Neuropsychiatric Disease and Treatment

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CLINICAL TRIAL REPORT

Esketamine Optimized the Efficacy of Dexmedetomidine in Treating Sleep Disorders with Comorbid Depression

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Purpose: Although Dexmedetomidine (DEX) can induce sleep that resembles natural sleep, it has demonstrated limited efficacy in patients with comorbid insomnia and depression. On the other hand, Esketamine (ESK) has shown a potent antidepressant effect. Herein, we aimed to establish whether esketamine could enhance the therapeutic efficacy of DEX in treating patients with comorbid insomnia and depression.
Methods: We recruited 84 patients with comorbid insomnia and depression who were randomized into two groups for a 1-month follow-up study: the DE group (receiving dexmedetomidine and esketamine) and the DS group (receiving dexmedetomidine and saline). Outcome measures included polysomnographic monitoring (PSG), Montgomery-Åsberg Depression Rating Scale (MADRS), Pittsburgh Sleep Quality Index (PSQI), Sleep Numeric Rating Scale (SNRS), and serum brain-derived neurotrophic factor (BDNF) concentrations. The primary outcome was a comparison of PSG parameters recorded at baseline (D_0) and on treatment day 3 (D_3).
Results: After 3 days of treatment, patients in DE group had a significant increase in total sleep duration, duration and proportion of N3 sleep ($P < 0.05$), a significant decrease in proportion of N2 sleep and proportion of REM sleep ($P < 0.05$), and a significant decrease in depression score and sleep numeric rating scale score ($P < 0.05$), as compared with DS group. Improvements in sleep were associated with improvements in MADRS score and increases in BDNF. Oral dryness was the most frequent adverse event (AE).
Conclusion: When combined with ESK, DEX improved patients' depression scores, further extended total sleep time, increased the N3 sleep proportion, and enhanced deep sleep continuity, with few AEs.

Keywords: insomnia, depression, esketamine, dexmedetomidine, polysomnography

Introduction

Besides difficulty falling asleep, excessive dreaminess, and early awakening, insomnia, a prevalent type of sleep disorder, is also characterized by difficulty falling back asleep due to racing thoughts. One of the common approaches for evaluating insomnia and other sleep disorders is Polysomnography (PSG) monitoring, which primarily reveals prolonged latency of Non-Rapid Eye Movement (NREM) sleep and a reduced deep sleep proportion in insomnia patients.[1] Moreover, previous research reported a high comorbidity rate between insomnia and depression.[2,3] Long-term insomnia often leads to depression-like symptoms, primarily manifested as significantly shortened sleep durations without daytime sleepiness, as well as extreme fatigue and depression, which make individuals reluctant to participate in their normal activities. Additionally, some patients with insomnia often report somatic symptoms such as tightness in the throat and chest, appetite disorders, constipation, headaches, and stomach pain. Despite interventions with serotonin reuptake inhibitors, benzodiazepine sedatives, or both, improving insomnia symptoms in such patients has often been unsatisfactory. Therefore, exploring novel clinical methods for treating patients with comorbid insomnia and depression is imperative for improved clinical outcomes.

Received: 3 May 2025
Accepted: 3 July 2025
Published: 12 July 2025

According to research, Dexmedetomidine (DEX), a potent α2-adrenergic receptor agonist that selectively targets presynaptic α2 receptors in the locus coeruleus, can induce sleep that resembles natural sleep.[4] Furthermore, DEX can enhance delta oscillation waves, increasing the proportion of N3 sleep within NREM and ultimately enhancing sleep quality,[5] thus making it a potential intervention for insomnia. A randomized controlled trial demonstrated that supplementing intravenous analgesia with low-dose dexmedetomidine significantly enhanced sleep architecture—evidenced by increased N2 sleep proportion, prolonged total sleep time, reduced sleep fragmentation, and improved sleep efficiency—in elderly patients after major non-cardiac surgery, without increasing sedation levels.[6] Moreover, our previous study on the improvement of postoperative sleep disorders in patients with gastrointestinal tumors using DEX yielded similar results. However, we also found that while DEX demonstrated good therapeutic effects on patients with simple insomnia, it showed poor therapeutic efficacy in patients with comorbid insomnia and depression, highlighting the potential significance of optimizing its therapeutic effects.

