Sleep Disturbance Associated with the Menopause

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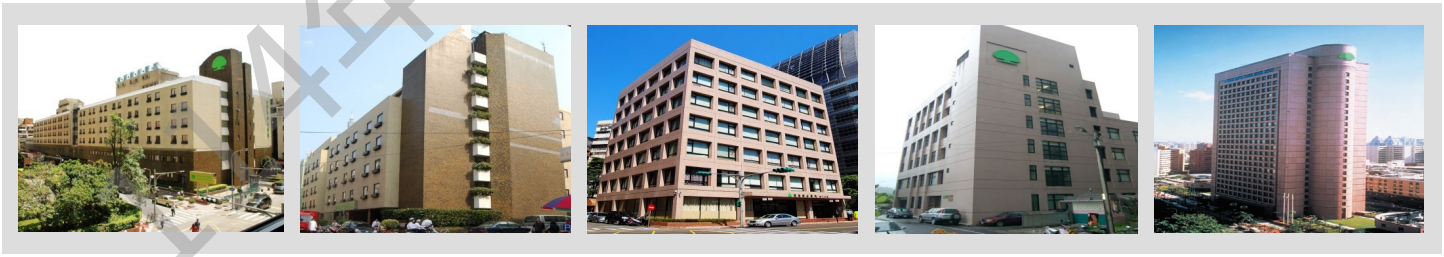
台灣婦產科醫學會 2025年會專題演講
地點：高雄萬豪酒店/ (1F) 103
時間：2025年3月23日(日)，11:30-11:50



國泰綜合醫院　國泰醫療財團法人

Prevalence of Sleep Disturbances

➢ **High Prevalence:** 更年期過渡期與睡眠障礙的頻率增加有關，失眠是女性最常報告的症狀之一。

Affect 40-69% of women undergoing menopause, significantly impacting their daily lives. (Table 1)

TABLE 1. *Prevalence of sleep disturbance associated with the menopause reported in studies*

Study	Country/region	Population	Assessment	N	Prevalence
Kravitz 2003[18]	Seven sites across the US	Women 40-55 yr of age in:	Self-reported sleep difficulties in past 2 wk		
		Early perimenopause		3,521	40%
		Late perimenopause		607	45%
		Natural postmenopause		1,739	43%
		Surgical postmenopause		701	48%
		Postmenopause on hormones		1,610	45%
Blumel 2012[14]	20 healthcare centers across 11 Latin American countries	Hispanic women 40-59 yr of age attending healthcare centers	Sleeping problems[a]	6,079	57%
			Poor sleep quality (PSQI)		46%
			Insomnia (AIS)		44%
Constantine 2016[19]	France, Italy, Spain, Germany, UK	Women ≥45 yr of age reporting menopausal symptoms that had received treatment	Self-reported sleep disturbances	2,610	54-65%
Zhang 2020[20]	China	Women 40-83 yr of age visiting menopause clinics due to symptoms	Self-report of sleep difficulties collected by healthcare providers	4,595	65%
Nappi 2021[4]	Europe (five countries)	Women 40-65 yr of age currently experiencing vasomotor symptoms	Self-reported experience of difficulty sleeping in past week	2,035	69%
	US			676	66%
	Japan			760	60%

AIS, Athens Insomnia Scale; PSQI, Pittsburg Sleep Quality Index; UK, United Kingdom; US, United States.
[a]Insomnia, poor sleep quality or both.

