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ORIGINAL RESEARCH

Effective Doses and Predictors of Dexmedetomidine for Inducing Specific Sleep Stages (N2/N3) in Chronic Insomnia: A Retrospective Cohort Study

Zhenxiu Liu[1,*], Zhouquan Wu[2,*], Renqun Wang[3,*], Dandan Yin[2], Huichan Xv[1], Panqi Wang[1], Fuhai Ji[4], Jingjing Shen[2]

[1]Department of Anesthesiology and Pain, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, People's Republic of China; [2]Department of Anesthesiology, The Second People's Hospital of Changzhou, The Third Affiliated Hospital of Nanjing Medical University, Changzhou, Jiangsu, People's Republic of China; [3]Department of Anesthesiology, Ningde People's hospital, Ningde, Fujian, People's Republic of China; [4]Department of Anesthesiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Fuhai Ji, Department of Anesthesiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, 215006, People's Republic of China, Email jifuhai@suda.edu.cn; Jingjing Shen, Department of Anesthesiology, The Second People's Hospital of Changzhou, The Third Affiliated Hospital of Nanjing Medical University, Changzhou, Jiangsu, 213164, People's Republic of China, Email 283403968@qq.com

Background: Dexmedetomidine (DEX) has emerged as a potential agent for sleep modulation; however, the effective doses required to induce multimodal electroencephalography (EEG)–defined sleep stages in patients with chronic insomnia remain unclear.

Objective: This study aimed to quantify the cumulative DEX doses required to induce non–rapid eye movement (NREM) stage N2 and N3 sleep and to identify clinical predictors of dose variability.

Methods: In this single-center retrospective cohort study, we analyzed 252 adults with chronic insomnia who underwent standardized intravenous DEX titration under continuous multimodal EEG monitoring. The primary outcomes were the cumulative DEX doses (μg) required to induce sustained N2 or N3 sleep. Univariable and multivariable linear regression models were used to identify independent predictors, including body mass index (BMI), depressive symptom severity assessed by the Montgomery–Åsberg Depression Rating Scale (MADRS), and other clinically relevant covariates. Restricted cubic spline analyses were performed to examine potential nonlinear associations between BMI and DEX dose. Prespecified subgroup analyses stratified by age (<60 vs. ≥60 years) were conducted to assess effect modification.

Results: The median effective dose was 40 μg (interquartile range [IQR], 33–48) for N2 sleep induction and 55 μg (IQR, 48–64) for N3 sleep induction. BMI was independently associated with higher DEX dose requirements for both N2 (adjusted β = 0.71; 95% CI, 0.25–1.17; P = 0.003) and N3 sleep (adjusted β = 0.48; 95% CI, 0.07–0.89; P = 0.022). Higher MADRS scores were independently associated with increased DEX dose for N2 sleep induction (adjusted β = 0.17; 95% CI, 0.01–0.34; P = 0.041) but not for N3 sleep. Restricted cubic spline analyses demonstrated significant overall associations between BMI and DEX dose for both sleep stages, while tests for nonlinearity were not statistically significant. Age was not significantly associated with DEX dose requirements, and no significant interaction by age group was observed.

Conclusion: In patients with chronic insomnia, higher cumulative doses of DEX are required to induce deeper NREM sleep stages. BMI is a key determinant of DEX dose requirements for both N2 and N3 sleep, whereas depressive symptom severity appears to selectively influence N2 sleep induction. These findings support the use of individualized, multimodal EEG-guided DEX titration strategies and provide preliminary data to inform future prospective dose-finding studies.

Keywords: dexmedetomidine, chronic insomnia, dose-finding, body mass index, depression, personalized medicine

Introduction

Insomnia disorder, characterized by persistent difficulty initiating or maintaining sleep accompanied by daytime impairment, is a common and burdensome condition affecting approximately 10–30% of adults worldwide.[1,2] It is associated

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with increased risks of mood disorders, cognitive impairment, reduced quality of life, and cardiovascular and metabolic diseases.[3–6] Despite the availability of established treatments, many patients continue to experience inadequate symptom control.

Normal sleep architecture consists of non-rapid eye movement (NREM) stages N1, N2, and N3, as well as rapid eye movement (REM) sleep. Stages N2 and N3 are considered the most restorative phases and play essential roles in memory consolidation, synaptic homeostasis, and physiological recovery.[7–9] Disruption of these stages is common in chronic insomnia and contributes to poor subjective sleep quality and daytime dysfunction.[10]

Current management strategies include cognitive-behavioral therapy for insomnia (CBT-I) as first-line treatment, with pharmacological therapies used when CBT-I is unavailable or insufficient.[11,12] However, conventional hypnotics have limitations, including tolerance, dependence, and limited ability to promote deep N3 sleep.[13] These limitations have prompted interest in alternative agents with distinct mechanisms of action.

