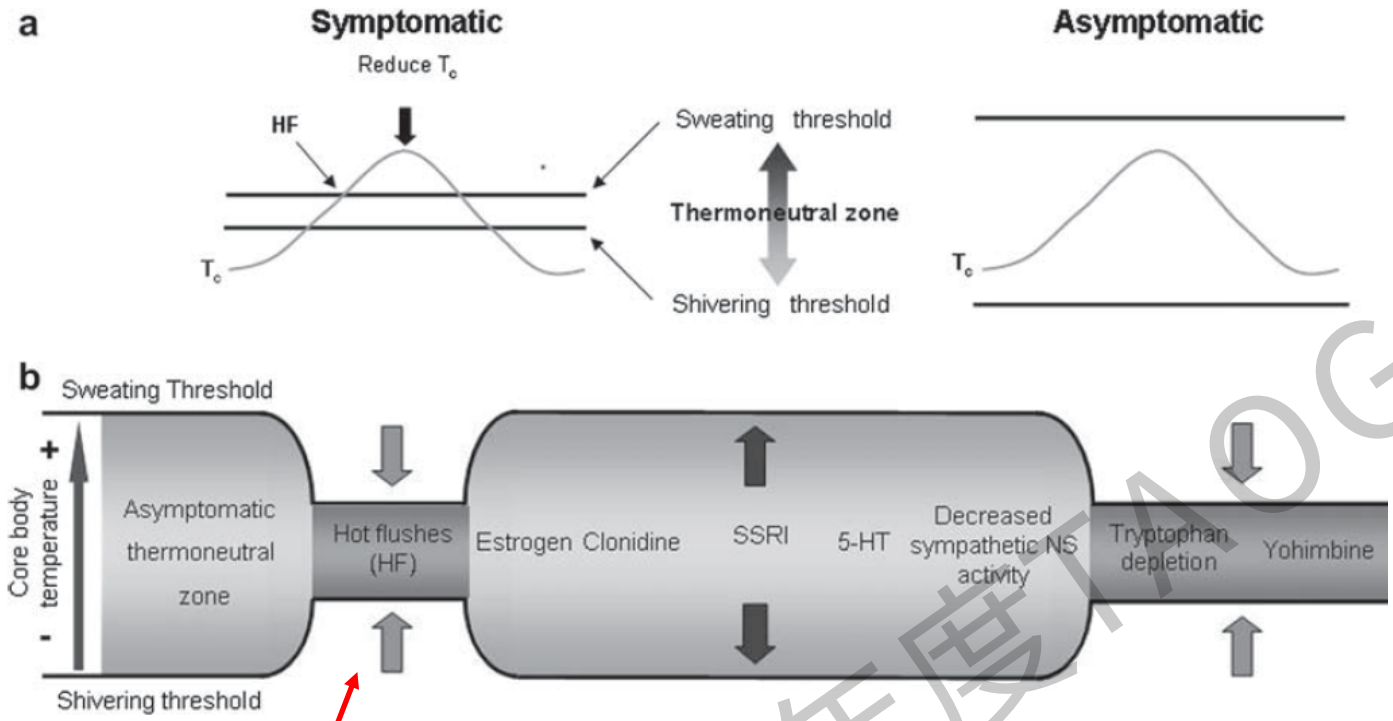
Am J Obstet Gynecol 2000;182:277–82





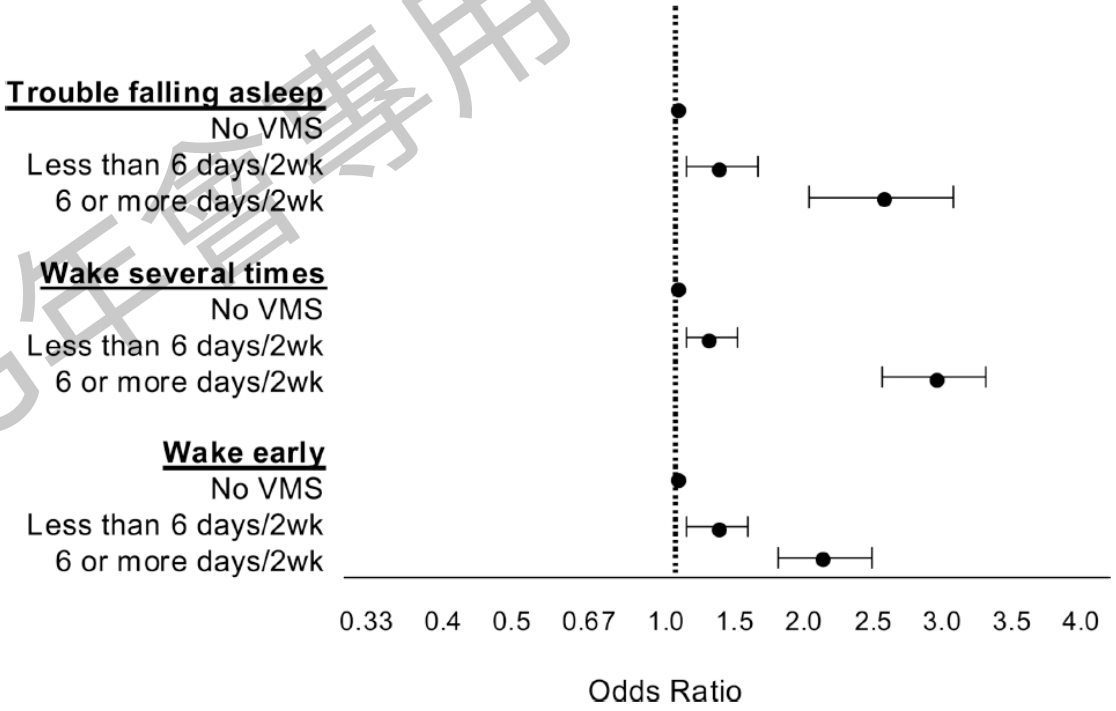
oral micronized progesterone (Progesterone) or placebo for 3 months

VMS has adverse effects on sleep



Elevated central noradrenergic activity

Climacteric 2011, 14, 515–528.



Obstet. Gynecol. Clin. N. Am. 2011, 38, 567–586.

