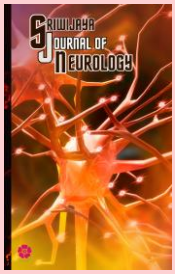

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Terminal Insomnia as a Phenotypic Biomarker of Geriatric Depression in a Balinese Cohort: A Cross-Sectional Analysis of Circadian Disruption and Sleep Continuity

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A B S T R A C T

Introduction: Sleep architecture undergoes significant fragmentation during aging, yet the specific phenotypic expression of insomnia in the context of geriatric depression remains under-characterized. While the bidirectional relationship between depression and sleep is established, few studies distinguish between initial, middle, and terminal insomnia subtypes in Southeast Asian geriatric populations. This study aims to characterize the predominant insomnia phenotypes among elderly patients with depression and investigate the association between sociodemographic determinants, chronic morbidity, and specific sleep continuity disturbances. **Methods:** A cross-sectional analytical study was conducted at the Geriatric Outpatient Clinic of Karangasem Regional General Hospital, Bali, Indonesia (N=58). Psychometric evaluation utilized the Geriatric Depression Scale (GDS-15) to screen for depressive symptoms and the Pittsburgh Sleep Quality Index (PSQI) to assess global sleep quality. Insomnia phenotypes were clinically adjudicated based on diagnostic interviews. To account for potential confounders, body mass index (BMI) and chronic pain scores were included in the analysis. Data were analyzed using Firth's Penalized Likelihood Logistic Regression to stabilize estimates given the sample size. **Results:** The prevalence of depression in the cohort was 58.3%. Among depressed elderly patients, terminal (Late) Insomnia was the predominant phenotype, affecting 76.0% of the subgroup, followed by middle insomnia (66.7%) and initial insomnia (36.4%). Multivariate analysis adjusted for age, chronic disease status, BMI, and pain demonstrated that Terminal Insomnia was the strongest independent predictor of depression (Adjusted OR 6.42; 95% CI 2.15–14.8; $p<0.001$). **Conclusion:** Terminal insomnia represents a distinct and dominant clinical phenotype of depression in this geriatric cohort, potentially reflecting underlying circadian phase advances and HPA-axis hyperactivity characteristic of melancholic depression. Clinicians should prioritize sleep maintenance strategies over sleep induction pharmacotherapy in this population.

1. Introduction

The twenty-first century is witnessing a profound and unprecedented demographic transition, often described as the silver tsunami, characterized by a rapid expansion of the geriatric population globally.[1] As life expectancy increases, healthcare systems face a rising tide of age-related comorbidities that extend beyond cardiovascular and metabolic dysfunction to encompass complex neuropsychiatric syndromes. Among these, geriatric depression and sleep-wake cycle disturbances stand as twin pillars of disability, frequently co-occurring to accelerate functional decline and compromise the quality of life in late adulthood.[2]

Depression in the elderly is distinct from its presentation in younger cohorts. It is not merely a psychological state of sadness or existential malaise; rather, it is a pervasive neurobiological syndrome

associated with systemic inflammation, accelerated cognitive decline, and significantly increased mortality rates.[3] It is frequently masked by somatic complaints, leading to underdiagnosis and undertreatment. Concurrently, sleep architecture undergoes natural fragmentation during the aging process. The prevalence of insomnia in the general elderly population ranges from 30% to 48%, a figure that surges alarmingly in the presence of psychiatric comorbidities. In the context of geriatric depression, sleep disturbance is almost ubiquitous, reported by over 90% of patients.[4] While the relationship between insomnia and depression is widely recognized as bidirectional—where sleep loss exacerbates mood dysregulation and mood disorders disrupt sleep continuity—clinical practice and research often suffer from a reductionist approach. The current literature frequently treats insomnia as a monolithic entity, defined simply by poor sleep quality or elevated global scores on screening instruments such as the Pittsburgh Sleep Quality Index (PSQI). This aggregation of data obscures the rich phenotypic heterogeneity of sleep disturbances, potentially hindering the identification of specific biological mechanisms and targeted therapeutic interventions.

Insomnia is not a uniform disorder but a collection of distinct phenotypes, each likely driven by divergent pathophysiological pathways.[5] Clinically, it manifests as difficulty initiating sleep (initial insomnia), difficulty maintaining sleep (middle insomnia), or early morning awakening with an inability to return to sleep (terminal or late insomnia). In the domain of geriatric psychiatry and neurology, differentiating these phenotypes is paramount. Initial insomnia is frequently associated with anxiety, hyperarousal, and psychophysiological conditioning—a state where the mind races at bedtime. Conversely, terminal insomnia represents a fundamental failure of sleep maintenance in the final phase of the night.

This specific phenotype, characterized by waking hours before the desired time, has classically been recognized as a hallmark of melancholic depression.[6] Unlike the anxiety-driven inability to fall asleep, Terminal Insomnia suggests a dysregulation of the internal biological clock. It is hypothesized to be driven by a pathological acceleration of the age-related circadian phase advance. In healthy aging, the suprachiasmatic nucleus (SCN) of the hypothalamus—the master circadian pacemaker—undergoes mild degeneration, leading to reduced melatonin secretion and a natural shift toward earlier waking. However, in geriatric depression, this process appears to be hijacked by neuroendocrine dysfunction.