Esketamine (ESK), an N-methyl-D-Aspartate (NMDA) receptor antagonist that forms a racemic ketamine with L-ketamine, has a greater affinity for NMDA receptors.[7] In 2019, the US Food and Drug Administration (FDA) approved the use of an ESK nasal spray for treating refractory depression. Furthermore, in April 2023, the China FDA licensed ESK for use in combination with other oral antidepressants to alleviate depressive symptoms in adults with depression and acute suicidal ideations or behaviors. Multiple studies have since been conducted on the efficacy of ESK. For instance, Liu et al screened 303 Breast Cancer (BC) patients with mild to moderate preoperative depression and found that subanesthetic doses of ESK administered perioperatively reduced the Hamilton Depression Rating Scale (HAMD) scores at 3 days, 1 week, and 1-month postoperatively.[8] Moreover, their studies linked the antidepressant effects of ESK with the modulation of Brain-Derived Neurotrophic Factor (BDNF) levels. Furthermore, Wang et al discovered that ESK could elevate plasma BDNF levels in patients post-surgery, mitigating postoperative depressive-like symptoms.[9] Adding to existing literature, this study aimed to establish whether ESK could swiftly ameliorate depressive symptoms while enhancing the therapeutic efficacy of DEX in treating insomnia. We hope that our findings will provide a scientific rationale for future clinical treatment planning.

Materials and Methods

Participants

Participants were recruited between November 2023 and March 2024 for this study. The inclusion criteria were: (1) Patients diagnosed with insomnia according to the ICD-10 Classification of Mental and Behavioral Disorders F51.0 diagnostic criteria for inorganic insomnia; and (2) Patients with Pittsburgh Sleep Quality Index (PSQI) scores ≥ 16 and Montgomery-Asberg Depression Rating Scale (MADRS) scores of 22–35. The exclusion criteria were: (1) Patients with bipolar disorder, narcolepsy, sleep apnea, or other organic disorders such as epilepsy, chronic diseases, pain, excessive alcohol use, or psychological side effects of specific medications; (2) Patients with aneurysms, vascular diseases, atherosclerotic malformations, or cerebral hemorrhage; (3) Patients with heart conduction abnormalities, severe combined cardiopulmonary and pulmonary dysfunction; (4) Pregnant and breastfeeding women; and (5) Patients with a documented history of allergic reactions to the study drug. This study was approved by the Institutional Ethics Committee of the Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University (Ethics No. [2023] YLJSA066) and was submitted to the Chinese Clinical Trial Registry (No. ChiCTR2400081021). Informed consent was obtained from both patients and their family members.

DEX Titration

All participants were required to undergo DEX titration before treatment. Briefly, the patients were laid quietly on the sleep therapy bed and underwent routine monitoring procedures, including Electrocardiogram (ECG), pulse, Blood Pressure (BP), and pulse oximetry. The patients received 200 μg DEX (200 μg/2 mL, Jiangsu Yangtze River Pharmaceutical Co., Ltd.) diluted in 48 mL 0.9% saline, and administered intravenously at a continuous infusion rate of 40 mL/h. At the same time, the patient's Electroencephalogram (EEG) was monitored (designed by Masimo in California), and DEX infusion was stopped when delta waves appeared (Figure 1). The DEX dose at this time served as