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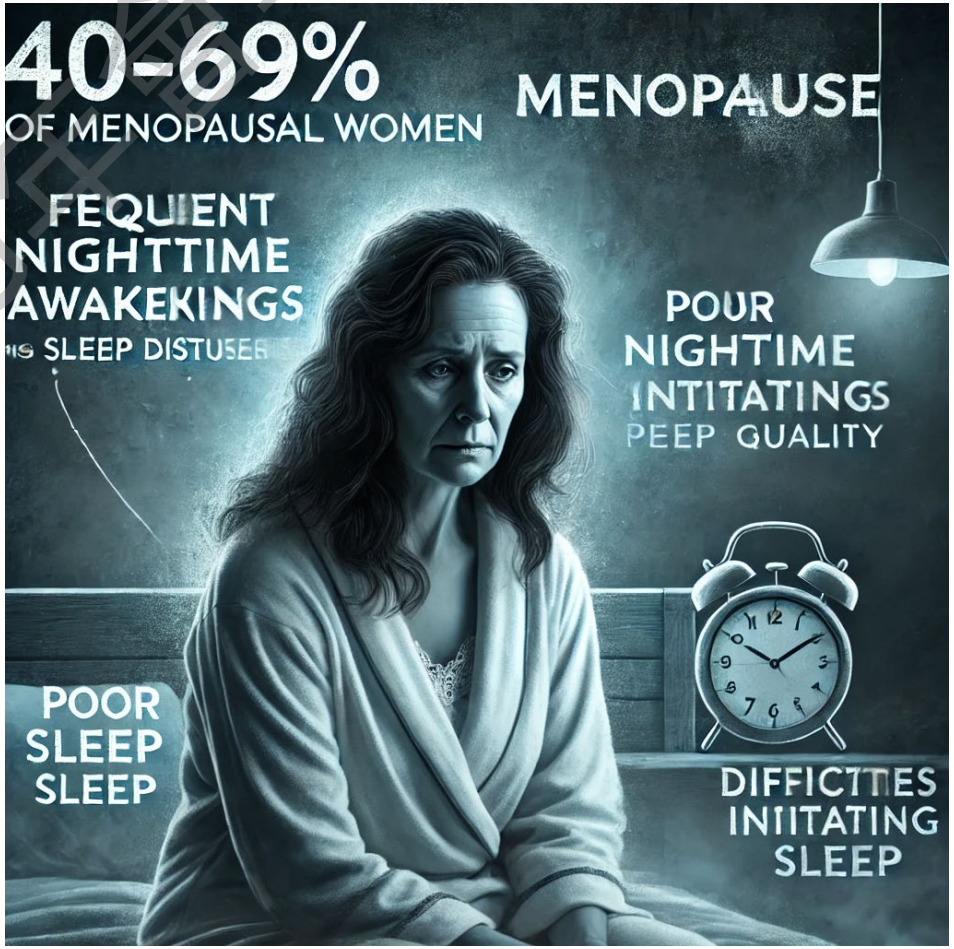
Impact on Health

Negative effects on:

- Physical health
- Mental well-being
- Personal relationships
- Work performance