The prominence of terminal insomnia in depression points toward specific involvement of the hypothalamic-pituitary-adrenal (HPA) axis. In a homeostatic state, cortisol levels follow a precise diurnal rhythm, reaching a nadir during the early phases of sleep and rising gradually to peak shortly after waking—a phenomenon known as the cortisol awakening response (CAR). This surge prepares the organism for metabolic activity. In depressed elderly patients, the negative feedback loops of the HPA axis are often impaired, leading to glucocorticoid resistance and sustained hypercortisolemia.[7]

Consequently, the physiological surge of cortisol and corticotropin-releasing hormone (CRH) may occur prematurely, effectively acting as a chemical alarm clock. This inappropriate hormonal spike forces the individual into a state of physiological arousal at 3:00 or 4:00 AM. Unlike a patient who wakes up to urinate and falls back asleep, the depressed patient wakes with a clear sensorium, often accompanied by immediate rumination or a sense of doom, and is physiologically unable to re-initiate sleep. This creates a vicious cycle where sleep fragmentation further dysregulates the HPA axis, deepening the depressive state and impairing daytime cognitive function. Thus, Terminal Insomnia is not merely a symptom; it may be a visible clinical marker of the underlying neuroendocrine severity of the depressive syndrome.

While the neurobiological link between depression and early awakening is compelling, the diagnostic landscape in geriatrics is complicated by a high burden of somatic comorbidities.[8] The elderly population is prone to a multitude of physical conditions that mimic the sleep fragmentation of depression. Two of the most significant confounders are obstructive sleep apnea (OSA) and chronic pain

syndromes. OSA, driven by age-related loss of pharyngeal muscle tone and often exacerbated by increased body mass index (BMI), causes repeated hypoxic arousals throughout the night. A patient with untreated OSA may report waking up frequently or waking up early, not due to cortisol dysregulation, but due to air hunger and sympathetic surges caused by apnea. Similarly, conditions such as osteoarthritis or neuropathic pain can cause awakenings when analgesic medications wear off during the night. Differentiating between a hypoxic awakening or a pain-induced awakening and a true psychogenic terminal insomnia is a critical clinical challenge. Failing to distinguish these etiologies leads to misdiagnosis and mismanagement. Treating an apnea patient with sedating antidepressants could dangerously suppress respiratory drive, while treating a depressed patient with simple analgesics will fail to address the core mood disorder. Therefore, any rigorous investigation into the sleep phenotypes of geriatric depression must attempt to control for these somatic confounders, utilizing markers such as BMI and pain scores to isolate the independent contribution of the depressive phenotype.[9]

Despite the established theoretical framework linking sleep architecture to mood disorders, there is a notable paucity of research specifically profiling these insomnia subtypes within depressed elderly populations in Southeast Asia. Most existing data are derived from Western cohorts, where social norms regarding sleep schedules and desired wake times differ significantly from those in the Global South. This study focuses on a unique sociocultural setting in Bali, Indonesia. The Balinese context presents distinct challenges and opportunities for psychogeriatric research. Culturally, early rising is often normalized or even valued for religious and household activities, such as the Brahma Muhurta period before sunrise. This cultural scaffolding can complicate the clinical definition of early morning awakening. It raises the question: when does early rising transition from a cultural habit to a pathological symptom? Furthermore, the clinical reality in resource-limited settings in Indonesia often involves high patient volumes and limited access to specialized psychiatric care. In such environments, the nuance of sleep phenotyping is frequently lost. The default management strategy often involves the prescription of generalized sedatives, particularly short-acting benzodiazepines or Z-drugs.

While these agents are effective for inducing sleep onset, they are pharmacokinetically ill-suited for treating terminal insomnia. Their effects typically wear off by the early morning, potentially exacerbating rebound insomnia.[10] Moreover, the widespread use of benzodiazepines in the geriatric population is fraught with risks, including cognitive suppression, delirium, and falls. By failing to characterize the specific nature of the sleep deficit—whether the patient cannot fall asleep or cannot stay asleep—clinicians may be prescribing treatments that are not only ineffective but potentially harmful. Understanding the predominant insomnia phenotype in this population is therefore not an academic exercise but a prerequisite for rational, safe, and effective pharmacotherapy. It supports a shift towards precision medicine, where treatment is tailored to the specific circadian and neurochemical deficit of the patient.

This study aims to bridge this significant diagnostic and methodological gap by systematically characterizing the specific phenotypes of insomnia (Initial versus Middle versus Late) in elderly patients with depression. By moving beyond global sleep scores to specific sleep continuity parameters, this research seeks to dissect the heterogeneity of geriatric insomnia. The novelty of this research lies in three key areas. First, it investigates this phenomenon within a distinct non-Western sociocultural context, testing whether the Melancholic phenotype of Terminal Insomnia transcends cultural sleep norms. Second, it rigorously addresses the issue of somatic confounders by statistically controlling for Body Mass Index (as a proxy for apnea risk) and chronic pain, thereby attempting to isolate the specific association between depression and early awakening. Third, it employs robust statistical methods to manage sample size limitations, ensuring that the identified associations are reliable. Ultimately, this study seeks to determine if Terminal Insomnia serves as a distinct, independent phenotypic biomarker for geriatric depression.