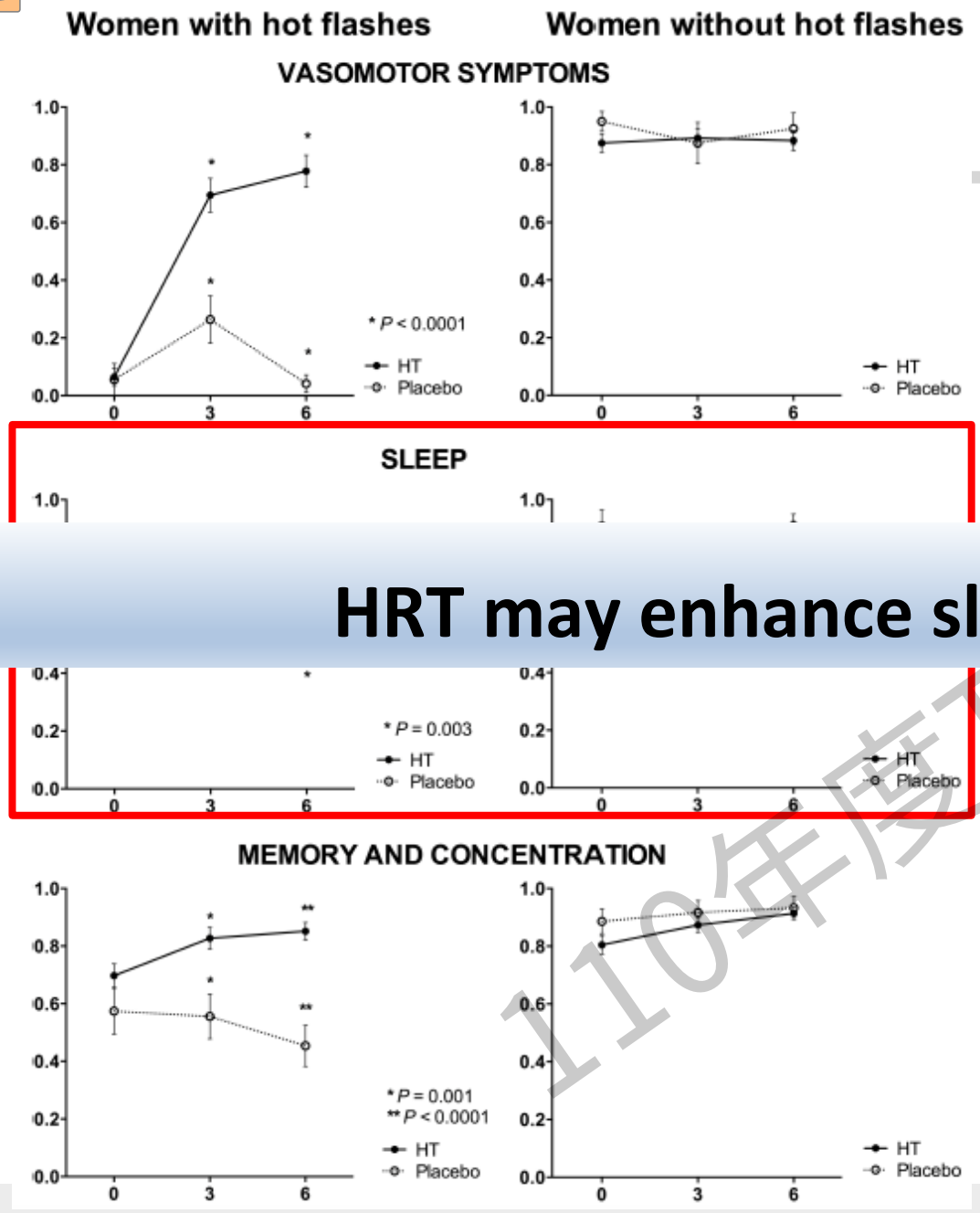


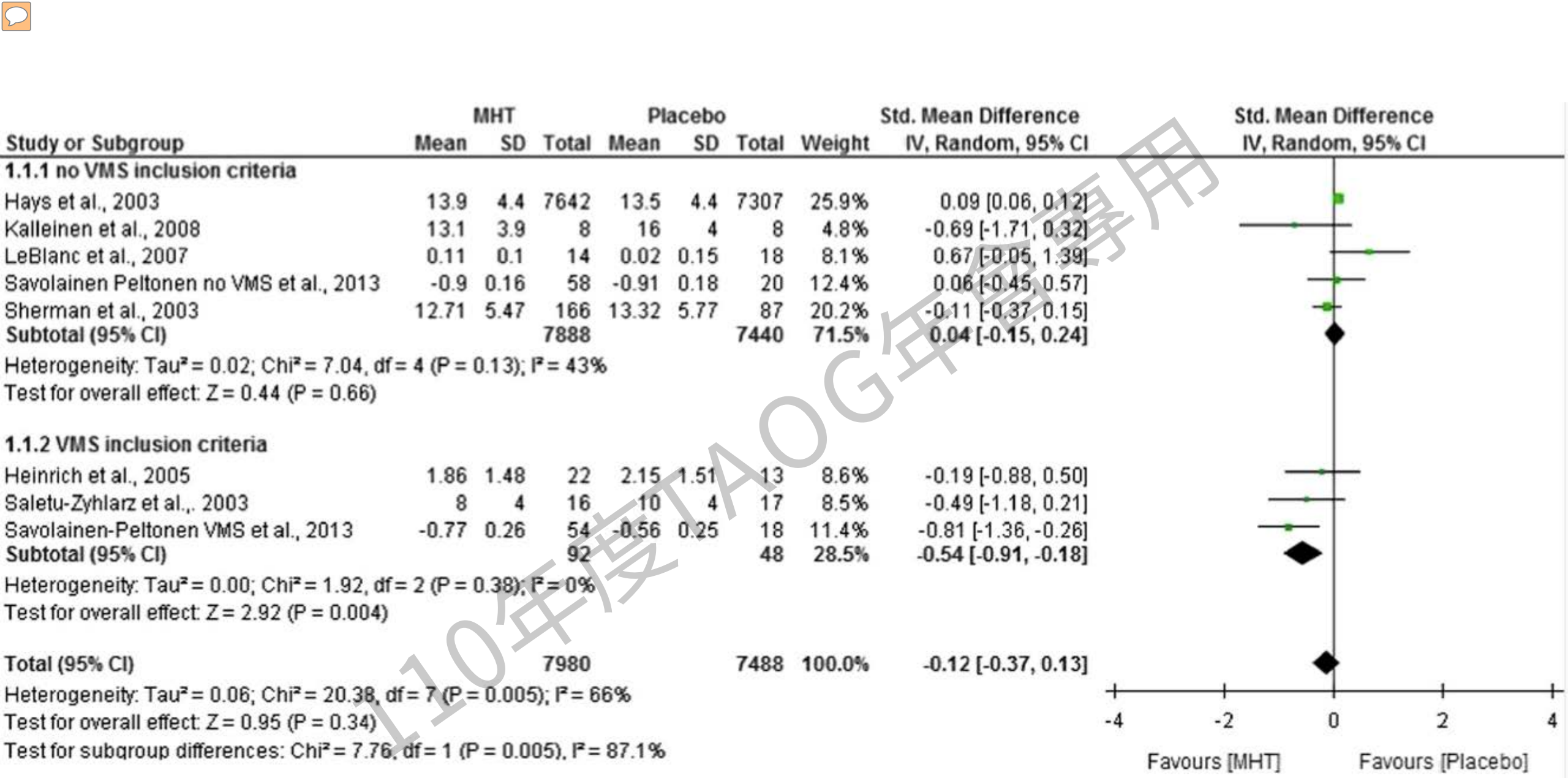
Table 1 | Mean (SE) scores on health related quality of life as measured with women's health questionnaire by treatment group

Component	Baseline		One year		Adjusted† difference at one year (95% CI)	P value
	Combined HRT (n=1043*)	Placebo (n=1087*)	Combined HRT (n=1043*)	Placebo (n=1087)*		
Depression	0.803 (0.004)	0.797 (0.004)	0.803 (0.004)	0.805 (0.004)	0.00 (−0.01 to 0.01)	0.39
Sexual	0.679 (0.012)	0.679 (0.013)	0.764 (0.0110	0.721 (0.012)	0.05 (0.02 to 0.08)	‹0.001‡
Sleep	0.637 (0.010)	0.657 (0.010)	0.740 (0.009)	0.703 (0.009)	0.05 (0.02 to 0.07)	‹0.001‡
Menstrual	0.906 (0.005)	0.905 (0.005)	0.905 (0.005)	0.907 (0.005)	0.00 (−0.01 to 0.01)	0.77
Esteem	0.546 (0.004)	0.544 (0.004)	0.559 (0.004)	0.553 (0.004)	0.00 (−0.01 to 0.02)	0.40

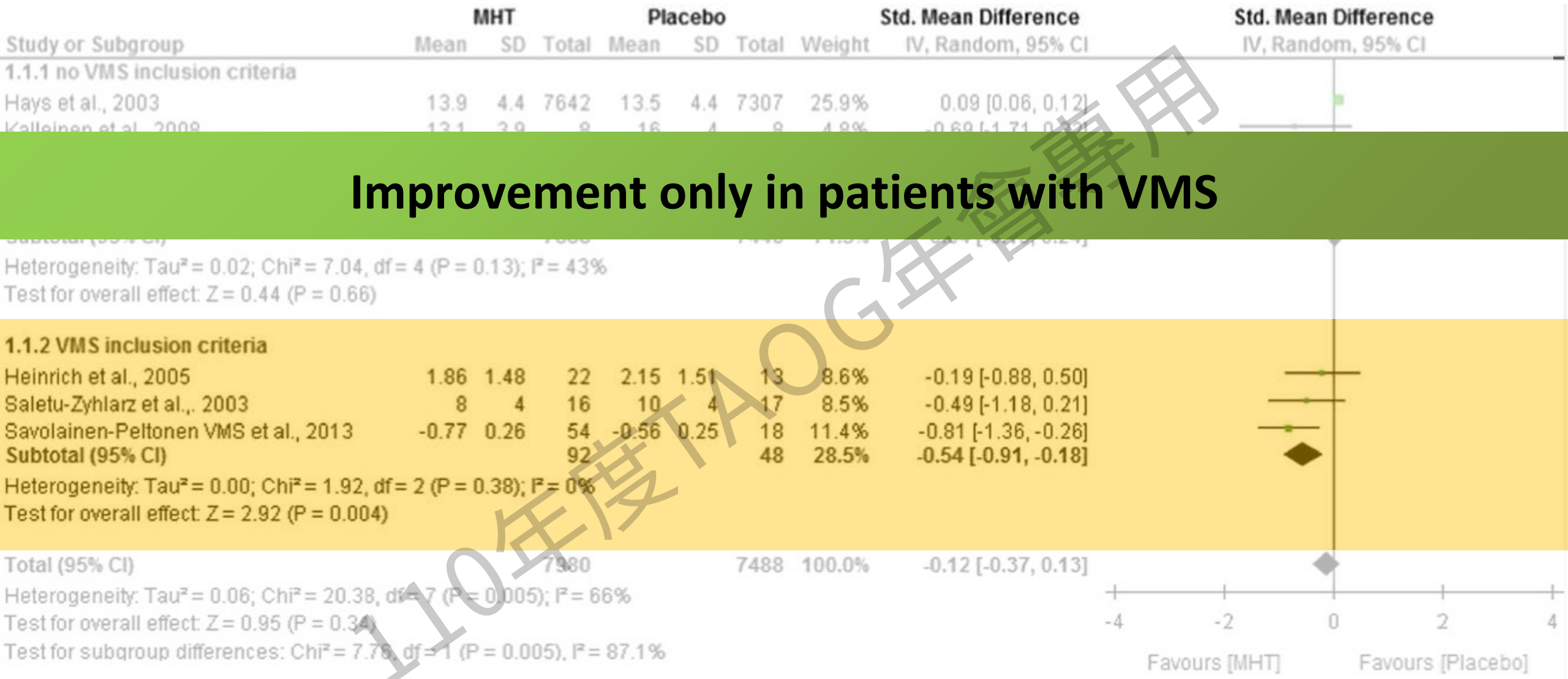
HRT may enhance sleep quality by improving VMS