風險因子：

•**更年期前就有中度到重度睡眠問題的女性**，更容易在更年期遭遇更嚴重的睡眠困擾。

•**手術性更年期**（卵巢切除）會顯著增加睡眠問題與失眠風險，且較自然更年期影響更大。

許多女性將「改善睡眠」列為治療更年期症狀的**首要需求**，甚至超過了治療血管舒縮症狀（如熱潮紅）。

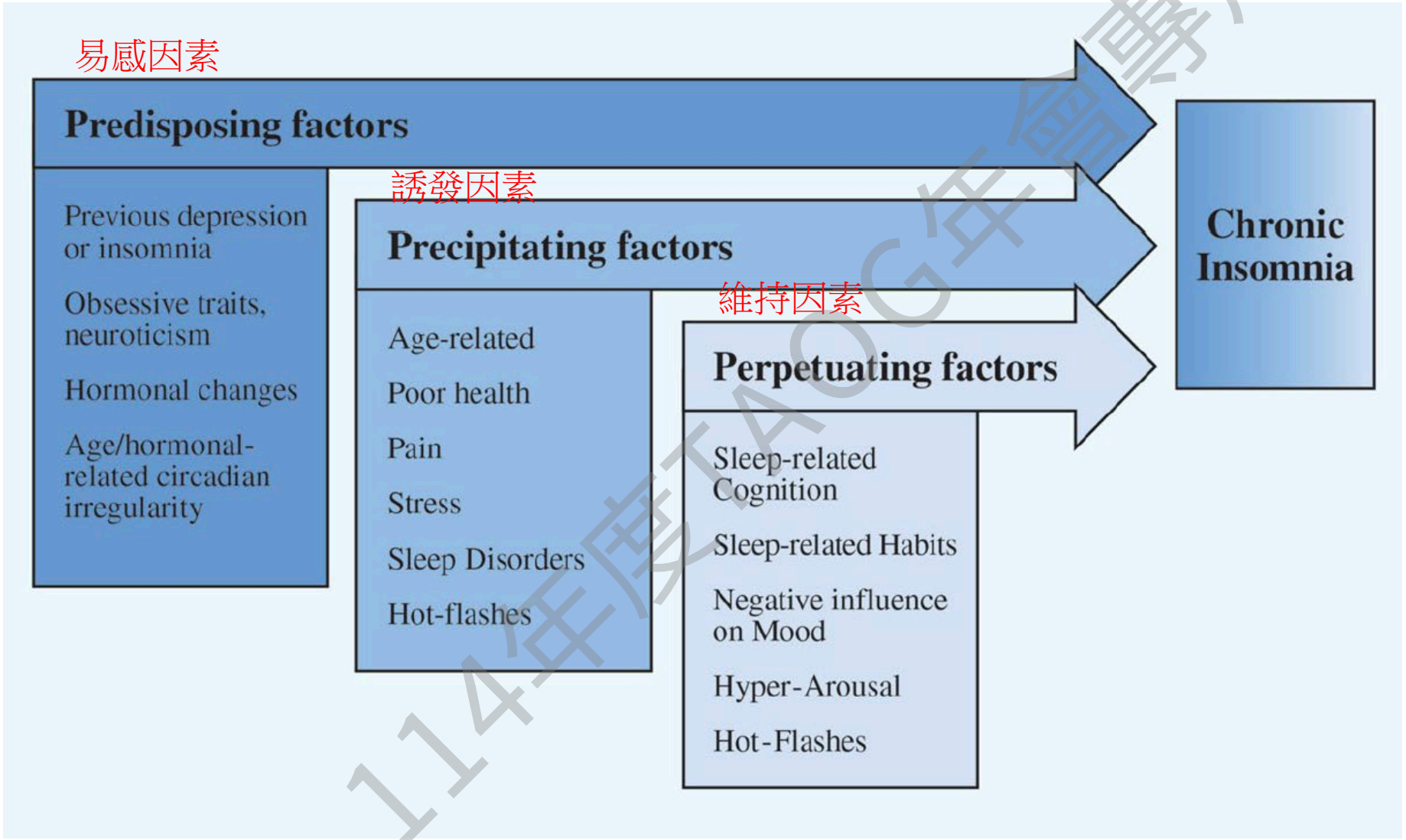
Characteristics of Menopausal Sleep Disturbances

➢ **Symptoms:**

1. Frequent nighttime awakenings
2. Increased wakefulness after sleep onset
3. Poor sleep quality
4. Difficulties in initiating sleep.
5. Often associated with VMS (hot flushes), mood fluctuations, anxiety, and disrupted circadian rhythms.

•熱潮紅與睡眠中斷密切相關，但兩者並非總是同時發生： **94%** 的夜間清醒發生在熱潮紅前後 **2 分鐘內**。
•**6%** 的清醒發生與熱潮紅**完全同步**。
•研究顯示 **80%** 的客觀熱潮紅（非主觀感受）會導致夜間清醒，但仍有 **2/3 的夜間清醒** 未必與熱潮紅直接相關。

Model of insomnia in perimenopause (3-P Model)



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	Sleep disturbance associated with the menopause	Insomnia disorders	Sleep-related breathing disorders	Sleep-related movement disorders
Cause	Hormonal changes, vasomotor symptoms and/or mood and anxiety symptoms that occur during the menopausal transition[15,41-44]	Primary insomnia disorder cannot be attributed to any underlying cause and may occur at any point in a person's life	OSA: muscles in the back of the throat relax during sleep and the airway narrows or closes as a result[40] CSA: occurs when the brain fails to send a signal to the breathing muscles to breathe[40]	Complex sensorimotor disorder, with genetic background, environmental factors and gene-environment interactions thought to play a role[39]
Clinical characteristics	Complaints regarding satisfaction with, duration, maintenance and quality of sleep[21-23] Disrupted sleep with night-time awakenings and increased WASO are most common[3,5,44]	Difficulty initiating sleep, maintaining sleep and/or early morning awakening with inability to return to sleep causing significant distress or impairment in daytime functioning[32] Occurs at least 3 nights/week for at least 3 months[32] Decreased total sleep time and generalized hyperarousal[3,10,32]	Snoring, upper airway obstruction, inspiratory flow limitation and excessive daytime sleepiness[3] Prolonged partial upper airway obstruction[3] Insomnia may be reported as a symptom[3]	Restlessness or urge to move the legs occurring during rest or worsened by rest, usually in the evening or at night, accompanied by or felt to be caused by uncomfortable or unpleasant sensations in the legs[39] Unpleasant sensations partially or totally relieved by movement[39] Disrupted sleep including difficulties initiating sleep and poor sleep efficiency[39]

Distinction from primary insomnia:

- Higher prevalence without prior sleep issues.
- May not meet insomnia diagnostic criteria.