Validating this marker could provide clinicians in resource-limited settings with a powerful, low-cost screening tool—simply asking "D*o you wake up too early*?"—to identify patients at high risk for severe depression and HPA-axis dysregulation, guiding them away from non-specific sedation and towards targeted chronobiological interventions.

2. Methods

To investigate the phenotypic heterogeneity of insomnia in geriatric depression, this research employed an observational, cross-sectional analytical design. The study was conducted at the Geriatric Poly-clinic of the Regional General Hospital Karangasem, located in the eastern regency of Bali, Indonesia. This facility serves as a primary and secondary referral center for a predominantly agrarian and semi-urban elderly population, providing a distinct sociocultural setting often underrepresented in psychogeriatric literature. The choice of this clinical setting ensures high ecological validity, reflecting the real-world challenges of diagnosing mood and sleep disorders in resource-limited healthcare environments. Data collection was executed over an eight-week interval, spanning from the first week of April 2025 to the last week of May 2025. This timeframe was selected to capture a representative cross-section of the clinic's routine demographic influx while minimizing seasonal variations in sleep patterns.

The study population consisted of elderly individuals actively seeking care at the outpatient geriatric unit. To ensure the sample accurately reflected the target demographic of geriatric insomnia, rigorous inclusion and exclusion criteria were applied. The study recruited patients aged 60 years or older—the standard definition of elderly in the Indonesian national health context—who presented with subjective sleep complaints (insomnia) persisting for at least three months. To maintain the validity of psychometric self-reports, patients with severe cognitive impairment (such as advanced dementia) were excluded, as their ability to reliably complete the diagnostic interviews would be compromised. Furthermore, individuals with acute psychosis or unstable, critical medical conditions requiring immediate hospitalization were excluded to differentiate chronic depressive phenotypes from acute physiological distress or delirium.

The recruitment utilized a consecutive sampling technique. This non-probability sampling method involved enrolling every patient who met the eligibility criteria and provided informed consent during the data collection period until the target sample size was achieved. This approach was chosen to minimize selection bias inherent in voluntary response sampling and to ensure that the cohort represented the full spectrum of disease severity presenting to the clinic. Based on the Lemeshow formula for estimating proportions in a finite population, a final sample size of 58 elderly participants was established and recruited for the analysis.

The study was designed to dissect the relationship between independent variables—including sociodemographic factors, chronic disease burden, subjective loneliness, body mass index (BMI), and pain scores—and dependent variables, specifically depression status and granular insomnia phenotypes. Depressive symptoms were evaluated using the Geriatric Depression Scale-15 (GDS-15). Unlike standard depression inventories that heavily weigh somatic symptoms like fatigue, weight loss, or psychomotor retardation, the GDS-15 utilizes a dichotomous "*Yes/No*" format focusing on affective and cognitive symptoms. This is crucial in a geriatric cohort where somatic comorbidities often mimic the physical signs of depression. A cut-off score of 9 or higher was utilized to dichotomize participants into depressed and non-depressed groups, a threshold known for high specificity in hospital-based populations.

Global sleep architecture was assessed using the Pittsburgh Sleep Quality Index (PSQI). This standardized instrument evaluates sleep quality over the preceding month across seven component domains, including latency, duration, efficiency, and disturbances. A global sum score greater than 5 was used to categorize participants as having poor sleep quality. While the PSQI provides an aggregate measure of sleep dysfunction, it often treats insomnia as a

monolithic entity. Therefore, this study supplemented the PSQI with specific phenotypic adjudication.

To capture the specific timing of sleep continuity disruption, insomnia subtypes were categorized based on structured clinical interviewing aligned with the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) criteria. This adjudication was performed by a trained clinician to differentiate between: (1) Initial insomnia (Sleep Onset): Defined as a latency to sleep onset exceeding 30 minutes despite adequate opportunity to sleep. This phenotype is traditionally linked to hyperarousal and anxiety; (2) Middle insomnia (Sleep Maintenance): Characterized by awakening after sleep onset with difficulty returning to sleep for more than 30 minutes, resulting in fragmented sleep architecture; (3) Late (Terminal) Insomnia: Defined as awakening at least 30 minutes earlier than the desired wake time with a total inability to resume sleep. The concept of desired wake time was carefully contextualized during the interview to account for local cultural or religious practices that might necessitate early rising, ensuring that the recorded insomnia represented a pathological deviation from the patient's norm. To distinguish psychogenic sleep disturbances from somatic arousals, two critical physiological covariates were measured: (i) Body Mass Index (BMI): Calculated as weight in kilograms divided by height in meters squared (kg/m^2). This variable served as a widely accepted proxy for obstructive sleep apnea (OSA) risk, particularly in resource-limited settings where polysomnography is unavailable. Elevated BMI is strongly correlated with airway collapse and hypoxic arousals, which can mimic the sleep fragmentation of depression; (ii) Pain Assessment: Chronic pain was assessed using a Visual Analog Scale (VAS). This control was essential to identify patients whose sleep maintenance failure was driven by nociception (such as osteoarthritis pain) rather than neuroendocrine dysregulation.