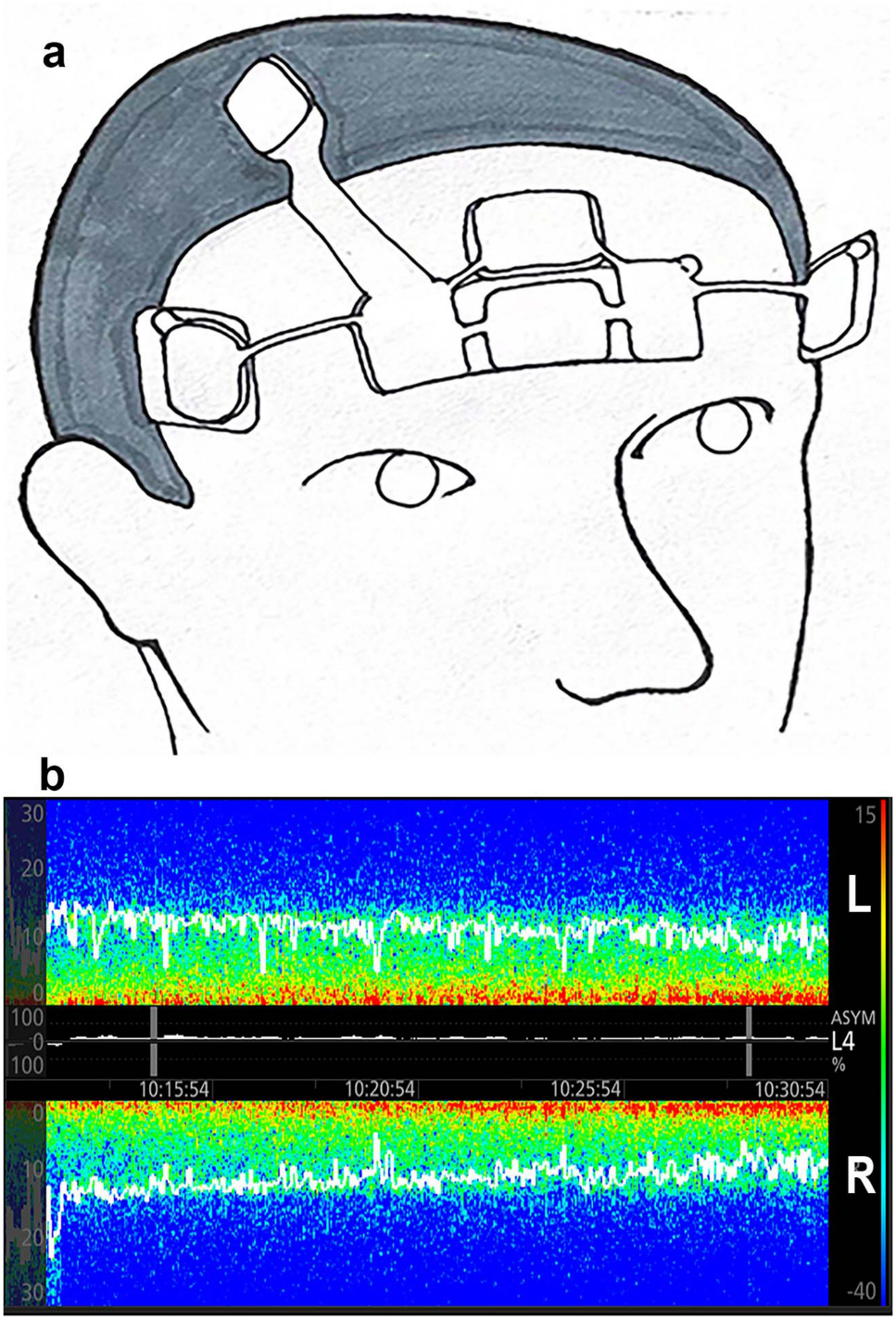

Figure 1 Schematic Representation of EEG Signal Power Distribution Monitoring via Multimodal EEG. (**a**): Schematic diagram of electrode connection; (**b**): EEG spectra during dexmedetomidine titration; 0–4Hz for delta wave, 4–8Hz for theta wave, 8–12Hz for alpha wave, 13–35Hz for beta wave; "L" means left hemisphere, "R" means right hemisphere.

the reference value for medication administration during treatment. According to previous research and the manufacturer's documentation (Jiangsu Hengrui Medicine Co., Ltd.), the absolute bioavailability of DEX Nasal Spray in adults is approximately 80%.[10] Therefore, we calculated the required nasal spray dose for patients in this study by dividing the intravenous target dose by 0.8. After regaining consciousness, the patients were monitored for 30 min in the treatment room to ensure they did not experience any discomfort. The patients were allowed to return to the general ward with their

https://doi.org/10.2147/NDT.S530265

family members if all indicators of normal functioning were observed. Experienced anesthesiologists monitored the entire process. During DEX titration, patients who developed apnea, periodic leg movements, severe bradycardia (<45 beats/min), or hypotension were excluded.