Dexmedetomidine (DEX), a highly selective α_2-adrenergic receptor agonist, has emerged as a promising off-label agent for sleep modulation due to its ability to induce a sleep-like state that closely resembles natural NREM sleep.[14] Unlike GABAergic hypnotics, DEX's sedative effect is mediated through inhibition of locus coeruleus noradrenergic activity, which may facilitate the natural transition into N2 and N3 sleep with less disruption of sleep architecture and a favorable side effect profile, notably a minimal risk of respiratory depression.[13] In clinical practice, DEX is often administered via controlled intravenous titration to achieve a targeted sleep state under monitoring, a strategy that may allow for personalized dose optimization.

Current research has primarily focused on establishing the overall feasibility and safety of DEX for sleep induction.[15,16] A critical gap remains in quantifying the effective doses needed to induce specific, EEG-confirmed N2 and N3 sleep in this population. Furthermore, how factors like body composition, depressive symptoms, and age modulate the dose-response relationship for each sleep stage is poorly understood.

Therefore, we conducted this retrospective study to address two primary aims: first, to determine the effective cumulative doses of DEX required to induce sustained N2 and N3 sleep in patients with chronic insomnia; and second, to identify which clinical and demographic factors independently predict the dose requirement for each sleep stage. The findings of this study are intended to provide preliminary, real-world evidence to inform future prospective trials and the refinement of dose-finding strategies for DEX in the management of refractory insomnia.

Materials and Methods

Study Design and Population Selection

The protocol of this single-center, retrospective cohort study was approved by the Institutional Ethics Committee of the Second People's Hospital of Changzhou (Approval No: [2025KY342-01]), which waived individual informed consent due to the use of anonymized retrospective data. The study adhered to the Declaration of Helsinki and is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patients were identified by searching the electronic medical record system of our center for all adults (aged ≥18 years) who underwent DEX titration under multimodal EEG monitoring for the management of chronic insomnia from April 1, 2025 until the end of November 2025. All patients were admitted to the sleep inpatient ward with a primary diagnosis of chronic insomnia for standardized evaluation and treatment. The typical duration of hospitalization ranged from 2 to 4 days, during which clinical assessments and DEX titration procedures were performed.

Inclusion criteria were: (1) primary diagnosis of chronic insomnia disorder according to the International Classification of Sleep Disorders, Third Edition (ICSD-3);[17] (2) completion of a standard multimodal EEG while receiving continuous intravenous DEX titration with the explicit goal of sleep induction; (3) attainment of at least stable stage N2 or N3 sleep, confirmed by multimodal EEG during the titration period; and (4) availability of detailed clinical records, including demographic data, medical history, and concomitant medication use.

Exclusion criteria were: (1) presence of other primary sleep disorders identified by multimodal EEG (eg, moderate-to-severe obstructive sleep apnea, periodic limb movement disorder, or narcolepsy); (2) failure to induce either N2 or N3

stage at the 80 μg ceiling; and (3) incomplete or technically unsatisfactory multimodal EEG recordings that precluded reliable sleep staging.

A total of 283 patients were initially identified. After applying the inclusion and exclusion criteria, 252 patients constituted the final analytical cohort. A detailed flowchart of patient selection is presented in Figure 1.

Baseline Assessments and Clinical Data Collection

As part of the standard clinical evaluation, all participants completed comprehensive assessments prior to the DEX titration procedure (details are provided in Additional file 1).

Sleep Quality Assessment: Subjective sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). This self-rated questionnaire assesses seven components of sleep over the past month, including latency, duration, efficiency, and disturbances. The global PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality. A score > 5 is typically indicative of significant sleep disturbance.[18]

Psychological Assessment: Depressive and anxiety symptom severity were assessed by trained clinicians using two validated, clinician-administered scales: the Montgomery–Åsberg Depression Rating Scale (MADRS)[19] and the Hamilton Anxiety Scale (HAMA).[20] The MADRS focuses on core depressive symptoms (score range 0–60, higher scores indicating greater severity), while the HAMA evaluates both psychic and somatic anxiety symptoms (score range 0–56, higher scores indicating greater severity).

Additional Clinical Data: Demographic information (age, gender), anthropometric measures (body mass index, BMI), and detailed medication history were extracted from electronic medical records. Medication use was categorized as: hypnotics use, antidepressant use, and antipsychotics use, each recorded as a binary (yes/no) variable based on active prescription at the time of the procedure. Data on opioid use, melatonin supplementation, alcohol intake, caffeine consumption, smoking status, and shift work were not consistently available in the medical records and were therefore not included in the analysis.