Menopause 2014, 21, 732–739

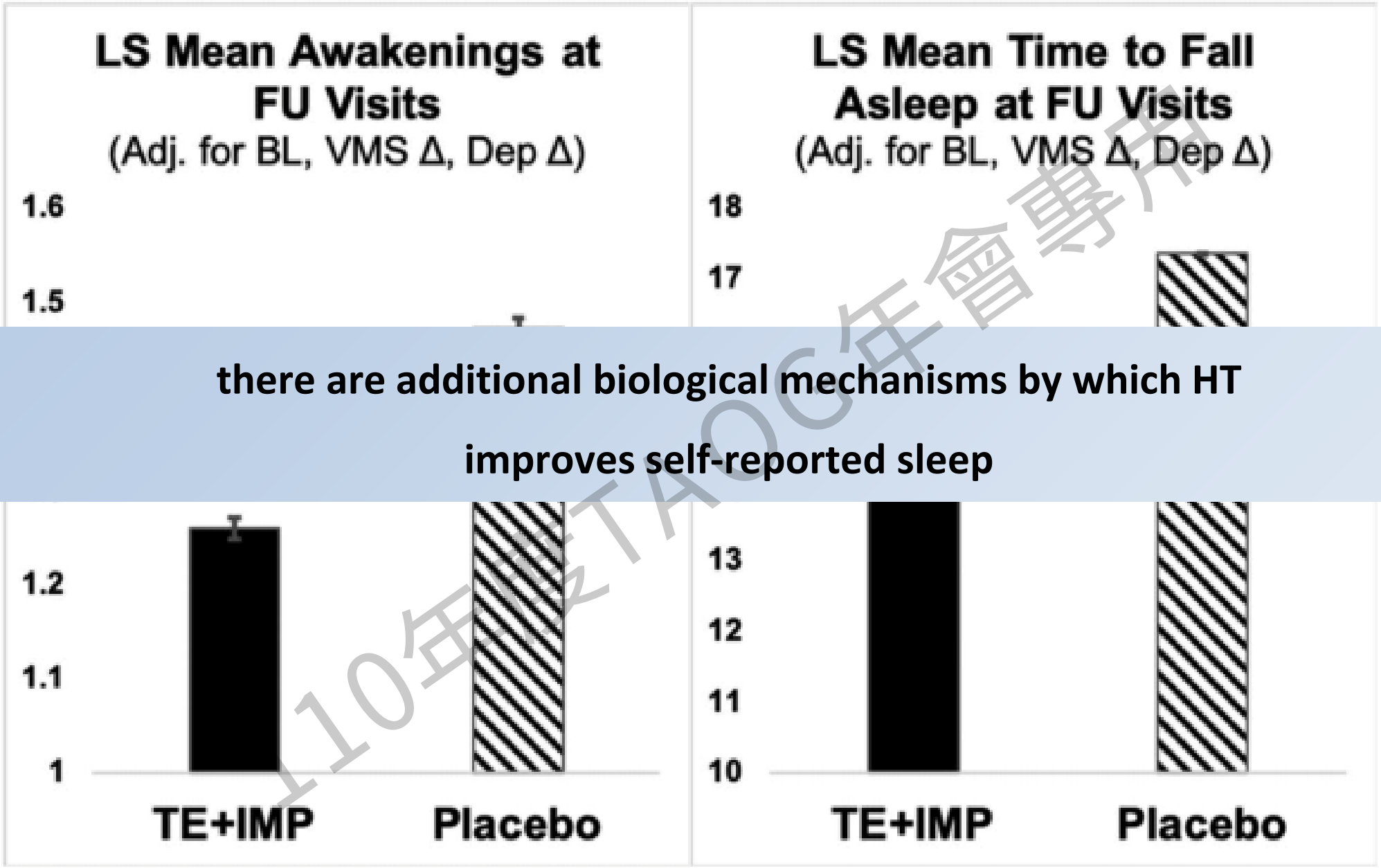
BMJ 2008, 337, a1190



Improvement only in patients with VMS



Endocrine 2017;55:702–11



there are additional biological mechanisms by which HT improves self-reported sleep

Menopause 2019 Vol. 26, No. 11, pp. 1318-1323

Epidemiology

Mechanism

Cognitive Behavioral Treatment

Hormone Thearpy

Other Treatment

Other Treatment

- Antidepressants
- Melatonin: prolonged-release melatonin (PRM) 2mg in patients > 55 y/o
- Benzodiazepine and Z-drugs: adverse effects in long-term users
- Gabapentin

Antidepressants

The most popular treatment for VMS other than MHT in menopausal women affected by insomnia

Escitalopram

- SSRI
- 10-20 mg/day
- Effective, especially comorbid depression

Citalopram & venlafaxine

- Effective in reducing sleep disturbance
- Citalopram: reducing hot flush
- Venlafaxine: postmenopausal depression

Mirtazapine (+ prolonged-release melatonin)

