Better sleep without the trade off: Safer hypnotic use in the frail elderly

A focus on DORA for dementia

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Outline

- Introduction
  - Relationship Insomnia & dementia
  - Importance of sleep in dementia patients
- Use of Lemborexant
- Concerns for insomnia treatment in dementia patients
- Summary
- Q&A

Ms. T, 84 y/o

- Major NCD, moderate-to-severe (GDS ~6), on palliative care.
- Prolonged-release melatonin was initiated for 1 month.
- Mostly sleeping, but not well. The caregiver aims to improve sleep quality.
- Dayvigo was added for 2.5 mg. Then the results were impressive.

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ORIGINAL RESEARCH ARTICLE

Efficacy and safety of insomnia treatment with lemborexant in older adults: analyses from three clinical trials

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3 RCT's, 453/1006 aged ≥ 65 y/o

Lemborexant (5 mg & 10 mg) significantly improved both sleep onset and maintenance, with better results compared to placebo and zolpidem.

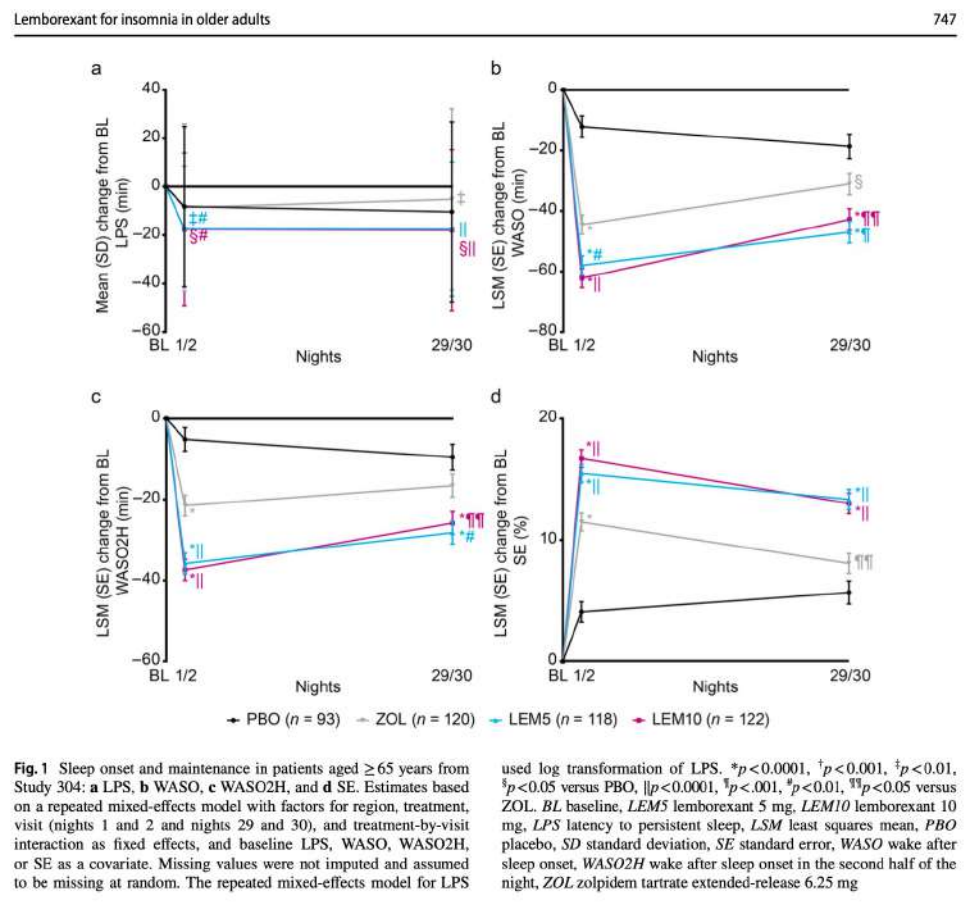


Fig. 1 Sleep onset and maintenance in patients aged ≥65 years from Study 304: **a** LPS, **b** WASO, **c** WASO2H, and **d** SE. Estimates based on a repeated mixed-effects model with factors for region, treatment, visit (nights 1 and 2 and nights 29 and 30), and treatment-by-visit interaction as fixed effects, and baseline LPS, WASO, WASO2H, or SE as a covariate. Missing values were not imputed and assumed to be missing at random. The repeated mixed-effects model for LPS used log transformation of LPS. *$p<0.0001$, †$p<0.001$, ‡$p<0.01$, §$p<0.05$ versus PBO, ‖$p<0.0001$, ¶$p<.001$, #$p<0.01$, ¶¶$p<0.05$ versus ZOL. *BL* baseline, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LPS* latency to persistent sleep, *LSM* least squares mean, *PBO* placebo, *SD* standard deviation, *SE* standard error, *WASO* wake after sleep onset, *WASO2H* wake after sleep onset in the second half of the night, *ZOL* zolpidem tartrate extended-release 6.25 mg

Figure 1A: Lemborexant significantly reduces the time taken to fall asleep compared to placebo and zolpidem.

Figure 1B Lemborexant reduces wakefulness during the night more effectively than placebo and zolpidem.

Figure 1C Lemborexant improves sleep maintenance during the second half of the sleep.

Figure 1D Lemborexant shows significantly higher sleep efficacy than other groups.