DEX Titration

The standardized intravenous DEX titration procedure was performed in a monitored sleep inpatient ward by experienced anesthesiologists under continuous multimodal EEG monitoring. Continuous monitoring of cardiovascular parameters—including electrocardiography, heart rate, blood pressure, and pulse oximetry—was conducted. EEG monitoring was performed using a system developed by Masimo (California, USA). Adverse events, including hypotension and bradycardia, were prospectively recorded using standard clinical monitoring systems. Detailed procedures have been described in our

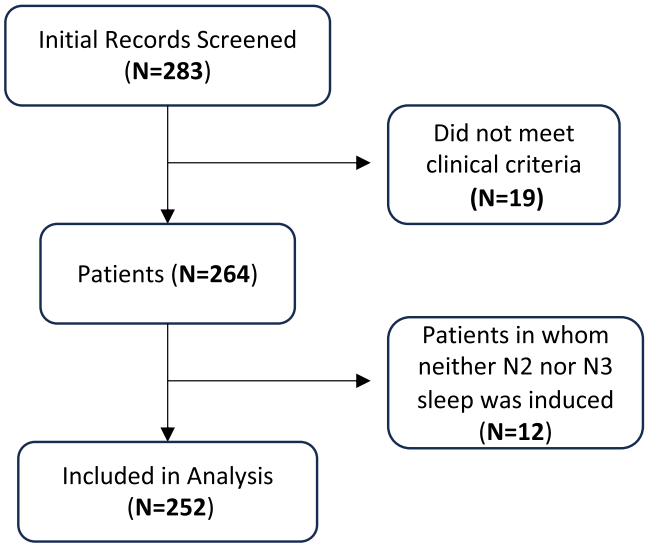

Figure 1 Flowchart depicting the participants' selection.

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previously published studies.[21] The DEX titration procedure was performed during a single monitored session for each patient, and the effective dose required to achieve target sleep stages was recorded during that session. After establishing routine monitoring (electrocardiogram, non-invasive blood pressure, pulse oximetry), a continuous intravenous infusion of DEX (200 μg/2 mL, Yangtze River Pharmaceutical Co., Ltd., Jiangsu, China) diluted in 48 mL of 0.9% saline was initiated at a fixed rate of 40 mL/h.[21] The infusion was terminated upon meeting one of two predetermined endpoints: (1) the induction of sustained stage N2 or N3 sleep, as confirmed by multimodal EEG criteria; or (2) the administration of the maximum allowable cumulative dose of 80 μg, irrespective of sleep stage attainment. This protocol yielded four possible outcomes for analysis: induction of both N2 and N3 sleep at ≤80 μg; induction of N2 only at ≤80 μg; induction of N3 only at ≤80 μg; or failure to induce either stage at the 80 μg ceiling. The maximum dose of 80 μg was selected based on established clinical dosing recommendations and pharmacokinetic–pharmacodynamic (PK–PD) evidence, balancing efficacy for sleep induction with the risk of dose-dependent cardiovascular adverse events.[22]

Sleep staging was performed by experienced anesthesiologists blinded to dosing information, in accordance with American Academy of Sleep Medicine (AASM) standards.[23] Stage N2 was identified by the presence of sleep spindles (11–16 Hz) and K-complexes, while stage N3 was defined by high-amplitude delta activity (0.5–2 Hz). The outcome measures were the effective cumulative doses of DEX required to induce stage N2 (Dex-N2 dose) and stage N3 (Dex-N3 dose). All multimodal EEG recordings underwent quality review, and epochs with significant artifacts were excluded (raw data are provided in Additional file 2).

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of quantile–quantile (Q–Q) plots. Data with normal distribution are presented as mean ± standard deviation (SD) and were compared between groups using Welch's t-test or one-way analysis of variance (ANOVA), as appropriate. Non-normally distributed continuous variables are reported as median with interquartile range (IQR) and were compared using the Mann–Whitney *U*-test or Kruskal–Wallis test. Categorical variables are expressed as frequency and percentage; group comparisons were performed using Pearson's chi-square test or Fisher's exact test when expected cell frequencies were <5.

To identify factors associated with the effective DEX dose required for N2 and N3 sleep induction, univariable linear regression analyses were first conducted for each candidate predictor, including age, sex, BMI, PSQI score, MADRS score, HAMA score, and use of hypnotics, antidepressants, or antipsychotics. Variables with a univariable $P < 0.10$ and/or considered clinically relevant were selected for inclusion in the multivariable model to minimize overfitting and ensure model stability. Results are reported as regression coefficients (beta) with 95% confidence intervals (CI) and corresponding P-values. Model fit was evaluated using the adjusted R^2.

To explore potential nonlinear associations between BMI and DEX dose, restricted cubic spline (RCS) models were fitted with three knots placed at the 10th, 50th, and 90th percentiles of the BMI distribution, adjusting for MADRS score. The overall association and the nonlinear component were tested using the Wald test. In addition, to examine whether age modified the relationship between BMI and dose, we performed stratified multivariable analyses by age group (<60 vs. ≥60 years) and formally tested for interaction by including a BMI-by-age-group product term in the regression models. The cutoff (<60 vs. ≥60 years) was prespecified based on commonly used definitions of older adults in sleep research, where age ≥60 years is frequently used as a threshold, as most age-related changes in sleep architecture and physiology occur before or around this age.[24] All analyses were performed using R software (version 4.2.2; R Foundation for Statistical Computing). A two-tailed p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The final cohort comprised 252 patients with chronic insomnia. As shown in Table 1, the population had a mean age of 50 ±14 years, a median BMI of 22.20 (IQR 20.68–23.89), and included 145 men (57.5%). Baseline scores indicated poor