- Improved quality of sleep
- Weight gain

Citalopram & fluoxetine

- Only reducing sleep disturbance in citalopram
- VMS not improved in both

Ecancermedicalscience 2019;13:909

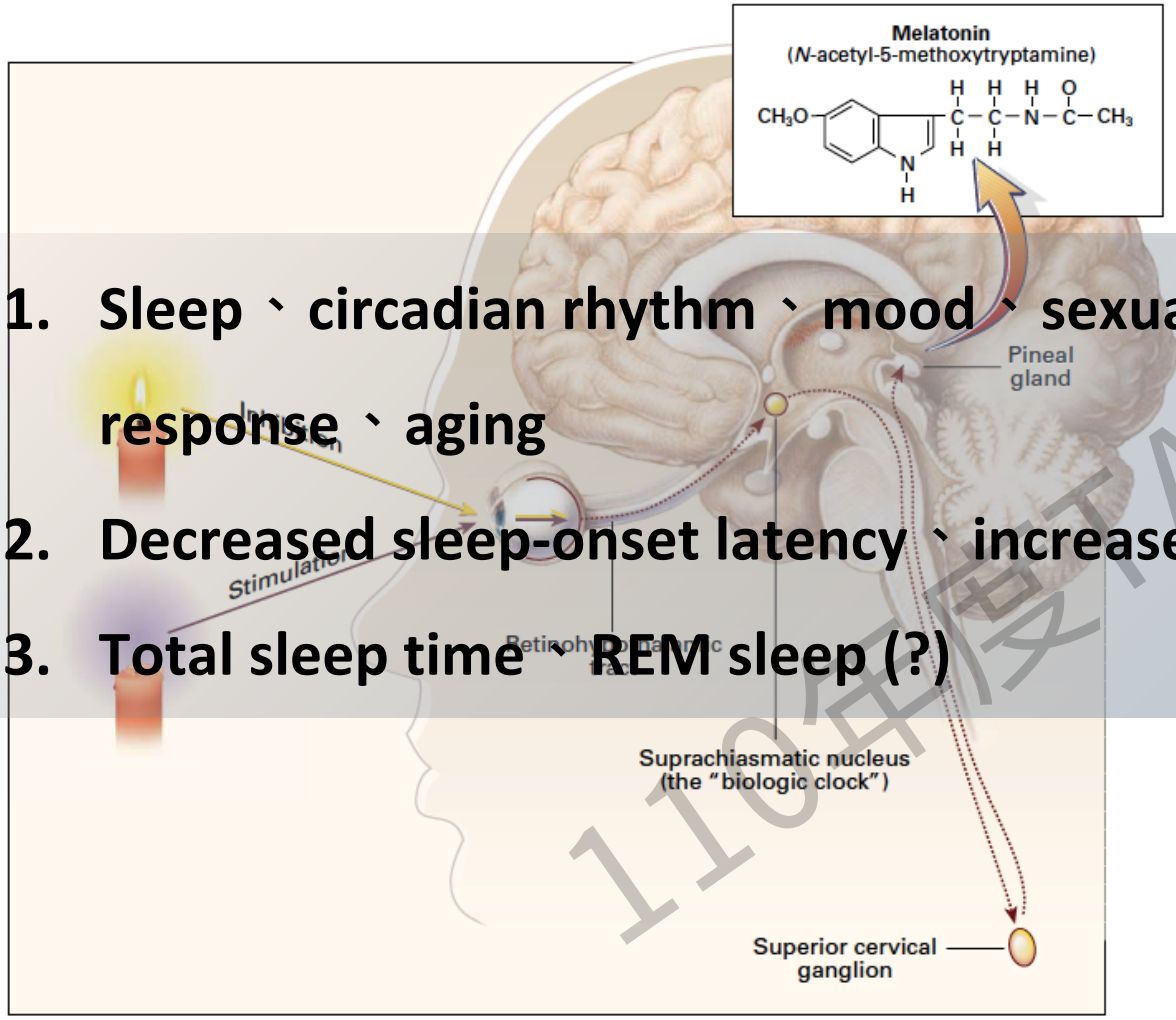
Menopause 2015;22:674–84

Menopause 2012;19:848–55

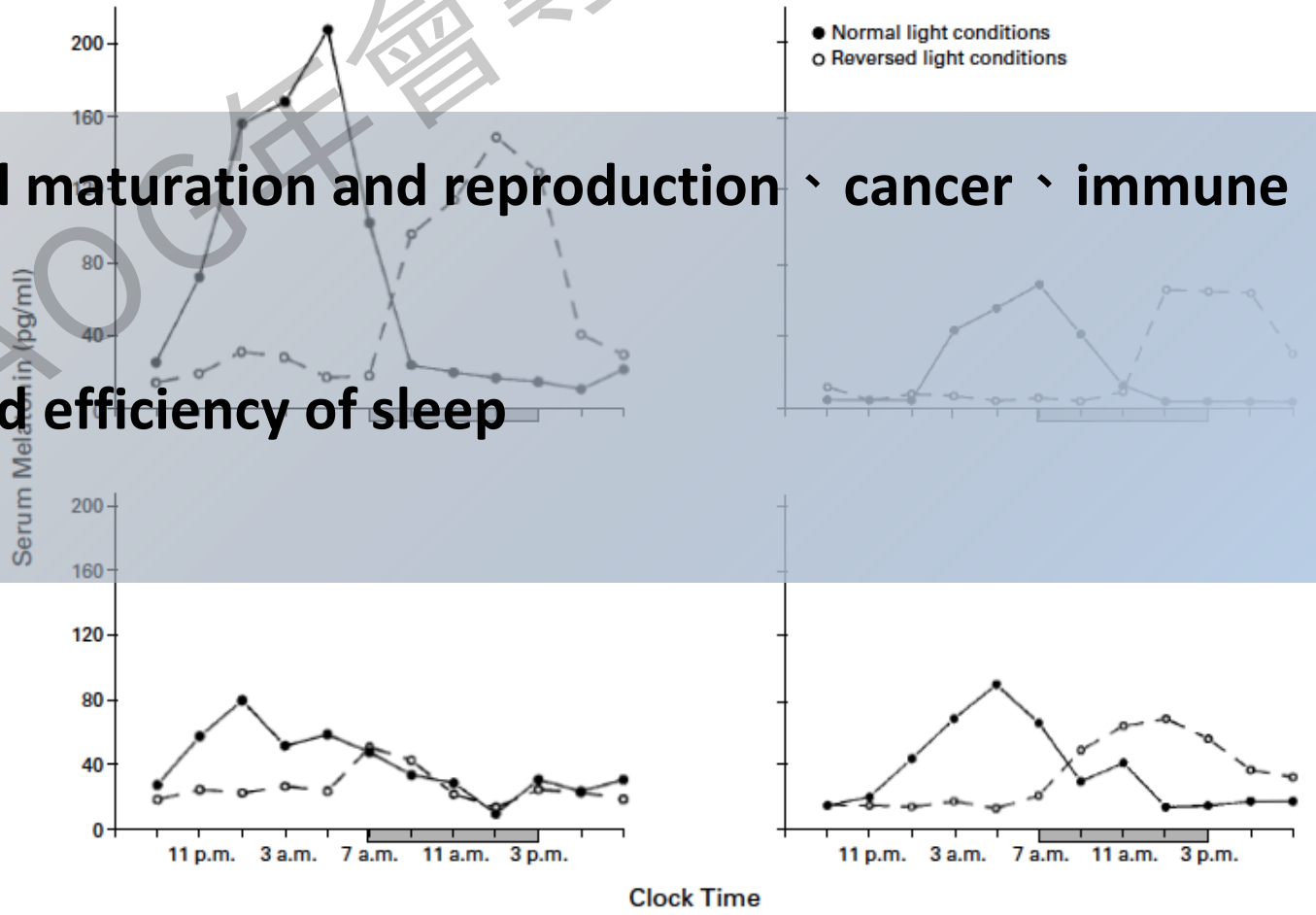
Arch Gynecol Obstet 2016;293:1007–13

Menopause 2005;12:18–26

Melatonin



1. Sleep、circadian rhythm、mood、sexual maturation and reproduction、cancer、immune response、aging
2. Decreased sleep-onset latency、increased efficiency of sleep
3. Total sleep time、REM sleep (?)