Randomization, Blinding, and Procedures

Participants were randomly assigned (1:1) to either the DS or DE group using a computer-generated randomization sequence created by an independent statistician not involved in the trial. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes (SNOSE) containing group assignment and medication instructions. Participants received visually identical syringes/nasal sprays. Outcome assessors conducting data collection, efficacy assessments, and safety evaluations remained blinded to allocation. Data analysts were denied access to group codes until database lock. Treatment administrators (unblinded) prepared and dispensed medications but had no contact with participants beyond administration and no involvement in data collection or clinical evaluations. Emergency unblinding was permitted exclusively for critical clinical management requiring knowledge of treatment allocation. After unblinding, the corresponding participant was withdrawn from subsequent study procedures and data collection.

Participants were treated for 3 days in the hospital, followed by DEX nasal spray at home for up to 30 days. Patients visited the sleep therapy room at 17:00 every day, after which an intravenous route was established. The patients were treated at bedtime with DEX nasal spray (25 μg/each) at a dose previously determined during DEX titration. Meanwhile, the DE group received esketamine intravenous (0.2 mg/kg over 40 min; 2 mL:50 mg, Jiangsu Hengrui Pharmaceutical Co., Ltd.), and the DS group received the same volume of saline. During treatment, the patient's BP, Heart Rate (HR), and oxygen saturation of the pulse (SpO2) were monitored. Trained medical staff supervised each treatment throughout the process until 2 h after completion.

Measures

The primary outcome measure was changes in Polysomnography (PSG) recordings. A polysomnographic sleep apnea monitor (Polymate iRem-A; Hangzhou Feisio Medical Technology Co., Ltd.) was used to objectively monitor patients' sleep at night pre-treatment (D_0) and on day 3 (D_3). Herein, PSG recordings comprised six-lead EEGs (F3/M2, F4/M1, C3/M2, C4/M1, O1/M2, and O2/M1), two-lead Electrooculograms (EOGs; E1/M2 and E2/M1), single-lead chin Electromyography (EMG; Chin 1-Chin 2), and a modified II-lead ECG (Figure 2). A qualified sleep technician analyzed the collected sleep timeline data, which were divided into 30s epochs. The analyst was blinded to the study protocol and was not involved in data collection or patient care. The primary variables included total sleep time, sleep onset latency, N2 sleep time and rate, N3 sleep time and rate, Rapid Eye Movement (REM) sleep time and rate, and deep sleep continuity scores.

The secondary outcome measures primarily included patients' scale scores. Patients' self-reported sleep quality was evaluated using the 11-point Sleep Numeric Rating Scale (SNRS; with scores of 0 and 10 indicating the best and worst quality, respectively) at baseline (D_0), at 8:00 a.m. on day 2 (D_2), day 4 (D_4), and on day 30 (D_{30}). Patients' sleep quality was also evaluated at baseline (D_0) and on day 30 (D_{30}) using the Pittsburgh Sleep Quality Index (PSQI). Additionally, patients' depression levels were evaluated using the 10-item MADRS. According to this scale, scores of <12, 12–21, 22–29, 30–34, and ≥35 indicate remission, mild depression, moderate depression, severe depression, and very severe depression, respectively. MADRS scores were collected at baseline (D_0), at 8:00 a.m. on day 2 (D_2), day 4 (D_4), and on day 30 (D_{30}).

On the other hand, serum BDNF concentrations were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) kit (Elabscience) per the manufacturer's instructions. Briefly, 5 mL venous blood was collected from patients at baseline (D_0) and at 8:00–10:00 a.m. on day 4 (D_4) into tubes without anticoagulants, kept for 1 h, and centrifuged at 2000 × g for 15 min. Following that, the supernatant was collected and stored in a refrigerator at −80°C, awaiting further tests.