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	N = 252
Age, years, Mean ± SD	50 ± 14
BMI, Median (Q1, Q3)	22.20 (20.68, 23.89)
Gender, n (%)	
Male	145 (57.5%)
Female	107 (42.5%)
PSQI Score, Median (Q1, Q3)	13.0 (11.0, 17.0)
MADRS Score, Median (Q1, Q3)	13 (8, 20)
Missing	2
HAMA Score, Median (Q1, Q3)	16 (12, 26)
Hypnotics use, n (%)	
No	103 (40.9%)
Yes	149 (59.1%)
Antidepressant use, n (%)	
No	161 (63.9%)
Yes	91 (36.1%)
Antipsychotics use, n (%)	
No	211 (83.7%)
Yes	41 (16.3%)
Dex-N2 dose, μg, Median (Q1, Q3)	40 (33, 48)
Missing	15
Dex-N3 dose, μg, Median (Q1, Q3)	55 (48, 64)
Missing	21

sleep quality (median PSQI, 13.0 [IQR, 11.0–17.0]) and the presence of mild-to-moderate comorbid depression (median MADRS, 13 [8–20]) and anxiety (median HAMA, 16 [12–26]). A majority (59.1%) reported active hypnotic use.

The median effective dose to induce stage N2 sleep was 40 μg (IQR 33–48; n=237), while the median dose for stage N3 sleep was higher at 55 μg (IQR 48–64; n=231). Stratification by dose quartiles (Additional file 3. Tables S1 and 2) revealed that only BMI was significantly associated with Dex-N2 dose variability (P=0.002), increasing across higher dose quartiles. No baseline characteristics, including age, gender, symptom scores, or concomitant medications, showed significant associations with Dex-N3 dose quartiles (all P>0.05).

Determinants of DEX Dose for N2 and N3 Sleep Induction

To identify the clinical factors independently associated with the effective dose of DEX, we performed univariable and multivariable linear regression analyses (Additional file 3. Tables S3 and 4, presented graphically in Figures 2 and 3).

In univariable analysis, higher body mass index (BMI) (Beta = 0.71, 95% CI: 0.25 to 1.17, P = 0.003), higher MADRS score (Beta = 0.20, 95% CI: 0.04 to 0.36, P = 0.015), and active antidepressant use (Beta = 3.18, 95% CI: 0.19 to 6.17, P = 0.038) were significantly associated with a higher Dex-N2 dose. Age, gender, PSQI score, HAMA score, hypnotic use, and antipsychotic use showed no significant association. In the multivariable model adjusted for these significant and clinically relevant factors, BMI (adjusted Beta = 0.71, 95% CI: 0.25 to 1.17, P = 0.003) and MADRS score (adjusted Beta = 0.17, 95% CI: 0.01 to 0.34, P = 0.041) remained as independent predictors of a higher Dex-N2 dose. The association with antidepressant use was attenuated and no longer statistically significant after adjustment (adjusted Beta = 2.04, 95% CI: −1.03 to 5.12, P = 0.192). The final multivariable model for the Dex-N2 dose explained a modest proportion of the total variance (adjusted R^2 = 0.059).

For the effective dose required to induce stage N3 sleep, only BMI was significantly associated in univariable analysis (Beta = 0.48, 95% CI: 0.07 to 0.89, P = 0.022). No other factor, including age, gender, PSQI, MADRS, or HAMA scores, or use of hypnotics, antidepressants, or antipsychotics, showed a significant association. In the multivariable