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Other sleep disorders in menopause

Table 1. Prevalence, physiopathology, symptoms, and treatments of other sleep disorders in menopause.

Sleep disorder	*Prevalence (%)*	*Physiopathology*	*Signs/symptoms*	*Treatment*
Obstructive sleep apnea 阻塞性睡眠呼吸中止症	16–20	Loss of protective effects of female hormones (progesterone) Weight gain and changes in fat distribution 女性更年期後 OSA 風險上升，與雌激素下降和體脂分佈變化有關。	Obesity Snoring and witness apneas Dry mouth Choking Nocturia Nocturnal sweating Daytime sleepiness Morning or nocturnal headache	Weight loss CPAP
RLS/PLM 不寧腿症候群（RLS）/ 週期性肢體運動障礙（PLM）	20–24	Aging Unknown role of female hormones (usually, high estrogen levels increase the risk of RLS) 更年期女性罹患 RLS 的風險增加。	An urge to move the legs, usually accompanied by unpleasant sensations in the legs. These symptoms must: • Begin or worsen during periods of rest or inactivity • Be partially or totally relieved by movement • Occur exclusively or predominantly in the evening or night	Dopamine agonists Gabapentin, pregabalin

CPAP, continuous positive air pressure; PLM, periodic leg movements; RLS, restless leg syndrome.

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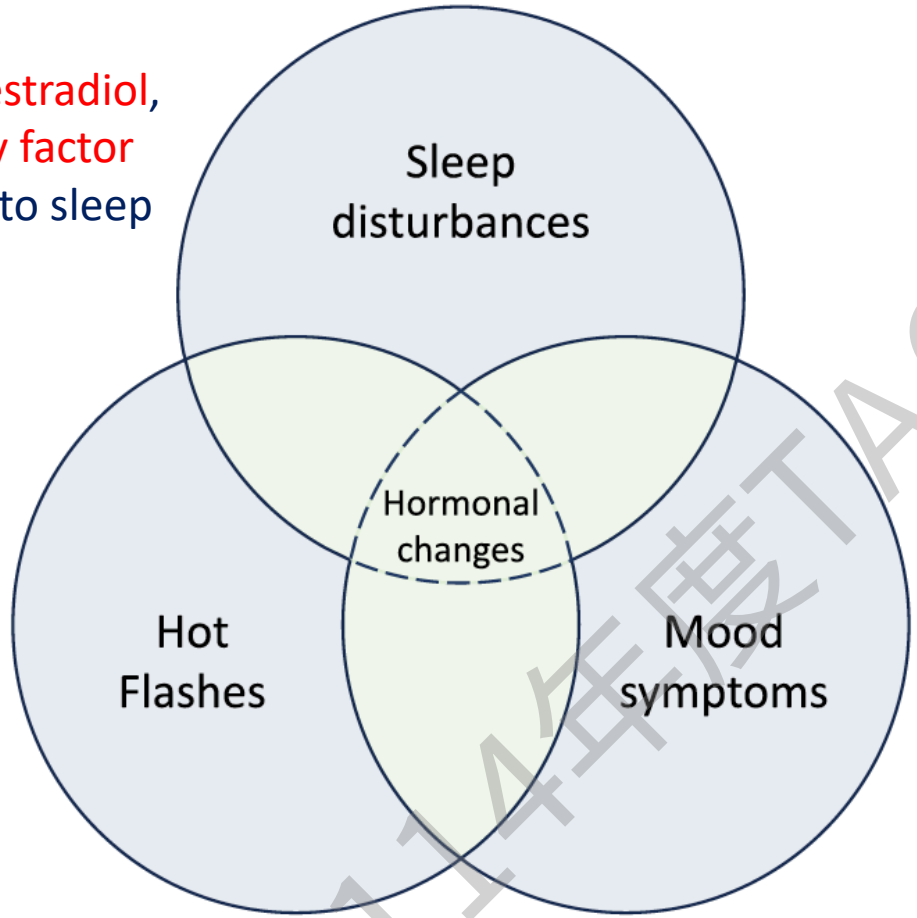
Etiology of Menopausal Sleep Disturbances

SLEEP DISTURBANCE ASSOCIATED WITH MENOPAUSE

•Fluctuations in hormones, particularly estradiol, are a primary factor contributing to sleep issues during menopause.