Gotfried et al. Drugs & Aging. 2024.

Relationship between sleep disturbance and Alzheimer's dementia

- Decreased memory consolidation
- β-amyloid deposition
- Orexin system change
- Glymphatic clearance

Naithsmith S. AAIC. 2025.

Orexin antagonists in AD patients

- Two studies
- N=323, mild-to-moderate AD
- Either insomnia or irregular sleep-wake disorder
- Results:
  - some beneficial effects
  - increase in nocturnal sleep time
  - reduction in the time awake after sleep onset
  - increase in sleep efficiency
  - reduced sleep latency

McCleery J et al. Cochrane Database Syst Rev. 2020.

Orexin antagonists in AD patients (cont’d)

- Results: (cont’d)
  - Little or no effect on the mean duration of a sleep bout and probably have no effect on carers' perception of participants' sleep quality. We found no evidence that the effects come at the expense of an excess of adverse events or impaired cognitive function.

    McCleery J et al. Cochrane Database Syst Rev. 2020.

Lemborexant in Patients With Irregular Sleep-Wake Rhythm Disorder and AD (RCT)

- Irregular sleep-wake rhythm disorder (ISWRD) is a common sleep disorder in AD patients.
- US, Japan and UK
- Age 60 to 90 years old
- MMSE 10-26
- Circadian rhythm parameters, nighttime sleep, daytime wakefulness.
- Mild to moderate AD.

Moline et al. J Prev Alzheimers Dis. 2021.

- Placebo vs. Lemborexant 2.5 mg, 5 mg, 10 mg or 15 mg)
- Sixty-two participants
  - placebo, n = 12; lemborexant 2.5 mg [LEM2.5], n = 12; lemborexant 5 mg [LEM5], n = 13, lemborexant 10 mg [LEM10], n = 13 and lemborexant 15 mg [LEM15], n = 12).
- 4 weeks.
- Measurements:
  - Actigraph: least active 5 hours (L5), rest-activity rhythm (RA) and mean duration of sleep bouts (MDSB) during the daytime.
  - MMSE, ADAS-Cog

Moline et al. J Prev Alzheimers Dis. 2021.

- Results:
  - Reduction in restlessness): decreased from baseline to week 4 for LEM2.5, LEM5 and LEM15 was significantly greater than with placebo (all $p < 0.05$)
  - Rest-activity rhythm): changed from baseline to week 4 for LEM5 and LEM15 that was significantly greater than with placebo (all $p < 0.05$)
  - Mean duration of sleep for LEM5 and LEM15 ($p < 0.01$ and $p = 0.002$, respectively).
  - No serious adverse events or worsening of cognitive function
  - No subjects discontinued treatment.

Moline et al. J Prev Alzheimers Dis. 2021.