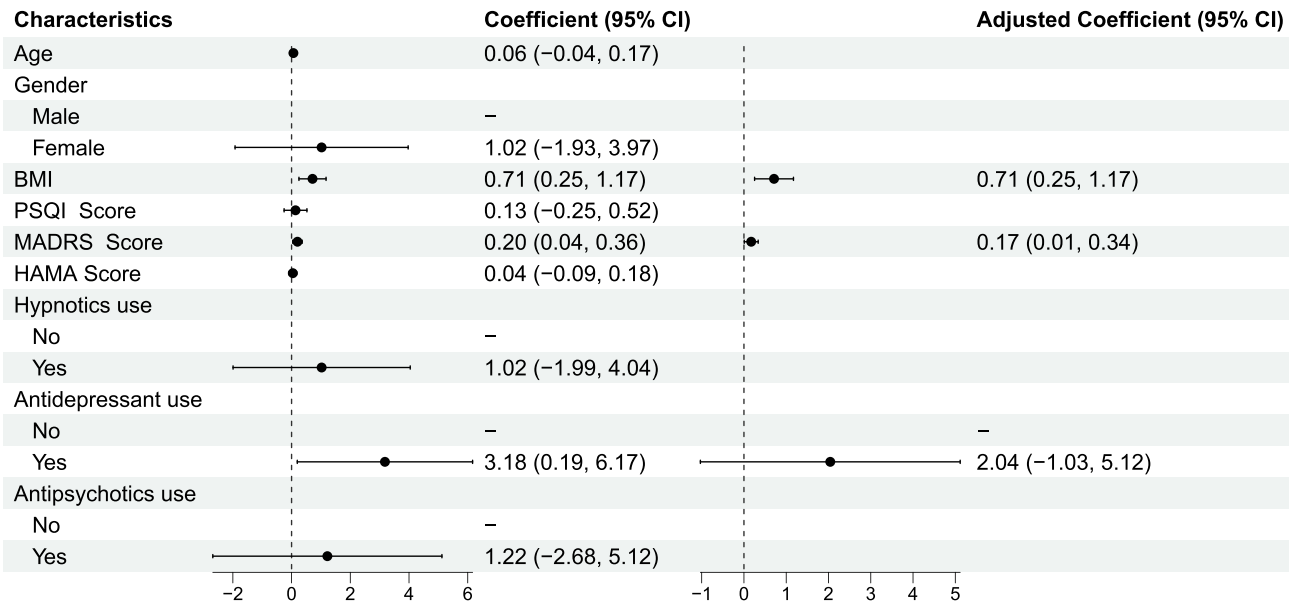

Figure 2 Forest Plot of Factors Associated with the DEX Dose for N2 Sleep Induction.

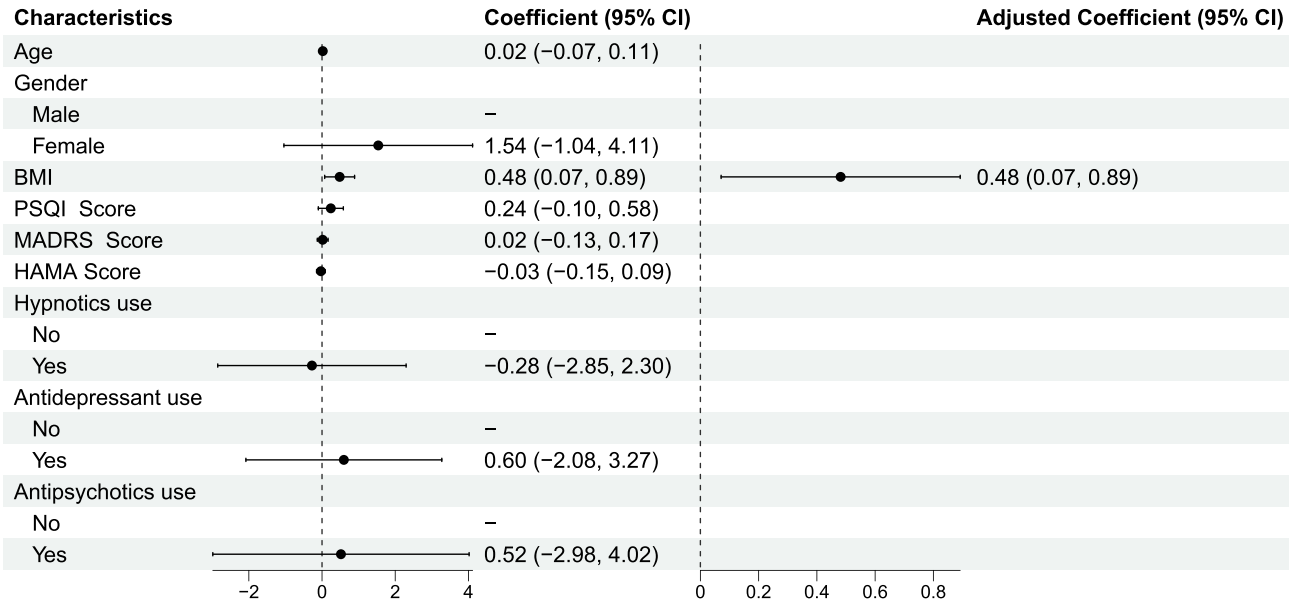

Figure 3 Forest Plot of Factors Associated with the DEX Dose for N3 Sleep Induction.

analysis, BMI remained the sole independent predictor of a higher Dex-N3 dose (adjusted Beta = 0.48, 95% CI: 0.07 to 0.89, P = 0.022). The model's explanatory power for Dex-N3 dose variability was low (adjusted R^2 = 0.019).

Nonlinear Association Between BMI and DEX Doses

Given that BMI was identified as a consistent predictor in the linear models, we further explored potential nonlinear relationships between BMI and the effective DEX doses using restricted cubic splines (RCS) (Figure 4a and b).