•Anxiety and depression often accompany menopause and contribute to sleep problems.

焦慮與憂鬱：與睡眠障礙有雙向關聯，部分女性的憂鬱症狀會因失眠而惡化。

Concomitant medical conditions
(e.g. obesity, sleep anpnea)

Psychosocial stressors
(e.g. personal relationships, work performance)

壓力與生活變遷：包括職業變化、家庭責任（如照顧年邁父母）等，會影響睡眠品質。

The interplay between hormonal changes, vasomotor symptoms, and psychological factors involves complex neuronal circuits in the hypothalamus that regulate reproduction, body temperature, sleep, and mood.

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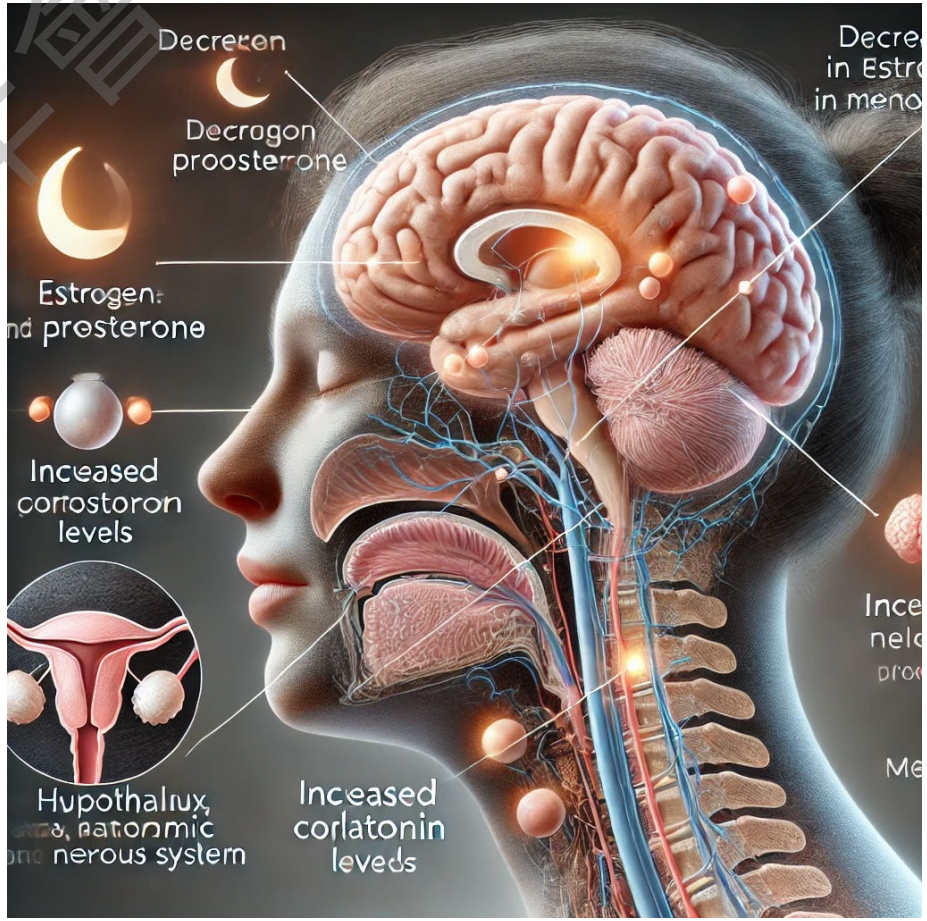
Physiological Mechanisms

- Hypothalamic kisspeptin/neurokinin B/dynorphin (KNDy) neurons play a critical role in regulating reproduction, thermoregulation, and sleep-wake cycles.
- Estrogen decline leads to hyperactivity of KNDy neurons, contributing to impaired thermoregulation and sleep disruption.
- Reduced melatonin secretion and circadian rhythm dysregulation further exacerbate sleep issues.



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Current Treatment Landscape

- Lack of Targeted Treatments:

There are currently no therapies specifically approved for treating menopausal sleep disturbances.

- Existing treatments may not adequately address these unique challenges.