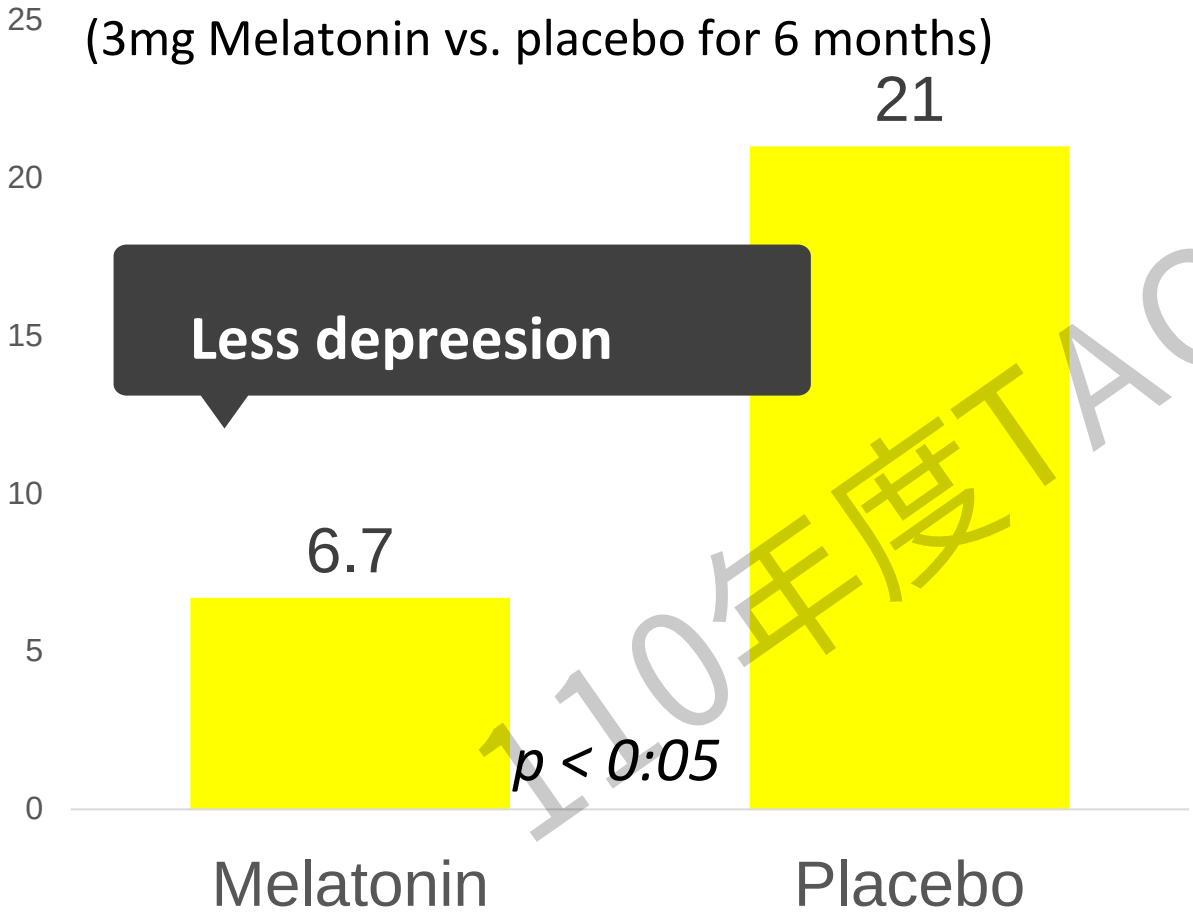


N Engl J Med 1997; 336:186-195

Melatonin

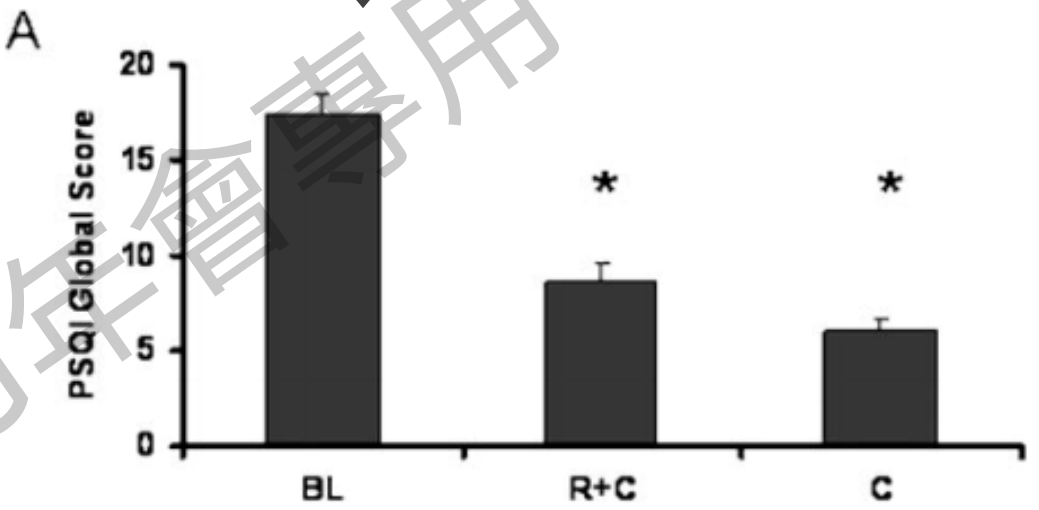
Morning depression

(3mg Melatonin vs. placebo for 6 months)

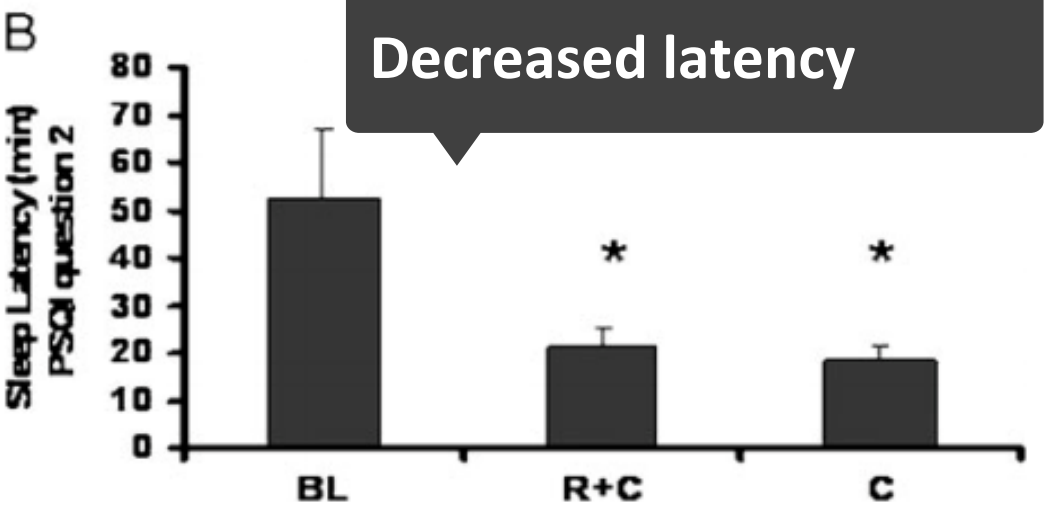


Less depreesion

Improved sleep quality



Decreased latency



Exp Gerontol 2001;36:297–310

Arch Womens Ment Health 2011 ; 14 : 269 – 73

Melatonin

Postmenopausal breast cancer survivors: 3mg melatonin or placebo for 4 months

	Placebo			Melatonin			Total			*p* value
	N	Average	SD	*N*	Average	SD	*N*	Average	SD	
PSQI										
Sleep quality	42	0.1	0.4	42	−0.4	0.8	84	−0.1	0.7	<0.001
Sleep latency	43	−0.3	0.6	42	−0.5	0.9	85	−0.4	0.8	0.21
Sleep duration	42	0.1	0.6	42	−0.3	0.7	84	−0.1	0.7	0.03
Sleep efficiency	42	0.1	0.8	42	−0.2	1.0	84	0.0	0.9	0.23
Sleep disturbances	43	−0.0	0.3	43	−0.2	0.5	86	−0.1	0.5	0.14
Medication use	42	−0.3	0.8	43	−0.3	0.8	85	−0.3	0.8	0.53
Daytime dysfunction	42	0.1	0.6	43	−0.3	0.5	85	−0.1	0.6	0.001
Total PSQI Score*	39	−0.1	2.0	41	−1.9	2.4	80	−1.0	2.4	0.001

Breast Cancer Res Treat (2014) 145:381–388

Prolonged-released melatonin (PRM)

Approved for primary insomnia in people aged ≥ 55

Mimics the internal melatonin secretion profile

Without withdrawal effects, negative impacts on psychomotor functions, memory recall, and postural stability in older adults

Concomitant therapy with other drugs

Ramelteon

MT1 and MT2 melatonergic receptor agonist

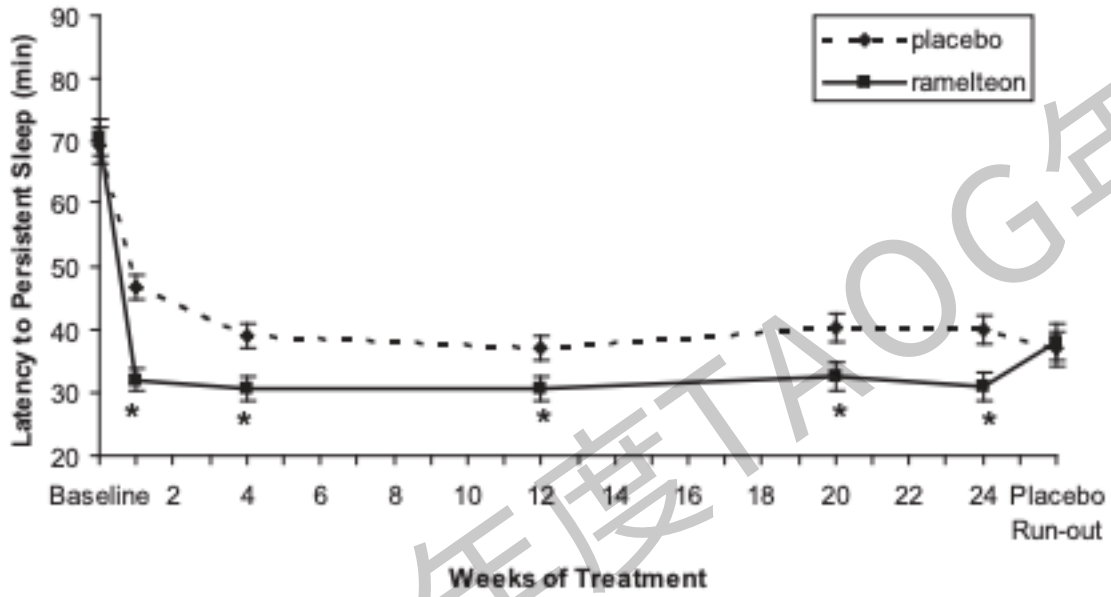


Figure 2—Polysomnography-measured latency to persistent sleep over 6 months of nightly ramelteon, 8 mg, or placebo treatment. Data are least-squares means with standard error bars. Last observation carried forward data were used at each time point except placebo run-out, which was observed data only. *P < 0.05 versus placebo, obtained from t tests from an analysis of covariance model of overall treatment comparison.