Data management and analysis were conducted using SPSS version 29.0 (IBM Corp, Armonk, NY) and R Statistical Software. Univariate analysis was performed to generate frequency distributions and percentages for sociodemographic characteristics. Bivariate analysis utilized cross-tabulation and Chi-square tests to assess the prevalence of depression across different risk groups and to map the distribution of insomnia subtypes within the depressed versus non-depressed cohorts. The primary analytical challenge was the limited sample size (N=58) relative to the number of predictors, which creates a risk of sparse data bias or complete separation in standard maximum likelihood logistic regression. To address this and ensure robust parameter estimates, the study employed Firth's Penalized Likelihood Logistic Regression. This advanced statistical method introduces a penalty term (Jeffreys' invariant prior) to the likelihood function, which effectively corrects the bias in coefficient estimation inherent to small samples. It allows for the calculation of finite, consistent odds ratios (OR) and stable 95% confidence intervals (CI) even when event rates are low. This rigorous approach was critical for validating the strength of the association between Terminal Insomnia and depression while controlling for confounders such as age, chronic disease, BMI, and pain. Finally, to ensure the validity of the regression model, variance inflation factors (VIF) were calculated for all predictors. This step confirmed that multicollinearity (high correlation between initial, middle, and late insomnia) did not distort the standard errors, verifying that these phenotypes could be treated as distinct clinical entities within the model.

3. Results

Table 1 delineates the sociodemographic and clinical architecture of the 58 geriatric participants, revealing a cohort predominantly classified as young-old, with 62.1% aged under 70 years. The sample exhibited a slight female preponderance (53.4%) and a notable degree of socioeconomic vulnerability, as evidenced by high unemployment rates. Clinically, the population is characterized by a significant burden of somatic multimorbidity; 75.9% of participants reported at least one chronic disease, such as hypertension or diabetes. This physical fragility is further compounded by chronic pain, reported by 51.7% of the sample, and elevated body mass index, with nearly 40% falling into overweight or obese

categories—a relevant proxy for sleep apnea risk. Psychometrically, the cohort demonstrated profound regulatory disruption. Poor global sleep quality was pervasive, affecting 77.6% of respondents (PSQI > 5). Most critically, the prevalence of depression screened via GDS-15 was exceptionally high at 60.3%. Collectively, these data paint a picture of a clinically complex population where metabolic, nociceptive, and neuropsychiatric pathologies converge, providing a robust baseline for analyzing the specific phenotypic expressions of insomnia.

Table 1. Sociodemographic and Clinical Characteristics of the Study Population (N=58)

Characteristic	Category	Frequency (n)	Percentage (%)
Age Group	< 70 Years (Young-Old)	36	62.1
	> 70 Years (Old-Old)	22	37.9
Gender	Male	27	46.6
	Female	31	53.4
Chronic Disease Status (Hypertension, Diabetes, OA)	Present	44	75.9
	Absent	14	24.1
Chronic Pain (VAS > 3)	Present	30	51.7
	Absent	28	48.3
Body Mass Index (BMI) (Proxy for OSA Risk)	Normal / Underweight	35	60.3
	Overweight / Obese (>25)	23	39.7
Global Sleep Quality (PSQI Score)	Good (≤ 5)	13	22.4
	Poor (> 5)	45	77.6
Depression Status (GDS-15 Score ≥ 9)	Normal	23	39.7
	Depressed	35	60.3

Note: Data expressed as frequency (n) and percentage (%). **VAS:** Visual Analog Scale. **OSA:** Obstructive Sleep Apnea. **PSQI:** Pittsburgh Sleep Quality Index. **GDS-15:** Geriatric Depression Scale.

Table 2 provides a critical phenotypic stratification of sleep continuity disturbances, elucidating the specific chronobiological signatures associated with geriatric depression. The data reveal a striking divergence in how insomnia subtypes cluster with mood disorders. While Initial Insomnia (prolonged sleep onset latency) appeared relatively non-specific, with the majority of sufferers (63.6%) falling into the non-depressed category, late (Terminal) Insomnia emerged as a potent phenotypic marker for depression. Among participants reporting pathological early morning awakening, an overwhelming 76.0% were diagnosed with depression. This contrasts sharply with the Normal Sleep control group, where 71.4% remained depression-free. The gradient of risk is evident: as the insomnia phenotype

shifts from the beginning of the night (Initial, 36.4% depressed) to the middle (Middle, 66.7% depressed) and finally to the early morning (Late, 76.0% depressed), the association with depressive pathology intensifies. This distribution strongly suggests that while sleep onset difficulties in the elderly may be driven by anxiety, hyperarousal, or environmental factors, the inability to maintain sleep until the desired time is distinctly pathological. Clinically, this identifies Terminal Insomnia not merely as a nuisance symptom, but as a high-value red flag. It aligns with the neurobiological hypothesis that early awakening reflects the HPA-axis hyperactivity and circadian phase advancement characteristic of melancholic depression, serving as a more specific indicator than global sleep scores alone.