DORA For Sleep Disturbance in AD Patients

- Suvorexant and Lemborexant
- Results:
  - Suvorexant may improve total sleep time (TST), wakefulness after sleep onset (WASO), and sleep efficiency (SE) in AD patients with insomnia.
  - Lemborexant improved circadian rhythm parameters, particularly in patients with irregular sleep-wake rhythm disorder (ISWRD).
  - Safety profiles of DORA medications appeared favorable, with mild to moderate adverse events reported.
  - Potential adverse events: falls

Alshiban et al. Am J Geriatr Psychiatry. 2025.

Importance of healthy sleep in older people

- Healthy sleep is associated with
  - Positive emotions: BPSD
  - Cognitive function: ⬇ Maintaining function
- Sleep deprivation links to negative emotions.
- Healthy sleep is associated with QoL, prolongs independence, and avoids frailty in older people.

Tomaso et al. Sleep. 2021.; de Melo Chagas et al. Sleep Sci. 2023.

Growth hormone and aging

- Growth hormone releases at night.
- Growth hormone declines with age.
  - Peak during puberty
  - Decline by 15% every decade
- Due to lack of day-night GH rhythm resulting from loss of nocturnal sleep-related GH pulses
- Growth hormone is demonstrated to be beneficial in the treatment of mild cognitive impairment.

Available drugs for insomnia treatment in older people

GABA agonist: Zolpidem

Serotonin

- Trazodone

Prolonged-release melatonin

Orexin antagonist

Benzodiazepines

- Lorazepam, temazepam, oxazepam

Choosing sleep pills based on drug safety and side effects

- Benzodiazepines
- Zolpidem
- Trazodone
- Lemborexant
- Long-acting melatonin

Addiction Potential

Drug interaction

Drugs	CYP enzymes involved	CYP inhibitors interaction	CYP inducers Interaction
Benzodiazepines			
- Diazepam	CYP2C19, CYP3A4	Increased sedation (e.g., ketoconazole, erythromycin)	Reduced efficacy (e.g., rifampin, carbamazepine)
- Lorazepam	Minimal CYP involvement (glucuronidation)	Minimal impact from CYP inhibitors	Minimal impact from CYP inducers
- Alprazolam	CYP3A4	Increased sedation (e.g., ketoconazole, erythromycin)	Reduced efficacy (e.g., rifampin, carbamazepine)
Long-acting melatonin	CYP1A2, CYP2C19	Increased effects (e.g., fluvoxamine)	Reduced efficacy (e.g., smoking, carbamazepine)
Lemborexant	CYP3A4, CYP2C19	Increased sedation (e.g., ketoconazole)	Reduced efficacy (e.g., rifampin)
Trazodone	CYP3A4	Increased side effects (e.g., ritonavir, ketoconazole)	Reduced efficacy (e.g., phenytoin)
Zolpidem	CYP3A4, CYP1A2, CYP2D6	Increased sedation (e.g., clarithromycin, itraconazole)	Reduced efficacy (e.g., rifampin)

Aspects	Z-Drugs	Lemborexant
Mechanism of action	GABA-Alpha 1 sub-unit (similar to benzodiazepines).	Dual orexin receptor antagonist (OX1R, OX2R).
Primary use	Short-term treatment of insomnia.	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.
Onset of action	Rapid onset, typically within 30 minutes.	Rapid onset, usually within 30 minutes.
Duration of action	Generally short to intermediate (e.g., 6-8 hours).	Moderate duration (8 hours).
Dependence and tolerance	Potential (actually low)	Least risk
Cognitive impairment	Higher risk with long-term use.	Lower risk
Daytime Sedation	May	Less
Drug Interactions	Potential	Fewer, with CYP3A4 inhibitors
Common side effects	dizziness, headache, and gastrointestinal issues	Headache, somnolence, and potential for complex sleep behaviors
Withdrawal symptoms	May if long-term use or abruptly stopped.	Less likely
Elderly considerations	Higher risk of falls, cognitive decline, and adverse effects in older adults.	Considered safer for older adults but still requires careful monitoring.
Cost	5-10 Baht/day, non-ED	3X-4X Baht/day, non-ED

Concerns for insomnia treatment in dementia patients

Safety Profile

- Lemborexant was well-tolerated with no significant residual next-day effects, such as postural instability or impaired memory.
- Lemborexan did not impair the ability to awaken in response to auditory stimuli.