After adjusting for MADRS score, the RCS analysis revealed a significant overall association between BMI and the Dex-N2 dose (P-overall = 0.009). The fitted curve suggested a complex, non-monotonic relationship (Figure 4a). Visually, the curve indicated a slight downward trend in the estimated Dex-N2 dose as BMI increased from

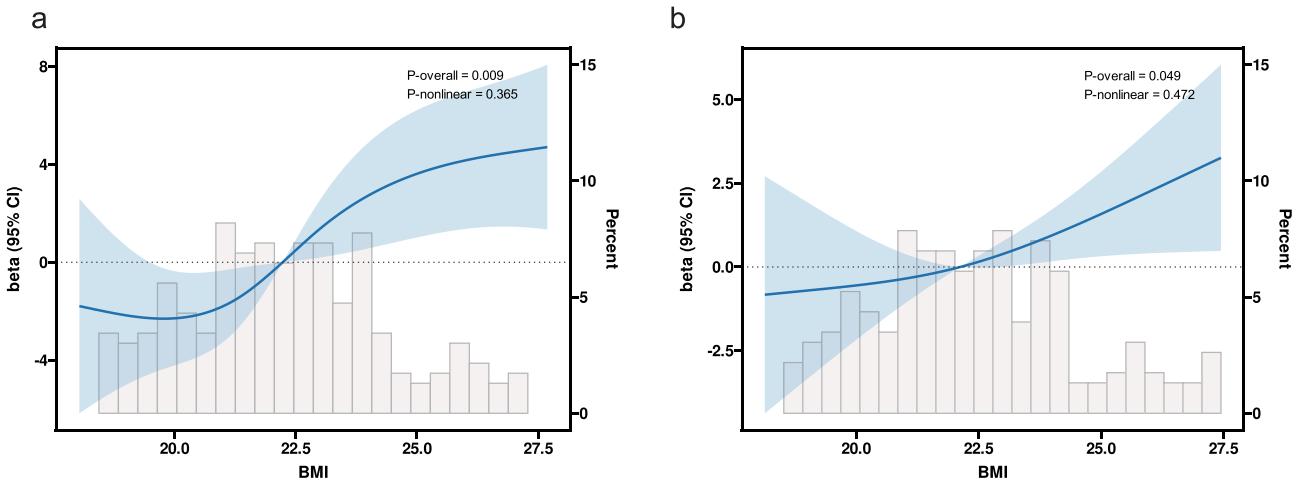

Figure 4 Association of body mass index with DEX dose for N2 and N3 sleep: results from restricted cubic spline analyses. (**a** and **b**). Plots depict the relationship between BMI and the effective dose for inducing stage N2 (**a**) and stage N3 (**b**) sleep. Analyses were adjusted for MADRS score. Solid lines represent estimated beta coefficients, with shaded 95% confidence intervals. Dashed vertical lines indicate potential inflection points suggested by the curve. Although a significant overall association was observed (P-overall < 0.05 for both), the test for nonlinearity was not statistically significant (P-nonlinear > 0.05).

approximately 18 to 22 kg/m^2, followed by a steady upward trend with further increases in BMI beyond 22 kg/m^2. However, the test for nonlinearity did not reach statistical significance (P-nonlinear = 0.365), suggesting that within the observed BMI range of this cohort, a linear approximation of this relationship may be statistically acceptable, despite the visual suggestion of a potential threshold or inflection point around 22 kg/m^2. The model fit was modest (adjusted R^2 = 0.056).

For the Dex-N3 dose, adjusted for MADRS score, the RCS analysis indicated a statistically significant overall association with BMI (P-overall = 0.049), though the association was weaker compared to that for the N2 dose. The fitted curve (Figure 4b) showed a relatively flat relationship for BMI values between approximately 21 and 25 kg/m^2, with a suggestion of an increasing trend in the required Dex-N3 dose at BMI values above 25 kg/m^2. Similar to the N2 model, the test for a nonlinear relationship was not statistically significant (P-nonlinear = 0.472). The explanatory power of this model was low (adjusted R^2 = 0.014).

Subgroup Analyses Based on Age

To further examine the potential modifying effect of age on the relationship between BMI and the effective DEX dose, we performed stratified multivariable linear regression analyses by age group (<60 years and ≥60 years), adjusting for MADRS score. The results are illustrated in Figure 5a and b.

For the induction of N2 sleep (Figure 5a), the overall positive association between BMI and Dex-N2 dose was significant (adjusted Beta = 0.73, 95% CI: 0.27 to 1.18, P = 0.002, n=235). In the age-stratified analysis, this association remained significant in patients younger than 60 years (adjusted Beta = 0.80, 95% CI: 0.26 to 1.34, P = 0.004, n=174). However, in patients aged 60 years or older (n=61), the association was not statistically significant (adjusted Beta = 0.59, 95% CI: −0.31 to 1.50, P = 0.204). The P-value for interaction was 0.700, indicating no statistically significant evidence of effect modification by age on the BMI-Dex-N2 dose relationship.

For the induction of N3 sleep (Figure 5b), the overall association between BMI and Dex-N3 dose was also significant (adjusted Beta = 0.50, 95% CI: 0.09 to 0.91, P = 0.019, n=229). Similar to the N2 findings, stratification by age revealed a significant association in the <60 years group (adjusted Beta = 0.58, 95% CI: 0.10 to 1.06, P = 0.020, n=166), but not in the ≥60 years group (adjusted Beta = 0.33, 95% CI: −0.49 to 1.16, P = 0.429, n=63). The P-value for interaction was 0.610, suggesting no significant statistical interaction by age group for the N3 endpoint.