Benzodiazepine and Z-drugs

Short-acting benzodiazepines—

Ex: triazolam, brotizolam…

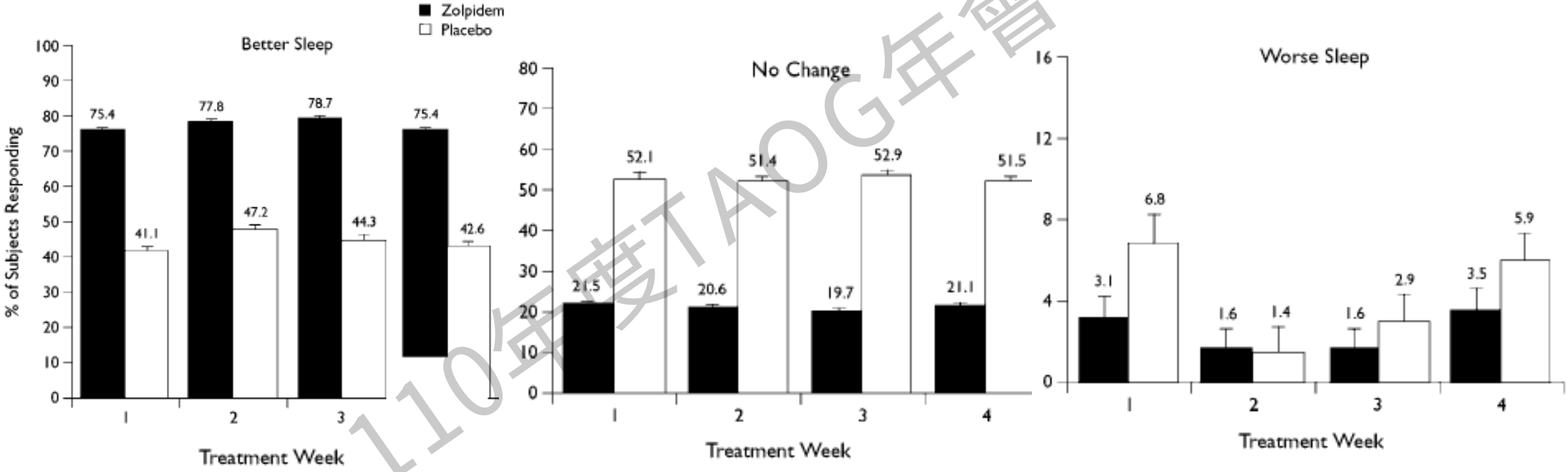
Z-drugs—

Ex: zolpidem, zoplicone, zaleplon…

A buffered sublingual zolpidem: patients with early awakening insomnia and at least 4 h of bedtime remaining