Gotfried et al. Drugs & Aging. 2024.

Cognition

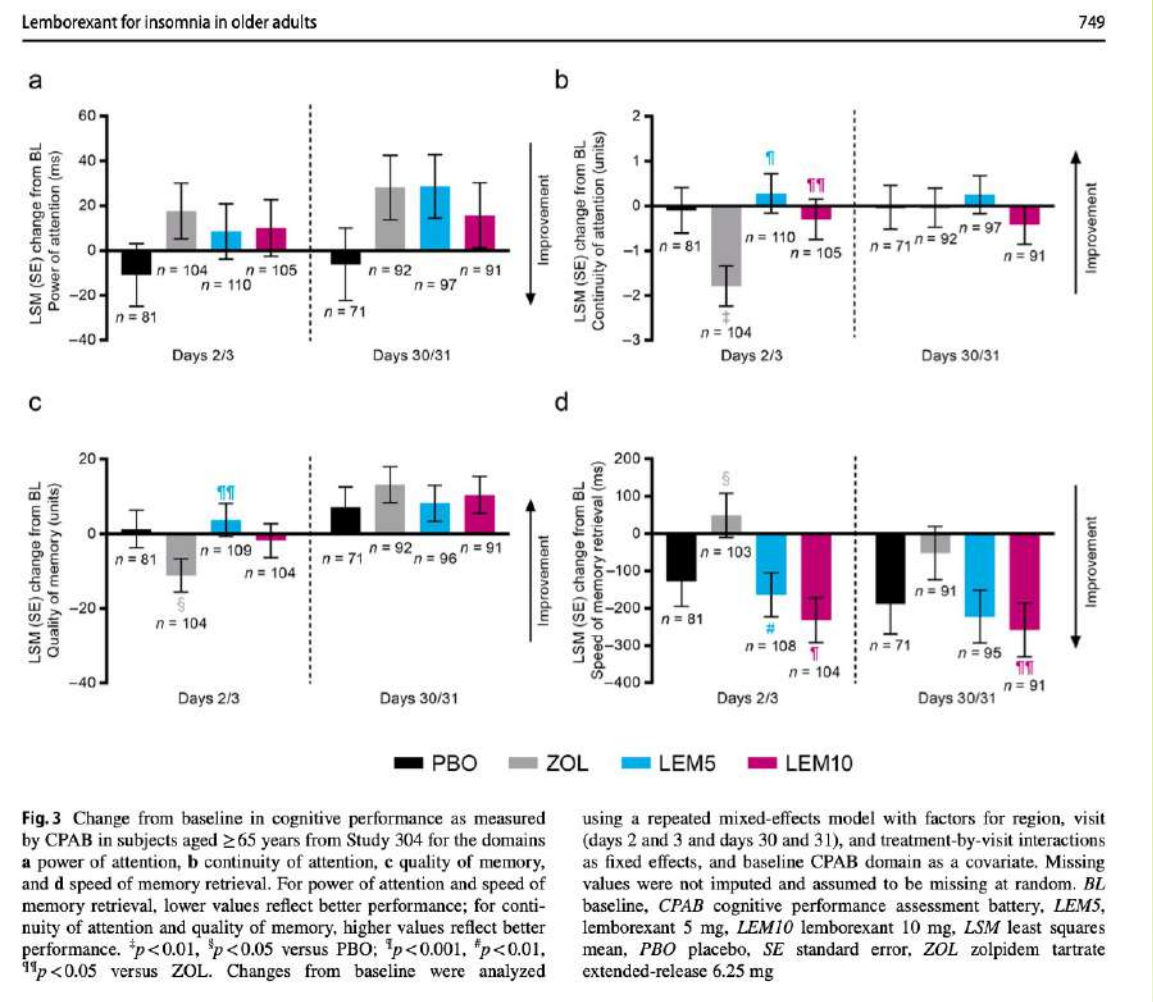


Fig. 3 Change from baseline in cognitive performance as measured by CPAB in subjects aged ≥65 years from Study 304 for the domains **a** power of attention, **b** continuity of attention, **c** quality of memory, and **d** speed of memory retrieval. For power of attention and speed of memory retrieval, lower values reflect better performance; for continuity of attention and quality of memory, higher values reflect better performance. ‡$p<0.01$, §$p<0.05$ versus PBO; ¶$p<0.001$, #$p<0.01$, ¶¶$p<0.05$ versus ZOL. Changes from baseline were analyzed using a repeated mixed-effects model with factors for region, visit (days 2 and 3 and days 30 and 31), and treatment-by-visit interactions as fixed effects, and baseline CPAB domain as a covariate. Missing values were not imputed and assumed to be missing at random. *BL* baseline, *CPAB* cognitive performance assessment battery, *LEM5*, lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LSM* least squares mean, *PBO* placebo, *SE* standard error, *ZOL* zolpidem tartrate extended-release 6.25 mg

- Figure 3: Lemborexant showed **no significant impairment** in the domains of **memory, attention, or speed of memory retrieval** compared **to placebo**. In contrast, zolpidem demonstrated impairments in these domains

Gotfried et al. Drugs & Aging. 2024.