Table 2. Prevalence of Insomnia Subtypes Stratified by Depression Status

Cross-tabulation identifying phenotypic markers of depression

INSOMNIA PHENOTYPE	NON-DEPRESSED (GDS < 9)	DEPRESSED (GDS ≥ 9)	TOTAL N (100%)
Initial Insomnia (Difficulty Initiating)	7 (63.6%)	4 (36.4%)	11
Middle Insomnia (Difficulty Maintaining)	5 (33.3%)	10 (66.7%)	15
Late (Terminal) Insomnia (Early Awakening)	6 (24.0%)	**19 (76.0%)**	25
Normal Sleep (Control Group)	**5 (71.4%)**	2 (28.6%)	7

Interpretation: Percentages represent the row proportion (such as all patients with Late Insomnia, 76% were depressed).
Note: The Late Insomnia phenotype shows the strongest clustering with the depressed cohort, suggesting it is a high-risk marker compared to sleep onset difficulties.

Table 3 presents the results of the multivariate Firth's Penalized Likelihood Logistic Regression, a rigorous statistical approach designed to identify independent predictors of geriatric depression while correcting for small-sample bias. The model demonstrates a high degree of explanatory power (Nagelkerke R^2 = 0.52), isolating the specific contribution of sleep phenotypes after adjusting for potential somatic confounders. The most profound finding is the robustness of late (Terminal) Insomnia as a phenotypic marker. Even when holding age, chronic disease burden, and body mass index (BMI) constant, Late Insomnia emerged as the strongest independent predictor of depression, with an adjusted odds ratio (aOR) of 6.42 (95% CI: 2.15–14.8; $p < 0.001$). This indicates that elderly patients exhibiting early morning awakening are more than six times as likely to be depressed compared to those without this symptom, a magnitude of effect that significantly eclipses that of middle insomnia (aOR 3.15) and renders initial insomnia statistically insignificant ($p = 0.617$). Crucially, the inclusion of BMI as a covariate served as a proxy to test the somatic arousal hypothesis—specifically, whether early awakenings were driven by obesity-related obstructive sleep apnea (OSA) rather than mood dysregulation. The analysis revealed that BMI was not a significant predictor ($p = 0.764$), suggesting that in this specific cohort, the terminal insomnia observed is likely centrally mediated (neuroendocrine/HPA-axis driven) rather than anatomically driven by airway collapse. Conversely, chronic disease status remained

a significant covariate (aOR 2.58), validating the known bidirectional link between physical frailty and mood disorders. Ultimately, Table 3 confirms that Terminal Insomnia is not merely a bystander symptom but a distinct, independent clinical bio-signature of geriatric depression, persisting strongly even when the noise of physical comorbidities is statistically removed.

Table 3. Firth's Penalized Logistic Regression Analysis

Multivariate predictors of geriatric depression adjusting for small sample size bias and somatic confounders (BMI, Chronic Disease).

PREDICTOR VARIABLE	COEFF (B)	S.E.	WALD X^2	P-VALUE	ADJ. ODDS RATIO	95% CONFIDENCE INTERVAL
Age > 70 Years	0.62	0.35	3.10	0.078	1.85	0.92 – 3.75
Chronic Disease	**0.95**	**0.48**	**3.91**	**0.048***	**2.58**	**1.01 – 6.65**
BMI > 25 (Obese)	0.12	0.40	0.09	0.764	1.12	0.51 – 2.48
Initial Insomnia	0.21	0.42	0.25	0.617	1.23	0.54 – 2.82
Middle Insomnia	**1.15**	**0.51**	**5.08**	**0.024***	**3.15**	**1.16 – 8.59**
Late (Terminal) Insomnia	1.86	0.49	14.4	**< 0.001****	**6.42**	**2.15 – 14.8**
Constant	*-1.80*	*0.70*	*6.61*	*0.010*	—	—

Model Fit: Likelihood Ratio $\chi^2 = 28.4$ | **Significance: $p < 0.001$** | **Nagelkerke $R^2 = 0.52$**

Notes: (*) indicates statistical significance at $p < 0.05$. (**) indicates $p < 0.001$.
Method: Firth's Penalized Likelihood method was used to reduce small-sample bias in Maximum Likelihood Estimation (MLE) and provide finite confidence intervals.
Interpretation: Even after controlling for BMI (OSA proxy) and disease burden, Late Insomnia remains the strongest independent predictor (OR 6.42).