Benzodiazepine and Z-drugs

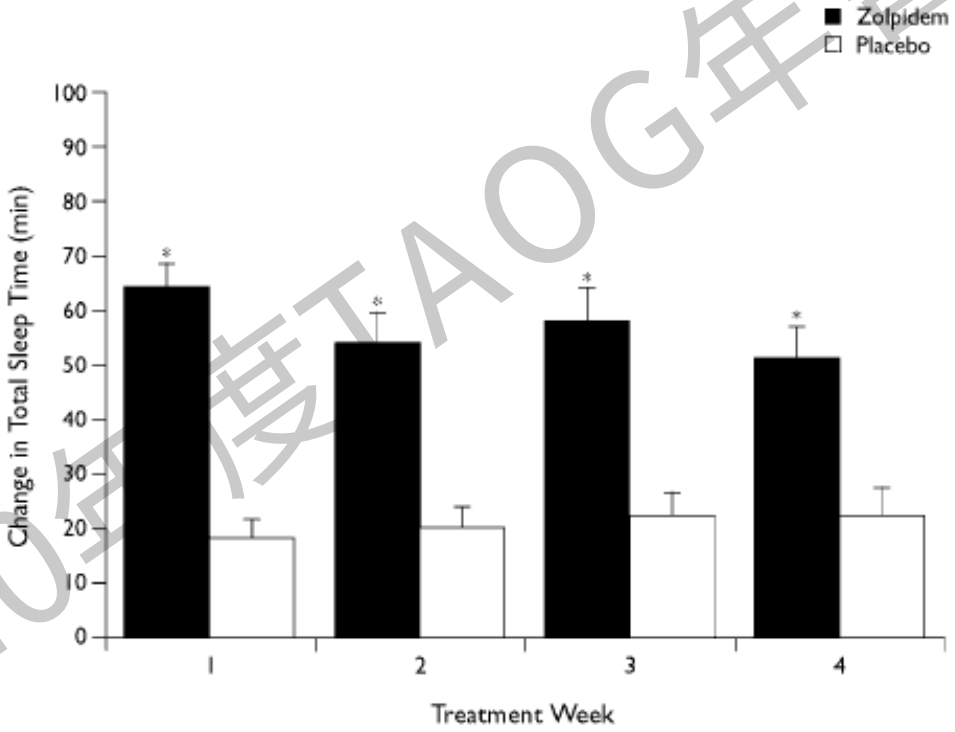
In menopausal women: Zolpiderm



Clin Ther 2004;26:1578–86

Benzodiazepine and Z-drugs

In menopausal women: Zolpiderm

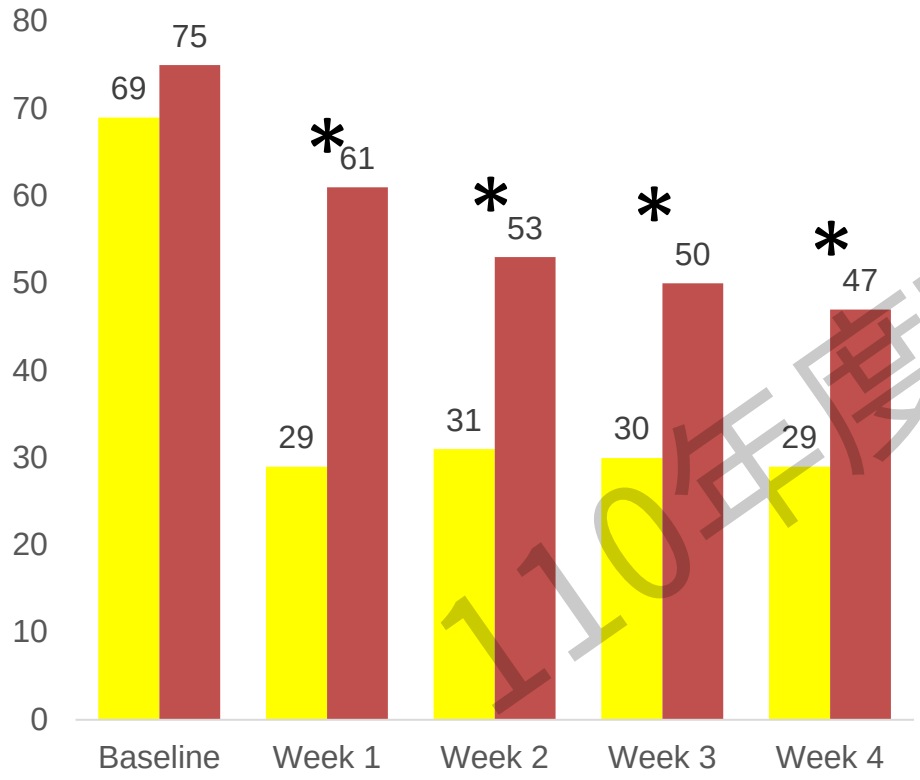


Clin Ther 2004;26:1578–86

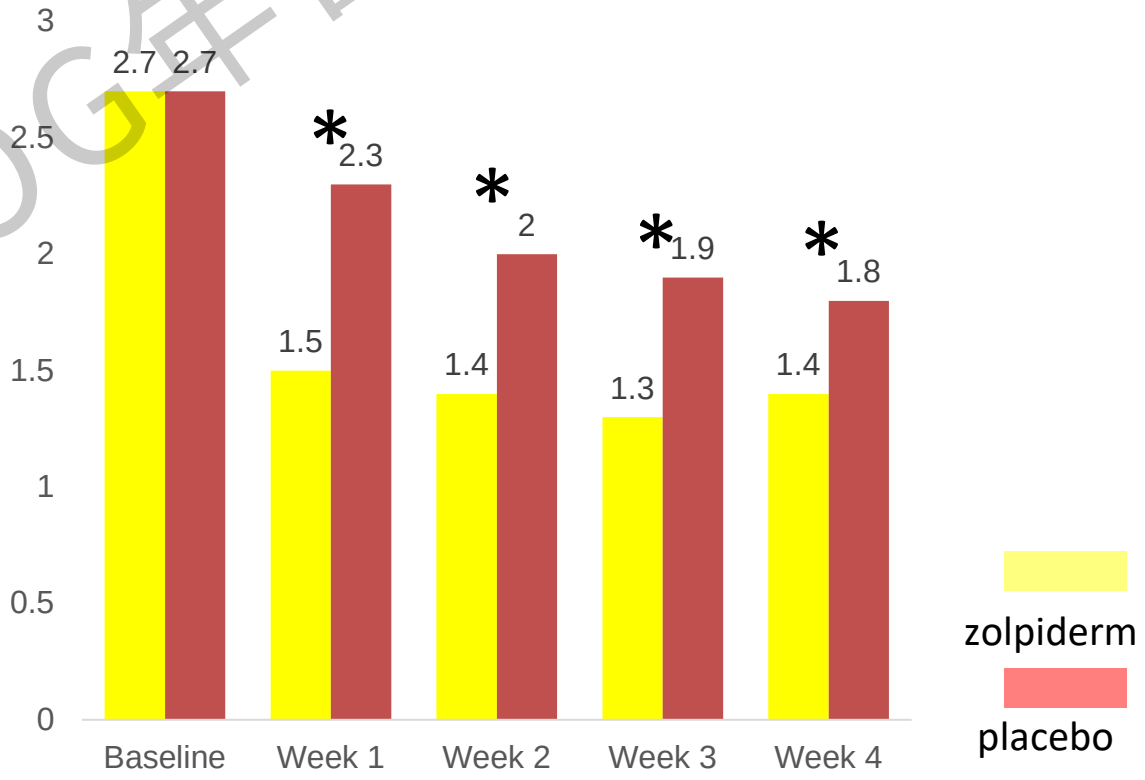
Benzodiazepine and Z-drugs

In menopausal women: Zolpiderm

Wake After Sleep Onset



No. of Awakenings



Clin Ther 2004;26:1578–86

Benzodiazepine and Z-drugs

In menopausal women: Eszopiclone

Variable	Difference between eszopiclone and placebo	Effect of eszopiclone compared with placebo	
		F	*P* value
Insomnia Severity Index	8.7 ± 1.4	40.8	< .0001
Sleep latency, min	17.8 ± 14.4	4.4	.04
Total sleep time, min	66.5 ± 17.6	6.7	.01
Wake time after sleep onset, min	37.7 ± 8.6	4.0	.05
Sleep efficiency, %	14.6 ± 3.7	7.2	.01
Montgomery-Åsberg Depression Rating Scale	8.9 ± 2.3	15.8	.0004
Beck Anxiety Inventory	1.5 ± 1.1	7.2	.03
Menopause-Specific Quality of Life Questionnaire	0.93 ± 0.27	16.4	.0002
Sheehan Disability Scale	3.2 ± 1.8	2.8	.09
Nighttime hot flashes	1.5 ± 0.3	4.2	.047
Daytime hot flashes	0.7 ± 0.3	1.8	.18

Am J Obstet Gynecol 2010;202:171.e1–171.e11

Benzodiazepine and Z-drugs

Adverse health associations in long-term users

postural instability and falls

cognitive impairment

Tolerance or rebound

Car accidents

Benzodiazepine and Z-drugs

BZD or Z-drugs: significant increase in fracture risk

BZD use is a major osteoporosis risk factor in women 50-65 y/o

Progesterone may potentiate the behavioral effects of BZD→ BZD use and abuse

Osteoporos Int 2014;25:105–20

Age Ageing 2018;47:201–8

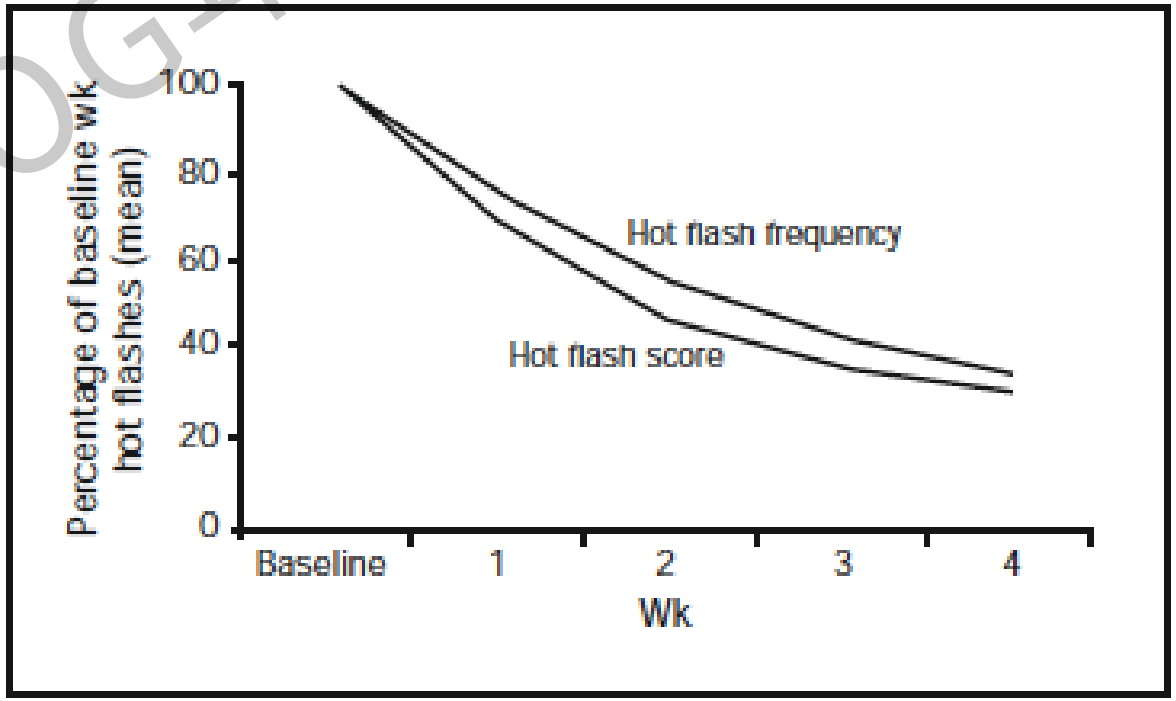
Open Rheumatol J 2008;2:58–63

Psychopharmacology (Berl) 2011;215:429–39

Gabapentin

- Anticonvulsant
- Chronic neuropathic pain
- Relieving hot flushes in menopausal women
- binds to the **α2**δ subunit of the voltage-gated calcium channel and inhibits neuronal calcium currents in vitro