Postural stability

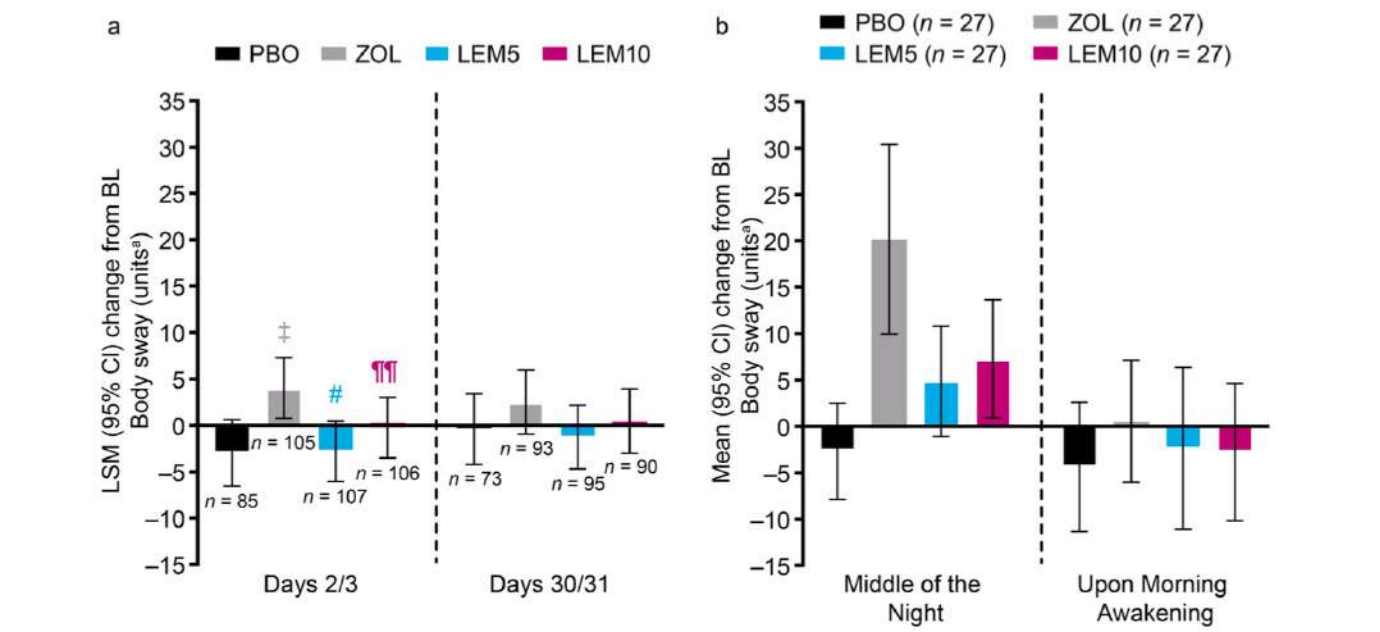


Fig. 2 Postural stability, as measured by body sway, in subjects aged ≥65 years: **a** Study 304 at days 2 and 3 and days 30 and 31 of treatment and **b** Study 108 4 h and 8 h post dose. For Study 304, changes from baseline were assessed using a repeated mixed-effects model analysis with factors for region, visit (time point), and treatment-by-visit interaction as fixed effects, and baseline body sway as a covariate. For Study 108, mean change from baseline and associated 95% CIs were calculated for body sway and CPAB domains for 4 h post dose (middle of the night) and 8 h post dose (morning). [a]A unit of body sway is defined as 1/3° angle of arc movement of the ataxiameter. A higher value represents more body sway and less postural stability. [‡]$p<0.01$ versus PBO; [#]$p<0.01$, [¶¶]$p<0.05$ versus ZOL. *BL* baseline, *CI* confidence interval, *CPAB* cognitive performance assessment battery, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LSM* least squares mean, *PBO* placebo, *ZOL* zolpidem tartrate extended-release 6.25 mg

Figure 2A: Lemborexant **did not** significantly increase body sway in the morning compared to placebo.
In contrast, zolpidem caused a noticeable increase in body sway.

Gotfried et al. Drugs & Aging. 2024.

Miscellaneous

Medication	Initial Insomnia (Sleep Onset)	Middle Insomnia (Night Awakenings)	Terminal Insomnia (Early Waking)	Suitability/Safety in Dementia	Notes
Lorazepam	★☆☆☆ (Not recommended)	★☆☆☆ (Not recommended)	★☆☆☆ (Not recommended)	❌ High risk (falls, delirium)	Avoid in dementia due to high risks of confusion, sedation, addiction, and falls.