RCT trials on insomnia treatment in menopausal women

Insomnia treatment	Study	Population	Interventions	Sleep outcomes	Results
MHT	Hays *et al.*[68]	16,608 postmenopausal women	0.625 mg CEE + 2.5 mg MPA versus placebo	WHIIRS	CEE + MPA was associated with a statistically significant but small and not clinically meaningful benefit in terms of sleep disturbance. Among women aged 50–54 years with VMS, CEE + MPA improved VMS and resulted in a small benefit in terms of sleep disturbance
	Saletu-Zyhlarz *et al.*[69]	51 postmenopausal women	2 mg EV + 3 mg DNG versus 2 mg EV versus placebo	PSG parameters and PSQI	EV + DNG significantly improved subjective sleep quality and marginally improved variables concerning objective sleep and awakening quality
	Sherman *et al.*[70]	246 postmenopausal women with heart disease	0.625 mg CEE versus CEE + 2.5 mg/day MPA versus placebo	WHIIRS	MHT was not significantly associated with more favorable outcomes for any health-related quality of life
	Heinrich and Wolf[71]	51 hysterectomized women	2 mg EV versus EV + 100 mg MP versus placebo	ADSK Sleep item + Sleep item from Menopausal Index (combined)	EV or EV + MP treatment had no effect on mood, well-being, menopausal symptoms, sleep quality, and depressive symptoms
	Savolainen-Peltonen *et al.*[74]	150 postmenopausal women (half of women with severe VMS, half of symptom free)	Transdermal 1 mg E2 versus oral E2 2 mg with or without 5 mg MPA versus placebo	WHQ sleep item	In women with baseline VMS, MHT significantly improved the scores for sleep
	Cintron *et al.*[75]	727 perimenopausal or postmenopausal women	Oral CEE versus transdermal E2 plus MP (200 mg) versus placebo	PSQI	Sleep quality improved with both MHT formulations
	LeBlanc *et al.*[76]	37 postmenopausal women	2 mg E2	OHSU SL sleep diary	Women receiving E2 had greater improvements in menopausal symptoms and sleep

改善熱潮紅與睡眠品質

更年期荷爾蒙療法（MHT）：
對於伴隨血管運動症狀（如熱潮紅）的失眠有效，但須權衡風險（如血栓）。

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RCT trials on insomnia treatment in menopausal women

Insomnia treatment	*Study*	*Population*	*Interventions*	*Sleep outcomes*	*Results*
Antidepressants	Ensrud *et al.*[88]	205 perimenopausal and postmenopausal women with VMS	Escitalopram (10–20 mg/day) versus placebo	ISI, PSQI	Escitalopram at 10–20 mg/day reduced insomnia symptoms and improved subjective sleep quality at 8 weeks of follow-up
	DeFronzo *et al.*[89]	25 menopausal women	Escitalopram (10–20 mg flexibly dosed) versus placebo	PSQI	Escitalopram induced a decrease in both VMS frequency and severity and an improvement in dysphoria, anxiety, quality of life, and sleep
	Davari-Tanha *et al.*[90]	20 postmenopausal women	Venlafaxine (75 mg/day) versus citalopram (20 mg/day) versus placebo	PSQI	Citalopram and venlafaxine are equally more effective than placebo in reducing sleep disturbance and severity of VMS. Citalopram is more effective in reducing frequency of VMS than venlafaxine. Venlafaxine is more effective than citalopram in treatment of depression
	Suvanto-Luukkonen *et al.*[91]	150 postmenopausal women	Fluoxetine (10–30 mg/day) versus citalopram (10–30 mg/day) versus placebo	Patient reports	Insomnia improved significantly only in the citalopram group; VMS did not improve in any of the three groups

改善憂鬱與熱潮紅，間接改善睡眠

抗憂鬱藥（SSRIs 如 Escitalopram, Venlafaxine）：對失眠與更年期憂鬱皆有幫助。

褪黑激素（Melatonin）：特別適用於 55 歲以上女性，改善睡眠品質且副作用少。

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RCT trials on insomnia treatment in menopausal women