In summary, while a higher BMI was consistently associated with an increased effective dose of DEX for inducing both N2 and N3 sleep in the overall cohort and specifically in patients under 60 years of age, this association appeared

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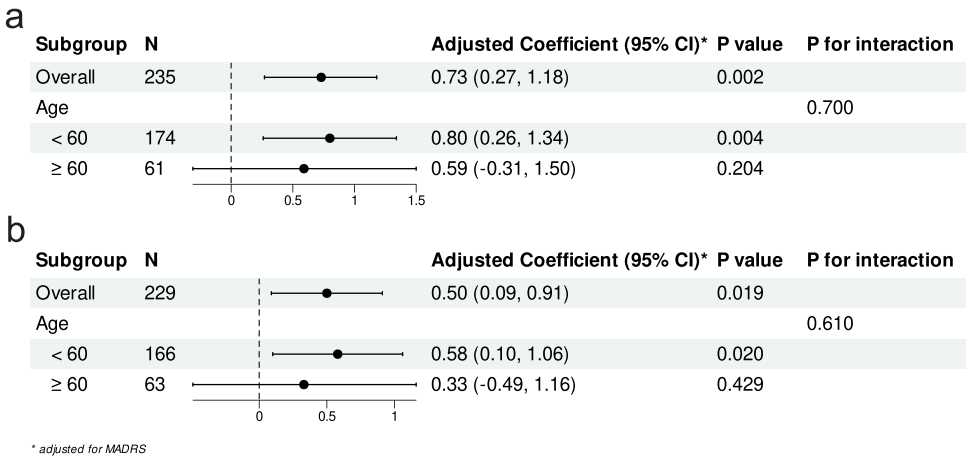

Figure 5 Association between body mass index and DEX dose for N2 and N3 sleep induction: results from age-stratified multivariable analyses. (**a**) Association with the effective DEX dose for inducing N2 sleep; (**b**) Association with the effective DEX dose for inducing N3 sleep. Analyses were adjusted for MADRS score. Data are presented as adjusted beta coefficients with 95% confidence intervals. The P-value for interaction was not statistically significant for either sleep stage (P-interaction > 0.05).

attenuated and was not statistically significant in patients aged 60 years or older. Formal tests for interaction, however, did not reach statistical significance for either sleep stage.

Discussion

In this retrospective cohort study of patients with chronic insomnia undergoing multimodal EEG-guided DEX titration, we provide real-world estimates of the cumulative doses required to induce sustained N2 and N3 sleep and identify clinical factors associated with interindividual dose variability. Three principal findings emerge. First, progressively higher cumulative doses of DEX were required to induce deeper stages of NREM sleep. Second, BMI was a consistent determinant of DEX dose requirements for both N2 and N3 sleep. Third, depressive symptom severity was selectively associated with the dose required to initiate N2 sleep but not N3 sleep. Together, these findings underscore the importance of patient-specific physiological and affective factors in modulating pharmacologically induced sleep architecture.

A central finding of this study is the robust association between BMI and DEX dose requirements across NREM sleep stages. This relationship is biologically plausible given the pharmacokinetic and pharmacodynamic properties of DEX, a highly lipophilic α2-adrenergic agonist characterized by a large volume of distribution and extensive tissue uptake.[22] Higher BMI, reflecting increased adiposity relative to stature, may therefore lead to greater peripheral drug distribution and reduced effective central nervous system exposure at a given infused dose. More broadly, substantial evidence indicates that obesity and body composition significantly alter drug disposition, particularly for lipophilic agents, through changes in distribution volume and clearance.[25] Our findings extend these pharmacokinetic principles to sleep-stage–specific endpoints, suggesting that BMI is a clinically relevant determinant of DEX dosing needs for both light and deep NREM sleep.

Importantly, while BMI was associated with dose requirements for both N2 and N3 sleep, the relationship appeared attenuated for N3 sleep. This observation may reflect fundamental neurophysiological differences between N2 and N3 sleep generation. N2 sleep represents a transitional state dominated by thalamocortical oscillations, including sleep spindles and K-complexes, whereas N3 sleep is characterized by large-scale cortical synchronization and slow oscillatory activity. Experimental and clinical EEG studies have demonstrated that DEX-induced sedation closely resembles endogenous NREM sleep, particularly slow-wave sleep, by engaging sleep-promoting neural circuits rather than non-specific cortical suppression.[16,26] Consequently, variability in network-level sleep homeostasis or cortical excitability—beyond drug distribution alone—may contribute disproportionately to interindividual differences in N3 sleep induction, potentially explaining the modest explanatory power of the N3 models.