Zolpidem	★★★☆ (Better tolerated) *	★★☆☆ (Limited)	★☆☆☆ (Limited)	⚠️ Caution: safer than lorazepam but still not first-line	Shorter half-life than lorazepam, less addictive, but watch for abnormal sleep behaviors and confusion in the elderly.
Trazodone	★★★☆ (Moderately effective)	★★★☆ (Effective)	★★★☆ (Effective)	✔ Generally safer in dementia	Can help with sleep and agitation, but may also increase the risk of daytime sedation and orthostatic hypotension.
Lemborexant (Dayvigo)	★★★☆ (Effective)	★★★★ (Very effective)	★★★☆ (Effective)	✔ Well tolerated; some dementia data	Especially useful for sleep maintenance; monitor for falls and excessive sedation.
Melatonin (Circadin)	★★☆☆ (Mild-moderate effect)	★☆☆☆ (Limited/variable effect)	★★★☆ (Effective)	✔ Safest in dementia	Effective for circadian rhythm disorders; less reliable for maintaining sleep.

**Zolpidem is generally safer and less addictive than lorazepam. However, it should still be used with caution in dementia or the elderly due to some risk of delirium, falls, or sleepwalking behaviors.*

Summary

- Identify and correct any treatable underlying causes of insomnia is a priority.
- Selection of hypnotics should prioritize proven efficacy, not just sedative properties.
- Lemborexant has minimal to no risk of addiction.
- Treatment decisions should also incorporate patient preferences and affordability considerations.
- Insomnia should be actively addressed in patients with neurocognitive disorders (dementia).

Why “Dayvigo”?

“**Day**” suggests daytime functioning—important because insomnia treatments aim to improve sleep without impairing next-day alertness.

“**Vi**” could evoke vitality or vigilance, hinting at restored energy or cognitive clarity.

“**Go**” might imply a smooth transition into sleep or readiness for the day after restful sleep.