Insomnia treatment	Study	Population	Interventions	Sleep outcomes	Results
BDZ and Z-drugs	Dorsey *et al.*[110]	141 perimenopausal or postmenopausal women	Zolpidem (10 mg/day) versus placebo	Diary-based sleep parameters and GSDS	Zolpidem induced an increase in TST, a decrease in WASO and number of awakenings, and an improvement in sleep-related difficulty with daytime functioning
	Soares *et al.*[111]	410 perimenopausal or early postmenopausal women	Eszopiclone (3 mg/day) versus placebo	Physician global assessments of menopause, GCS, MADRS, and SDS	Eszopiclone provided significant improvements in sleep and positively impacted mood, quality of life, and menopause-related symptoms
	Joffe *et al.*[112]	46 perimenopausal and postmenopausal women	Eszopiclone (3 mg/day) versus placebo	ISI and diary-based sleep parameters	Eszopiclone reduced ISI scores and improved all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and night-time but not daytime VMS
Gabapentin	Yurcheshen *et al.*[119]	59 perimenopausal women with VMS	Gabapentin (300 mg three times daily) versus placebo	PSQI	Gabapentin induced an improvement in the sleep quality factor score, in the sleep efficiency factor score, and in the global PSQI score

苯二氮平類（Benzodiazepine）與 Z-drugs（Zolpidem, Eszopiclone）：短期有效，但需小心依賴性與跌倒風險。

加巴噴丁（Gabapentin）：可減少熱潮紅，並改善睡眠結構。

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Advances in Pharmacological Treatment

- **Hormone Therapy (HT):** Effective for women with vasomotor symptoms but requires **high doses** and is not suitable for all due to contraindications and safety concerns.
- **Emerging Treatments: Elinzanetant** (a **dual NK-1/NK-3 receptor antagonist**) has shown promising efficacy in clinical trials for managing hot flushes and sleep disturbances, representing a potential breakthrough therapy.

神經激肽 B 受體拮抗劑（Neurokinin B antagonists，如 Fezolinetant） 抑制熱潮紅，改善夜間清醒

Non-Pharmacological Treatment Options

- **Cognitive Behavioral Therapy for Insomnia (CBT-i)**: The most evidence-based treatment for insomnia but is limited by accessibility and patient adherence.
- **Digital CBT-i**: A scalable and effective alternative for those unable to access in-person therapy.
- **Natural Remedies**: Melatonin, probiotics, and soy isoflavones are widely used but require further research to confirm their efficacy.

RCT trials on insomnia treatment in menopausal women

Insomnia treatment	*Study*	*Population*	*Interventions*	*Sleep outcomes*	*Results*
CBT-I	McCurry *et al.*[64]	106 perimenopausal or postmenopausal women	CBT-I, telephone-delivered menopause education	ISI, PSQI	CBT-I improves self-reported insomnia symptoms and VMS
	Guthrie *et al.*[65]	546 perimenopausal and postmenopausal women	CBT-I, escitalopram, yoga, aerobic exercise, omega-3 fatty acids, oral E2, venlafaxine	ISI, PSQI	CBT-I produced the greatest reduction in ISI. Effects on ISI were similar for exercise and venlafaxine; small decreases in ISI were observed with escitalopram, yoga, and E2. The largest reduction in PSQI was with CBT-I. PSQI decreases were significantly better than control with escitalopram, exercise, yoga, estradiol, and venlafaxine. Omega-3 supplements did not improve insomnia symptoms
	Drake *et al.*[66]	150 postmenopausal women	CBT-I, sleep hygiene education, sleep restriction therapy	ISI, sleep diaries	CBT-I and sleep restriction resulted in more effective insomnia treatment. CBT-I was superior to sleep restriction in improving sleep maintenance