We also recorded Adverse Events (AEs) during treatment, including respiratory depression, nausea, vomiting, oral dryness, bradycardia (<50 beats/min, or a 20% decrease from baseline), hypotension [Systolic Blood Pressure (SBP) < 90 mmHg, Diastolic Blood Pressure (DBP) < 60 mmHg, or a 20% decrease from baseline], separation sensation, and

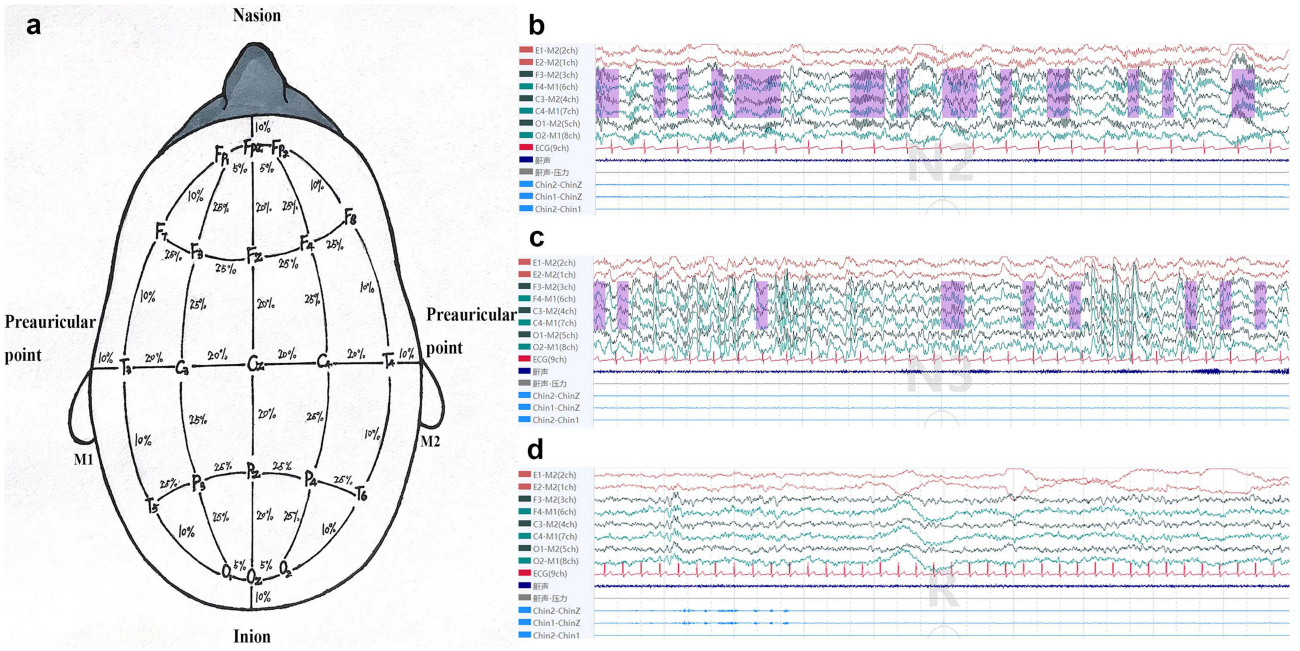

Figure 2 Polysomnographic Sleep Monitoring and Stage-Specific Waveforms (Schematic). (**a**) Schematic diagram of polysomnography monitoring electrodes; (**b**) Polysomnography of N2 sleep; (**c**) Polysomnography of N3 sleep; (**d**) Polysomnography of REM sleep.

nightmares, among others. The AEs were monitored until 24 h after the end of treatment or until they disappeared. Incidences of hypotension and bradycardia were intervened by interrupting study drug infusion and/or drug administration. On the other hand, interventions for desaturation and respiratory depression included interrupting study drug infusion, oxygen delivery, physical therapy, and/or noninvasive/invasive ventilation. Finally, interventions for dissociative symptoms included interrupting study drug infusion and/or sedative medication administration.