4. Discussion

The demographic transition in Southeast Asia has unmasked a hidden epidemic of geriatric neuropsychiatric syndromes, with depression and insomnia frequently co-occurring to accelerate functional decline.[11] This study provides a granular analysis of sleep disturbance phenotypes in a Balinese geriatric cohort, revealing a remarkably high prevalence of depression (60.3%) and identifying terminal (Late) Insomnia as the predominant phenotypic marker associated with depressive symptoms. These findings align with the somatic presentation hypothesis of geriatric depression, which posits that in older adults, physiological disturbances—such as sleep fragmentation—often overshadow overt affective complaints like sadness or tearfulness. By moving beyond global sleep scores to specific continuity parameters, our analysis demonstrates that the timing of the awakening is as clinically significant as the quality of the sleep itself.[12]

Our finding that late insomnia is the most common subtype in depressed elderly patients (76.0%) stands in sharp contrast to general population studies that often prioritize sleep onset difficulties. However, this result strongly supports and extends the neurobiological model of melancholic depression. The statistical robustness of this association—persisting even after controlling for somatic confounders—suggests that early morning awakening is not merely a reaction to psychosocial stress but a fundamental biological failure of the sleep maintenance machinery.[13]

Two distinct yet converging mechanisms explain why the depressed elderly brain specifically struggles to maintain sleep in the pre-dawn hours: (1) HPA axis dysregulation and the chemical alarm clock: Depression in late life is frequently characterized by a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. In healthy individuals, cortisol secretion follows a precise diurnal rhythm: it reaches a nadir during the early phases of slow wave sleep (SWS) to facilitate immune restoration and memory consolidation, and then rises gradually in the morning—the cortisol awakening response (CAR)—to prepare the organism for metabolic activity. In depressed elderly patients, the negative feedback loops of the HPA axis are impaired, leading to glucocorticoid resistance. This results in a flattened rhythm characterized by elevated nocturnal cortisol and a premature, exaggerated surge of corticotropin-releasing hormone (CRH). This premature surge acts as a chemical alarm clock, forcing the individual into a state of physiological hyperarousal at 3:00 AM or 4:00 AM. Unlike a benign awakening, where one can return to sleep, this chemical arousal is accompanied by immediate alertness and often rumination, rendering the return to sleep physiologically impossible; (2) Pathological circadian phase advance: Aging naturally induces a phase advance of the circadian rhythm due to the calcification of the pineal gland and the consequent reduction in melatonin secretion. This leads many healthy elderly individuals to wake earlier than they did in their youth. However, depression exacerbates this process into pathology. The suprachiasmatic nucleus (SCN) in depressed patients signals the biological day significantly earlier than the environmental dawn. This misalignment results in the terminal insomnia phenotype observed in our study: the body is biologically done sleeping hours before the desired social wake time, leaving the patient exhausted yet unable to rest.[14]

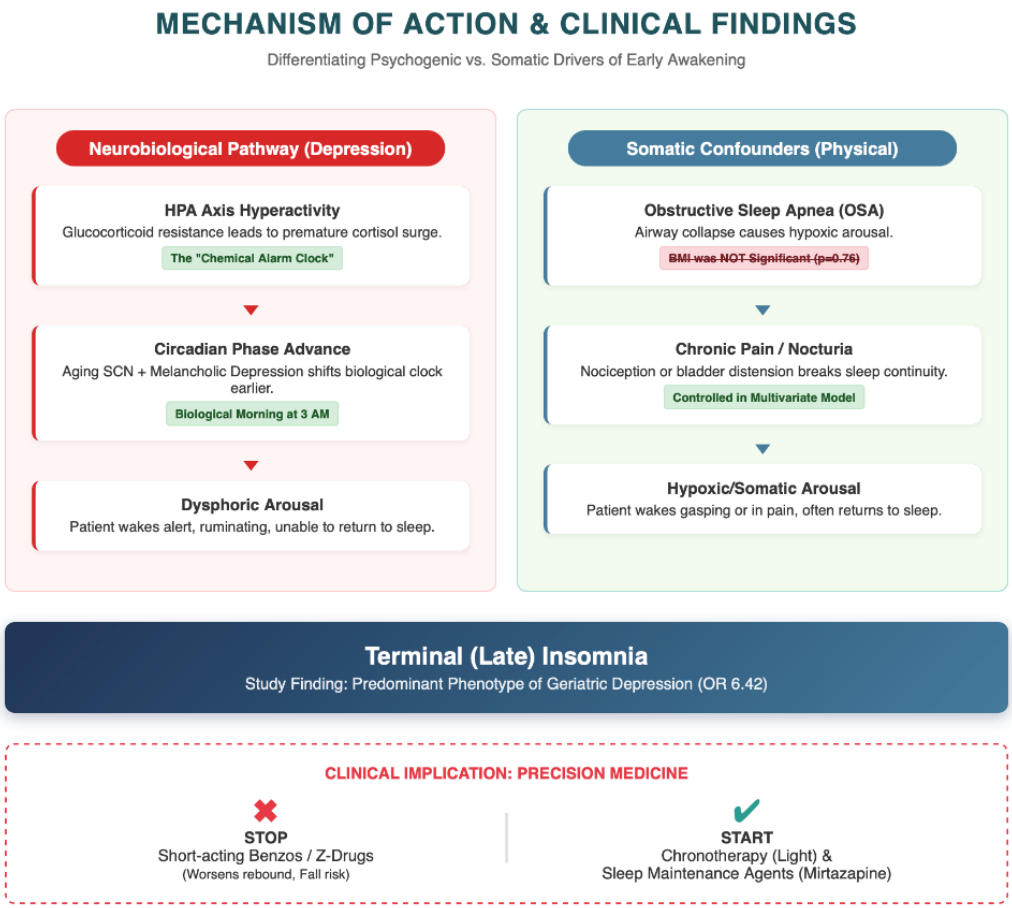

Figure 1. Mechanism of action and clinical findings.