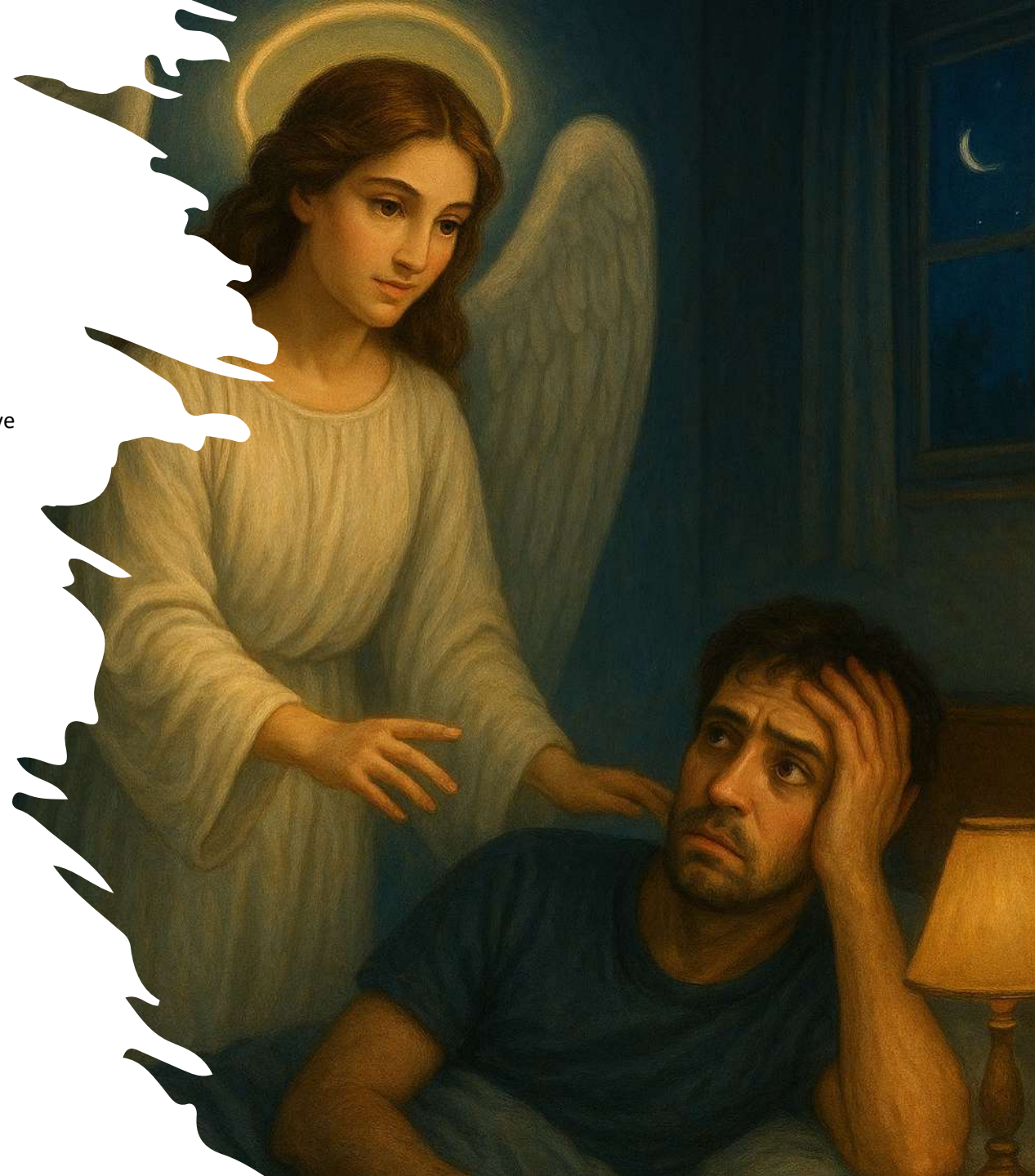
So, Dayvigo might symbolically mean: ***Sleep well, wake refreshed, and go about your day.***

In Thailand

- When insomnia strikes… Devi go!
  เมื่ออาการนอนไม่หลับมาเยือน… เทวีไป (หาคุณ)!

  or

- *When sleep flees… Devi, go forth!*
  เมื่อยามนิทราหลบหนี… เทวีจงไป



Thank you

Q&A