改善睡眠習慣與認知失調

認知行為治療（CBT-I）：被認為是最有效的非藥物治療方式，能顯著改善睡眠質量。

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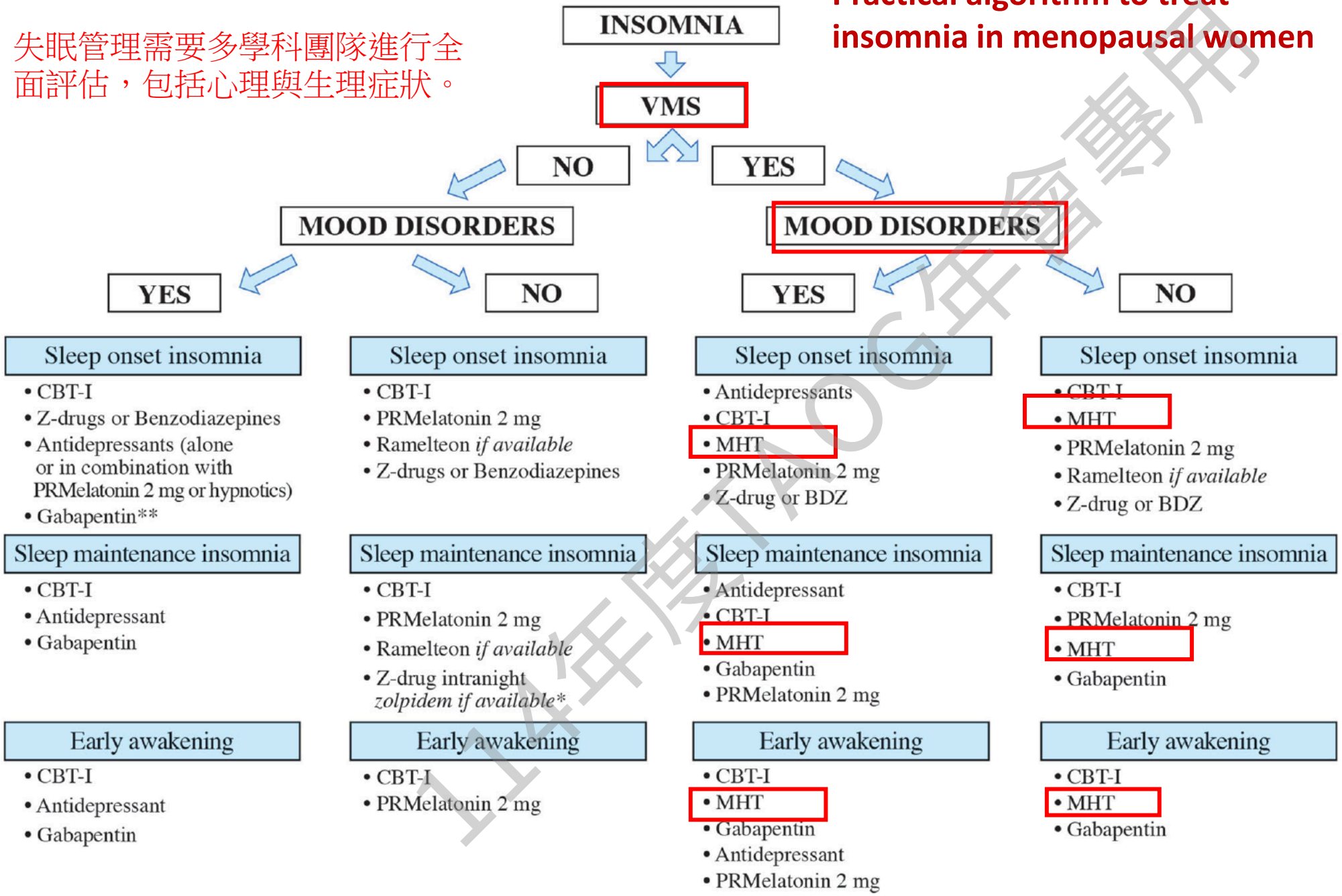
失眠管理需要多學科團隊進行全面評估，包括心理與生理症狀。

Practical algorithm to treat insomnia in menopausal women



第一線治療：認知行為治療（**CBT-I**）與褪黑激素（**2mg PRM**）。

•若仍無效：若有血管運動症狀（VMS），可考慮**更年期荷爾蒙療法（MHT）**。
•若伴隨焦慮或憂鬱，可考慮**抗憂鬱藥物**。
•若短期需要藥物，可使用**Z-drugs**或加巴噴丁。

- 若仍未改善，可轉診至睡眠專家進一步評估。

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總結

- 更年期睡眠障礙的發生率高，並受到多種生物、心理與社會因素影響。
- 更年期失眠的成因複雜，涉及賀爾蒙變化、熱潮紅、情緒障礙、晝夜節律改變等多因素。
- 失眠、OSA、RLS 是更年期女性最常見的睡眠障礙，應根據個別需求選擇適合的治療方式。
- 治療策略應個人化：
  - 第一線治療建議為非藥物介入（如 CBT-I）。
  - 若有熱潮紅，可考慮荷爾蒙療法(MHT)或新型藥物（如 Elinzanetant ）。
  - 藥物治療應短期使用，避免依賴性問題。
- 更年期女性應接受多學科評估，包括睡眠障礙、情緒健康、荷爾蒙變化，以制定最合適的個人化治療方案。
- 未來研究應聚焦於新型治療的長期安全性與有效性，特別是在熱潮紅相關的睡眠障礙領域。
- 開發基於了解神經元機制的專一治療。