Power and Sample Size Analysis

The sample size was estimated using the G*Power 3.1.9.7 software for Windows systems. For sample size determination, we assumed an error α of 0.05 and a power (1-β) of 0.8, along with a predetermined sample size. Based on these parameters, for the repeated measures Analysis of Variance (ANOVA) (F-test), considering an effect size (f) of 0.32, with 2 groups and 2 measurement time points, the total sample size was estimated to be 60 participants. Considering a 20% attrition rate, the total sample size was estimated to be 72 individuals. Finally, 84 participants were enrolled. Of these, 78 participants were included in the final analysis. A post-hoc power analysis using the observed effect size ($f = 0.40$) and $\alpha = 0.025$ confirmed power > 0.95 for the same ANOVA model (2 groups × 2 measurements). α was adjusted for multiplicity applying Bonferroni.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics v26.0 (IBM Corp). Normally distributed continuous variables were presented as mean [Standard Deviation, SD], while non-normally distributed continuous data were expressed as medians [Interquartile Ranges (IQRs)]. On the other hand, categorical variables were presented as frequencies and percentages. T-tests or Mann–Whitney *U*-tests were used for continuous variables of background characteristics between groups, and chi-square tests or Fisher's exact tests were used for categorical variables. Sleep structure, PSQI data, and BDNF concentrations were analyzed using 2 × 2 (Group × Time) repeated-measures ANOVA followed by Bonferroni-corrected post hoc tests. Since the design included only two repeated measures, the assumption of sphericity was inherently met. Consequently, Mauchly's test for sphericity and subsequent epsilon corrections were not performed. Between-group comparisons of MADRS and SNRS scores were conducted using Generalized Estimating Equations (GEE) with baseline scores included as a covariate, an identity link function, and an exchangeable working correlation

structure. Within-group comparisons used Friedman tests with Bonferroni-corrected post hoc analyses. The correlation between variables was measured using Spearman correlation coefficient. Results or differences with $P < 0.05$ were considered statistically significant.

Results

Patient Characteristics

A total of 98 participants were initially recruited, of whom 5 did not meet the inclusion criteria, 2 met the exclusion criteria and 3 were excluded for other reasons. Furthermore, during DEX titration, 2 patients developed severe bradycardia, 1 experienced hypopnea lasting >10 seconds, and 1 exhibited periodic limb movements; these 4 patients were consequently removed from the study. The remaining 84 participants were randomly assigned to the two study groups. Subsequently, 1 participant discontinued treatment, 4 failed polysomnography, and 1 was lost to follow-up; a total of 6 participants were excluded. Finally, 78 participants were included in the statistical analysis: 40 in the DS group and 38 in the DE group (Figure 3).

Table 1 summarizes the demographic and clinical characteristics. There were no significant statistical differences in general information such as age, gender, and BMI ($P > 0.05$). We also did not observe significant differences in clinical characteristics such as duration of insomnia, level of depression, MADRS scores, PSQI scores, and sleep numeric rating scale scores between the two groups ($P > 0.05$).

PSG Changes

Changes in Total Sleep Duration and Sleep Latency

Total sleep duration at D_3 was significantly increased compared to D_0 in both groups (DS group: mean difference = 111.53, 95% CI = 85.00 to 138.05, $P < 0.001$; DE group: mean difference = 163.32, 95% CI = 136.10 to 190.53, $P < 0.001$). There was no difference between the two groups before treatment ($P = 0.85$). At D_3 the total sleep time of patients in DE group was significantly longer than that of DS group (mean difference = 48.15, 95% CI = 23.33 to 72.98, $P < 0.001$).