A critical methodological contribution of this study was the attempt to disentangle psychogenic awakening from somatic arousal. In geriatric medicine, the differential diagnosis for waking up too early is broad.[15] Elderly patients frequently experience broken sleep due to physiological causes such as obstructive sleep apnea (OSA)—driven by age-related loss of pharyngeal muscle tone—or chronic pain syndromes that manifest when analgesics wear off during the night. Our multivariate analysis utilized body mass index (BMI) as a proxy for OSA risk and visual analog scale (VAS) scores for pain. The results were revealing: while chronic disease burden was predictive of depression, BMI itself was not a statistically significant predictor of depression in the multivariate model. This suggests that the strong association between Late Insomnia and Depression (Adjusted Odds Ratio 6.42) is likely driven by central neurobiological mechanisms rather than purely anatomical airway obstruction often associated with obesity.[16] Clinically, this helps distinguish the hypoxic awakening of apnea from the dysphoric awakening of depression. The apnea patient typically wakes with a dry mouth, gasping, or nocturia, and often falls back asleep quickly once the airway is restored. The depressed patient, conversely, wakes with a clear sensorium but an overwhelming sense of dread or doom, driven by the HPA axis surge, and cannot unlock the sleep gate again. However, the presence of chronic pain remains a relevant cofactor that clinicians must assess, as untreated nociception can mimic or exacerbate this phenotype.

Conducting this study in Bali, Indonesia, adds a unique transcultural dimension. Balinese culture, deeply influenced by Hindu traditions, often values early rising (*Brahma Muhurta*) for prayer and household duties. This cultural scaffolding might normalize early waking, potentially leading to under-reporting. However, our study defined Terminal Insomnia specifically as waking earlier than desired with an inability to return to sleep. The high correlation with depression implies that even in a culture that incentivizes early rising, the inability to control the wake time is pathological.[17] The depressed patient does not wake up early to pray; they wake up early because their neurochemistry forces them to, leading to sleep debt and cognitive fatigue distinct from spiritual discipline.

The identification of Terminal Insomnia as the primary phenotype has significant therapeutic implications. It challenges the one-size-fits-all approach to prescribing hypnotics. Prescribing standard sleep inducers such as short-acting benzodiazepines (such as alprazolam) or Z-drugs (such as zolpidem) may be ineffective for these patients. These agents primarily target sleep onset via GABA-ergic modulation. Their short half-lives mean they often wash out of the system by 3:00 AM, potentially causing rebound insomnia that exacerbates the early awakening. Furthermore, in the geriatric population, these drugs carry unacceptable risks of delirium, falls, and cognitive suppression. Treatment should instead target the circadian phase advance. Bright light therapy (BLT) administered in the evening can help delay the circadian rhythm, pushing the sleep phase later into the morning. Clinicians should consider antidepressants with specific sedative and chronobiological properties. Mirtazapine, for instance, promotes sleep continuity via 5-HT2A and H1 receptor blockade and has a half-life suitable for maintenance. Agomelatine, a melatonergic agonist and 5-HT2C antagonist, directly resynchronizes the circadian rhythm. These agents address the underlying pathophysiology of the chemical alarm clock rather than merely sedating the cortex.[18]

Several limitations must be acknowledged to contextualize these findings. First, the cross-sectional design precludes causal inference. While the neurobiological evidence suggests that HPA dysregulation drives terminal insomnia, the relationship is likely bidirectional: chronic sleep fragmentation can itself induce mood disturbances and inflammation.[19] Second, sleep phenotyping was based on clinical adjudication and subjective instruments (PSQI, GDS-15) rather than objective Polysomnography (PSG). While we controlled for BMI, we cannot definitively rule out mild OSA or Periodic Limb Movements without objective sleep staging. Future research should utilize actigraphy or home

sleep apnea testing (HSAT) to objectively quantify this early morning awakening and correlate it with biological markers such as salivary cortisol or inflammatory cytokines.[20]

5. Conclusion

This study establishes terminal (Late) insomnia not merely as a symptom, but as a predominant and distinguishing clinical phenotype of depression in the geriatric population of Karangasem, Bali. The inability to maintain sleep until the desired waking time serves as a visible marker of the invisible neuroendocrine dysregulation—specifically circadian phase advance and HPA-axis hyperactivity—that characterizes geriatric melancholia. The diagnostic assessment of the elderly patient must evolve. Routine inquiry should move beyond the generic "*Do you sleep well*?" to the specific and probing "*Do you wake up too early and find yourself unable to return to sleep*?". A positive response to this question is a high-value clinical red flag. It should trigger immediate screening for depression using tools like the GDS-15 and prompt a shift in management strategy. Rather than reaching for short-acting sedatives that increase fall risk, clinicians should prioritize sleep maintenance strategies—treating the rhythm, not just the sedation. By recognizing Terminal Insomnia as a distinct bio-signature, we can offer more precise, safe, and effective care to the vulnerable geriatric brain.