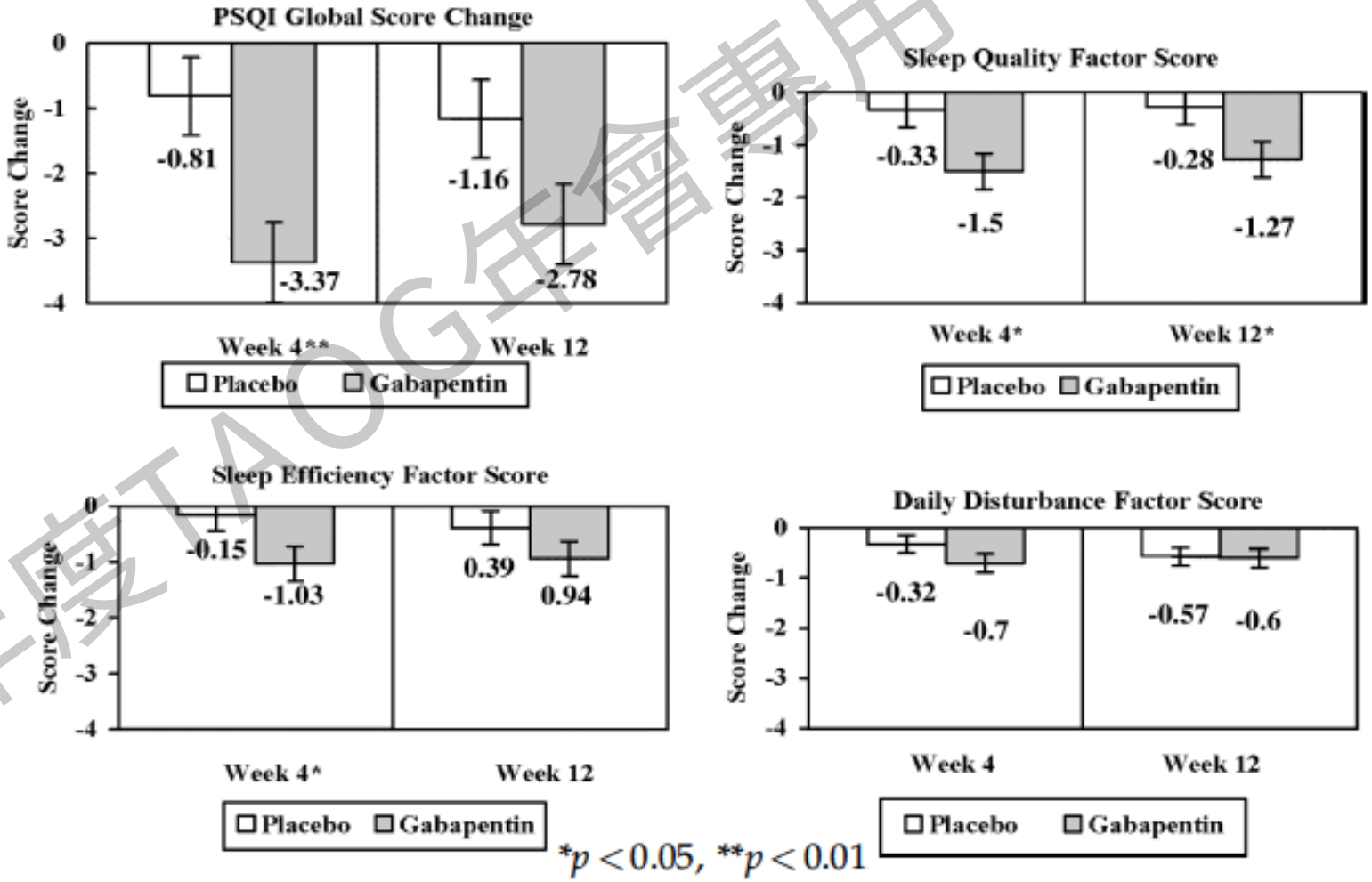
Reduce symptoms of hot flushes by 66%



Mayo Clin Proc 2002;77:1159–63

Gabapentin

- 59 postmenopausal women experiencing daily hot flushes
- Gabepentin vs. placebo for 12 wks
- 300mg three times daily



J Womens Health (Larchmt) 2009;18:1355–60

Gabapentin

low serum estradiol causing nighttime awakenings (LUNAs)

Patient age at onset of nighttime awakenings	History of hot flashes or night sweats?	Low early follicular phase serum estradiol?	Subjective improvement of nighttime awakenings with gabapentin qhs?	Final qhs gabapentin dose	Transient gabapentin side effects
45yo (Case 1)	yes	?	yes	600 mg	Dizziness
40yo (Case 2)	yes	yes (32.2pg/mL)	yes	900 mg	Sedation
40yo (Case 3)	yes	yes (50pg/mL)	yes	600 mg	None

Side effects: motor incoordination, drowsiness, fluid retention

J Clin Sleep Med 2012;8:187–9

Take Home Message

Epidemiology

- Definition: ≥ 3 / wk for 3 months
- 46-48% of menopausal women
- Main predictive factor: premenopausal sleep condition

Mechanism

- Hormonal changes: progesterone, estrogen, androgen
- Hot flushes
- Mood disorders: increased risk of major depressive episode in menopausal women
- Circadian modification: melatonin

Take Home Message

Cognitive Behavioral Treatment

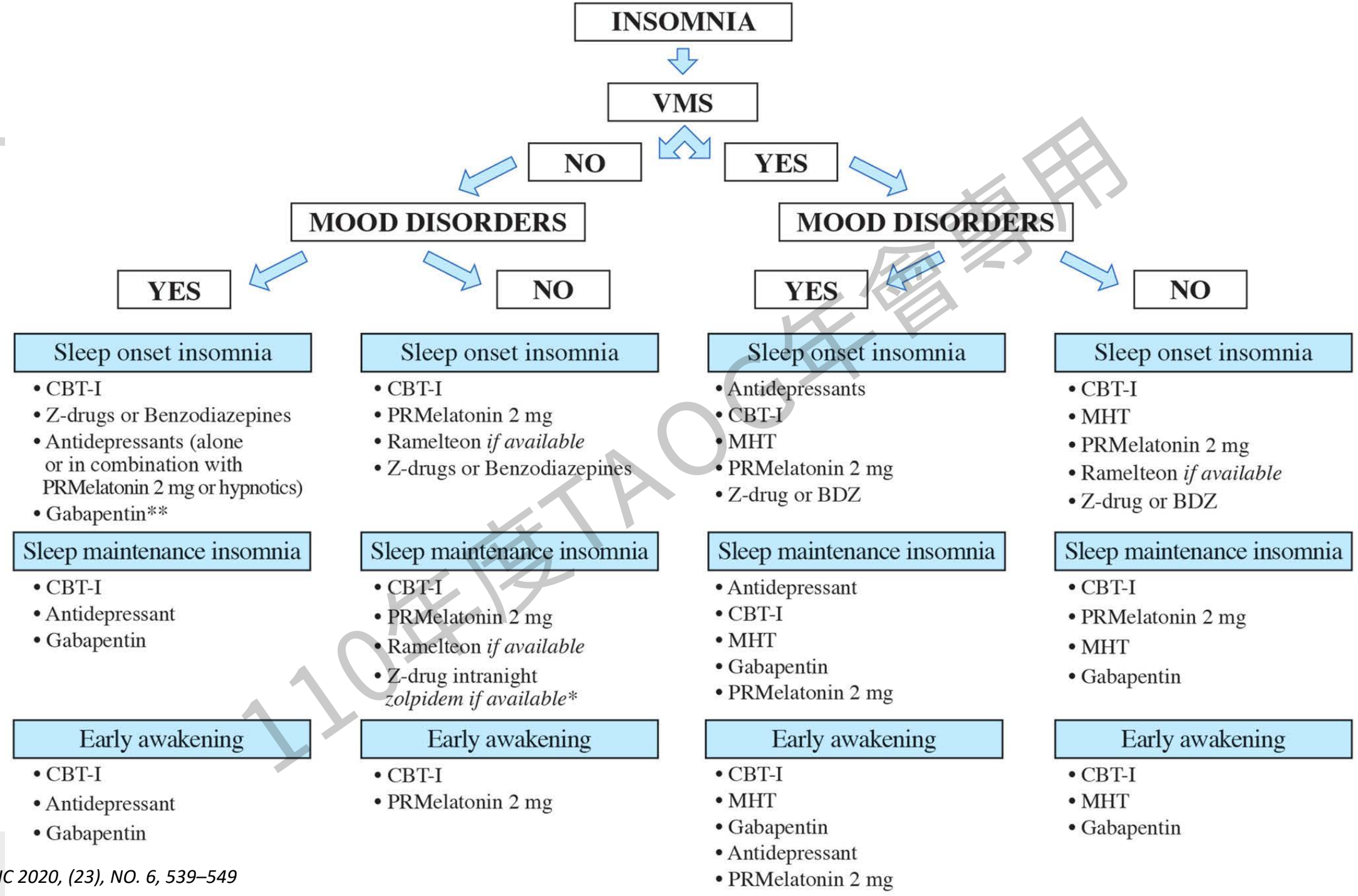
- Multicomponent treatment targeting cognitive and behavioral factors
- Efficacy proven from controlled trials

Hormone Thearpy

- Only in patients with VMS
- Estrogen: antidepressant, body thermoregulation
- Progesterone: sedative, anxiolytic, especially oral micronized progesterone

Other Treatment

- Antidepressants
- Melatonin: prolonged-release melatonin (PRM) 2mg in patients > 55 y/o
- Benzodiazepine and Z-drugs: adverse effects in long-term users
- Gabapentin



CLIMACTERIC 2020, (23), NO. 6, 539–549

Thanks for Your Listening