Another notable finding is the selective association between depressive symptom severity and the DEX dose required to induce N2 sleep. Depression is strongly linked to disturbances in sleep initiation, sleep continuity, and NREM microarchitecture, as well as dysregulation of large-scale brain networks involved in arousal and affective processing. Neuroimaging studies have shown that depressive symptoms are associated with altered functional connectivity within circuits that overlap with sleep–wake regulatory networks, including default mode and salience networks.[27] In parallel, large-scale psychiatric syntheses have emphasized that sleep initiation difficulties are among the most consistent and clinically relevant sleep abnormalities in depressive disorders.[28] In this context, our findings suggest that higher depressive symptom burden may increase the pharmacological threshold required to transition from wakefulness to N2 sleep, whereas the mechanisms underlying deeper slow-wave sleep may be comparatively less sensitive to affective state.

In contrast, we did not observe an independent association between age and DEX dose requirements in the overall cohort. Although aging is accompanied by well-documented changes in sleep architecture and altered sensitivity to many sedative–hypnotic agents, DEX exerts its sedative effects primarily by activating endogenous sleep-promoting pathways rather than through direct GABAergic potentiation. EEG-based studies indicate that this mechanism preserves key features of physiological NREM sleep across age groups.[26] While stratified analyses suggested some attenuation of the BMI–dose association in older adults, formal interaction testing did not support a statistically significant modifying effect of age, indicating that BMI remains a relevant consideration across the adult lifespan.

Compared with PK–PD modeling approaches,[22] the real-world titration protocol used in this study reflects routine clinical practice and allows for direct observation of individualized dose requirements under continuous EEG monitoring. While PK–PD models provide important insights into DEX dose–response relationships, they rely on model-based assumptions and plasma concentration measurements, whereas our EEG-guided titration approach reflects real-world individualized dosing responses.

Several limitations merit consideration. First, the retrospective design precludes causal inference and introduces the possibility of residual confounding. Second, the cumulative dose recorded reflects the amount infused until multimodal EEG-defined sleep onset was detected, which may modestly overestimate the minimum effective dose due to pharmacodynamic lag. Third, this single-center study may limit generalizability to other populations or titration protocols. Given that most patients with chronic insomnia are managed in outpatient settings, and intravenous DEX administration requires monitored conditions, the generalizability of our findings to broader clinical populations may be limited. The relatively narrow BMI distribution, with few patients in the overweight or obese range, may limit the clinical applicability of BMI as a predictor of DEX dose in more diverse populations. In addition, the small number of patients with BMI $\geq$25 kg/m^2 precluded meaningful subgroup analyses, as such analyses would have limited statistical power and potentially yield unstable estimates. Additionally, we were unable to account for certain lifestyle and pharmacological factors, including alcohol and caffeine intake, smoking status, shift work, and use of opioids or melatonin, which may influence sleep architecture. Finally, the modest explanatory power of the regression models suggests that additional factors—such as genetic variability, autonomic tone, or baseline sleep pressure—likely contribute to interindividual differences in DEX responsiveness.

Despite these limitations, this study has notable strengths, including the use of multimodal EEG to define objective, stage-specific sleep endpoints and the focus on clinically accessible predictors. By explicitly distinguishing between N2 and N3 sleep induction, our findings reinforce the concept that pharmacological sleep modulation is a stage-dependent process shaped by both physiological and affective factors.

In conclusion, higher BMI is consistently associated with increased DEX dose requirements for inducing both N2 and N3 sleep in patients with chronic insomnia, while depressive symptom severity selectively influences N2 sleep induction. These results support the use of personalized, multimodal EEG-guided DEX titration strategies and provide a rationale for future prospective studies integrating PK–PD modeling to optimize stage-specific sleep induction.

Conclusion

This retrospective study provides real-world estimates of the cumulative DEX doses required to induce multimodal EEG-confirmed N2 and N3 sleep in patients with chronic insomnia. Higher BMI was consistently associated with increased dose requirements for both sleep stages, while depressive symptom severity selectively influenced N2 sleep induction. These findings support individualized, multimodal EEG-guided DEX titration strategies and provide a foundation for future prospective dose-finding studies integrating PK–PD modeling.

Data Sharing Statement

The raw data used and analyzed during this study are all available in Additional file 2.

Ethics Approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of the Second People's Hospital of Changzhou (Approval No. 2025KY342-01). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The requirement for written informed consent was waived by the ethics committee due to the retrospective, observational nature of the study and the use of anonymized clinical data.

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Author Contributions

Zhenxiu Liu

Conceptualization, Formal analysis, Visualization, Writing - original draft, Writing - review & editing

Zhouquan Wu

Conceptualization, Formal analysis, Writing - review & editing

Renqun Wang

Investigation, Writing - review & editing

Dandan Yin

Investigation, Writing - review & editing

Huichan Xv

Investigation, Writing - review & editing

Panqi Wang

Investigation, Writing - review & editing

Fuhai Ji

Conceptualization, Formal analysis, Visualization, Writing - review & editing

Jingjing Shen

Conceptualization, Investigation, Formal analysis, Writing - review & editing

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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