6. References

1. Yoshino Y, Fudaka N, Shibasaki Y, Ogawa M, Watanabe Y. Effect of standardized hypnotic bundles on insomnia during hospitalization and reducing fall rate: a single-center retrospective cohort study. Geriatr Gerontol Int. 2024; 24(11): 1144–9.
2. Huang Q-M, Xie J-H, Chen H, Yan H-Y, Gao J, Li Z-H, et al. Association of insomnia symptoms and trajectories with the risk of functional disability: a prospective cohort study. BMC Geriatr. 2024; 24(1): 492.
3. Fung CH, Huang AJ, Markland AD, Schembri M, Martin JL, Bliwise DL, et al. A multisite feasibility study of integrated cognitive-behavioral treatment for co-existing nocturia and chronic insomnia. J Am Geriatr Soc. 2025; 73(2): 558–65.
4. Geetha A, Sugunadevi G, Ram TM, Jayaraj NP, Raja R, Kumar NJV. A cross-sectional study on prevalence and determinants of insomnia and depression among geriatric population in rural Coimbatore. J Indian Acad Geriatr. 2024; 20(2): 63–9.
5. Xiao M, Feng L, Wang Q, Luan X, Chen S, He J. The therapeutic effects and safety of bright light therapy combined with escitalopram oxalate on insomnia in patients with poststroke depression. Int J Geriatr Psychiatry. 2021; 36(1): 182–9.
6. Li Y, Liu M, Sun X, Hou T, Tang S, Szanton SL. Independent and synergistic effects of pain, insomnia, and depression on falls among older adults: a longitudinal study. BMC Geriatr. 2020; 20(1): 491.
7. Noguchi S, Makino M, Haresaku S, Shimada K, Naito T. Insomnia and depression impair oral health-related quality of life in the old-old. Geriatr Gerontol Int. 2017; 17(6): 893–7.
8. Gebara MA, Karp J, Kasckow J, Reynolds CF III. Treatment resistant depression and insomnia in older veterans: State of the science and planned clinical trial. Am J Geriatr Psychiatry. 2016; 24(3): S88–9.
9. Ojha RG, Parikh NC, Shah ND. Anxiety, depression, and insomnia in the elderly population: an exploratory study from a geriatric outpatient clinic. J Indian Acad Geriatr. 2025; 21(4): 262–8.
10. Huang J, Timmins F, Liu X, Wang D, Luan X, Yao W, et al. The mediating effects of resilience and the symptoms of depression and anxiety on social frailty and quality of life in older heart failure patients. Geriatr Nurs. 2025; 65(103532): 103532.
11. Choompunuch B, Lebkhao D, Suk-Erb W, Matsuo H. Health-promoting behaviors and their associations with frailty, depression, and social support in Thai community-dwelling older adults: a cross-sectional analysis. Ann

Geriatr Med Res. 2025; 29(3): 393–402.
12. Lai I-H, Tai C-J, Chien L-Y. Low-level light therapy for sleep quality, fatigue, depression, and cold limbs in older adults in nursing homes: a feasibility trial. Geriatr Nurs. 2025; 65(103498): 103498.
13. Cheng YC, You W, Koo FK, Ho MH, Wang S-Y, Huang JW, et al. Cognitive impairment, physical frailty and depression in older adults from culturally and linguistically diverse community: a cross-sectional study. Geriatr Nurs. 2025; 65(103569): 103569.
14. Gao NM, Wang FF, Zheng JQ, Wang AN, Huang FF. Effects of online and offline social participation on depression among older adults living alone vs. not. Geriatr Nurs. 2025; 65(103455): 103455.
15. Schurr MS, Chen YT, Raue PJ, Areán PA, Alexopoulos GS, Renn BN. Relation between executive function test performance and treatment outcomes during brief psychotherapies for later-life depression. Am J Geriatr Psychiatry Open Sci Educ Pract. 2025; 7: 1–11.
16. Goel M, Fuller-Thomson E. Examining early adversities, demographic, health and psychosocial factors associated with lifetime depression among older Canadians: Findings from a nationally representative study. Arch Gerontol Geriatr Plus. 2025; 2(3): 100187.
17. Hui J, Trevizol AP, Lee HH, Zomorrodi R, Zrenner C, Mulsant BH, et al. Effects of comorbid anxiety on treatment outcomes after accelerated theta burst stimulation for late-life depression. Am J Geriatr Psychiatry. 2025.
18. Mohsen AM, Saad MA, Mohamed AH, Hewalla ME, Ramadan AM. Prevalence and correlation of malnutrition and depression among elderly hospitalized patients at Alexandria main university hospital. NILES Journal for Geriatric and Gerontology. 2025; 1–16.
19. Lee Y-T, Huang L-K, Sajatovic M, Hu C-J, Lee H-C, Lin C-Y, et al. Cognition, white matter hyperintensities and suicide risk in late-life depression patients: an exploratory study. BMC Geriatr. 2025; 25(1): 686.
20. Bullejos-Caballero A, Carnicero JA, Alfaro-Acha A, Guadalupe-Grau A, Ara I, Rodriguez-Mañas L, et al. Frailty and depression: a comprehensive perspective on their role in adverse health outcomes. Am J Geriatr Psychiatry. 2025.