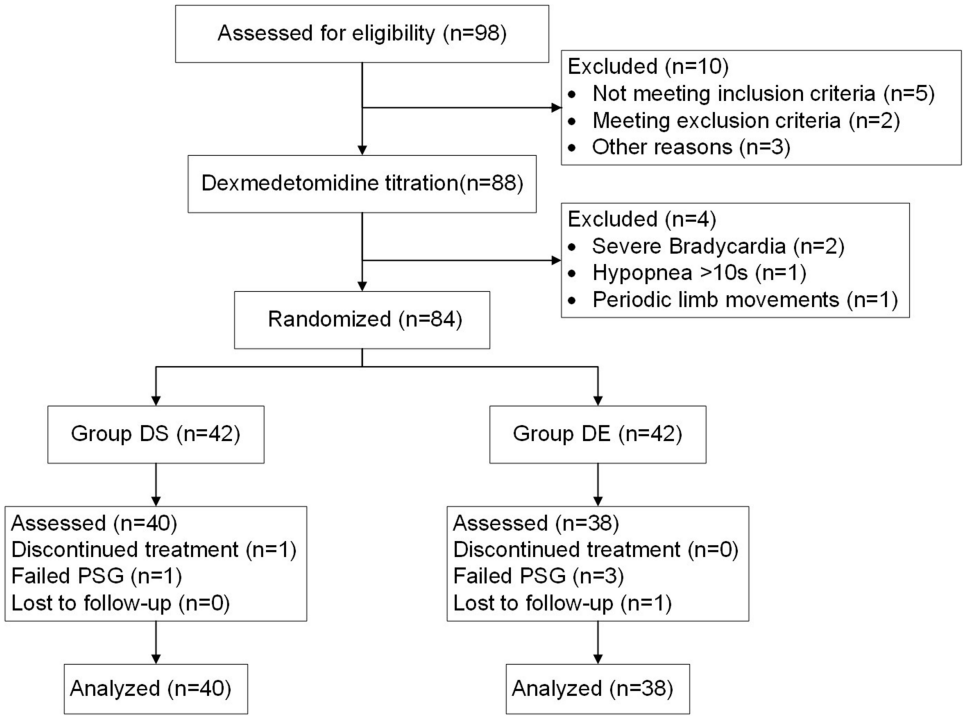

Figure 3 Participant Flowchart.

Table 1 Patient Characteristics

Characteristics	DS Group (n = 40)	DE Group (n = 38)	*P*
Age, Means (SD), years	43.00(14.98)	42.45(12.42)	0.86
Weight, Means (SD), kg	56.73(8.85)	59.34(7.70)	0.17
Height, Means (SD), m	1.64(0.08)	1.66(0.06)	0.38
BMI, Means (SD), kg/m^2	21.02(2.72)	21.60(2.02)	0.28
Gender, n (%)			0.60
Male	16(40.00)	13(34.21)	
Female	24(60.00)	25(65.79)	
Duration of insomnia, median (IQR), months	36.00(6.25–93.00)	49.00(17.25–87.00)	0.25
MADRS			0.80
Average score, median (IQR)	27.00(24.00–33.00)	28.00(24.00–33.00)	
Moderate depression (22 ≤ M < 30), n (%)	22(55.00)	20(52.63)	0.83
Severe depression (30 ≤ M < 35), n (%)	18(45.00)	18(47.37)	
PSQI score			0.48
Average score, Means (SD)	18.15(1.79)	18.42(1.57)	
Sleep Numeric rating scale, median (IQR)	8.0(8.0–9.0)	8.0(8.0–9.0)	0.92
Amount of medication, n (%)			0.76
Without any medication	9(22.50)	10(26.32)	
1-2 medications	18(45.00)	14(36.84)	
3-4 medications	13(32.50)	14(36.84)	
Hypertension, n (%)	8(20.00)	6(15.79)	0.63
Diabetes, n (%)	3(7.50)	2(5.26)	0.68
Dexmedetomidine Titration Dose, median (IQR), μg	61.40(53.60–79.00)	63.00(54.40–80.40)	0.76

Notes: Data are presented as the median (interquartile range)/means (SD).
Abbreviations: BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; MADRS, Montgomery-Asberg Depression Rating Scale.

Sleep latency was reduced at D_3 compared to D_0 in both groups (DS group: mean difference = −62.73, 95% CI = −68.02 to −57.42, $P < 0.001$; DE group: mean difference = −64.61, 95% CI = −70.05 to −59.17, $P < 0.001$), but there was no difference in group comparison at either time point (D_0: $P = 0.96$; D_3: $P = 0.33$)(Table 2).

Changes in Deep Sleep Continuity at Different Time Points

There was no significant improvement in sleep continuity in DS group patients at D_3 compared to that at D_0 (mean difference = 0.45, 95% CI = −2.15 to 3.05, $P = 0.73$); sleep continuity scores were significantly higher in patients in DE group at D_3 (mean difference = 14.95, 95% CI = 12.28 to 17.62, $P < 0.001$) and significantly higher than DS group (mean difference = 14.18, 95% CI = 10.88 to 17.48, $P < 0.001$) (Table 2).

Changes in N2 Sleep at Different Time Points

There was no difference between the two groups in N2 sleep duration ($P = 0.97$) and proportion of N2 sleep ($P = 0.392$) at D_0. At D_3, there was no difference between the groups in N2 sleep duration ($P = 0.91$), but the proportion of N2 sleep was significantly lower in patients in DE group compared to DS group (mean difference = −7.32%, 95% CI = −9.72% to −4.91%, $P < 0.001$). The duration of N2 sleep at D_3 was significantly higher than at D_0 in both groups (DS group: mean difference = 70.35, 95% CI = 46.22 to 94.48, $P < 0.001$; DE group: mean difference = 68.58, 95% CI = 43.82 to 93.34, $P < 0.001$), but the proportional change was opposite (DS group: mean difference = 5.52%, 95% CI = 1.63% to 9.42%, $P = 0.006$; DE group: mean difference = −4.03%, 95% CI = −8.08% to −0.04%, $P = 0.048$) (Table 2).

Changes in N3 Sleep at Different Time Points

Both groups showed a significant increase in N3 sleep duration from baseline (DS group: mean difference = 26.75, 95% CI = 18.82 to 34.68, $P < 0.001$; DE group: mean difference = 79.50, 95% CI = 71.36 to 87.64, $P < 0.001$), but there was no significant difference in the percentage of N3 sleep among patients in DS group (mean difference = 0.78%, 95% CI = −1.69% to 3.23%,$P = 0.53$), and patients in DE group had significantly higher percentage of N3 sleep (mean difference =

Table 2 Sleep Architecture Analysis

Outcome	Group	D_0	D_3	Mean Difference (95% CI)	Group × Time		
					P	*F*	Partial η^2
Total sleep time (min)	DS	274.90(94.19)	386.43(66.06)[a]	111.53(85.00 to 138.05)	0.01	7.37	0.088
	DE	271.26(77.32)	434.58(40.22)[ab]	163.32(136.10 to 190.53)			
Sleep onset latency (min)	DS	90.43(18.44)	27.70(7.62)[a]	−62.73(−68.02 to −57.42)	0.62	0.24	0.003
	DE	90.61(16.17)	26.00(7.60)[a]	−64.61(−70.05 to −59.17)			
The deep sleep continuity score	DS	55.93(7.91)	56.38(7.51)	0.45(−2.15 to 3.05)	0.00	60.09	0.442
	DE	55.61(9.65)	70.56(7.10)[ab]	14.95(12.28 to 17.62)			
Duration of N2 sleep (min)	DS	147.35(83.62)	217.70(46.25)[a]	70.35(46.22 to 94.48)	0.92	0.01	0.000
	DE	148.05(66.99)	216.63(40.47)[a]	68.58(43.82 to 93.34)			
Percentage of N2 sleep (%)	DS	50.86(11.89)	56.39(4.94)[a]	5.52(1.63 to 9.42)	0.00	11.63	0.133
	DE	53.11(11.08)	49.07(5.72)[ab]	−4.03(−8.08 to −0.04)			
Duration of N3 sleep (min)	DS	55.10(25.54)	81.85(23.89)[a]	26.75(18.82 to 34.68)	0.00	85.47	0.529
	DE	49.63(17.08)	129.13(23.56)[ab]	79.50(71.36 to 87.64)			
Percentage of N3 sleep (%)	DS	20.50(6.91)	21.27(4.41)	0.78(−1.69 to 3.23)	0.00	29.36	0.279
	DE	19.15(6.45)	29.51(5.19)[ab]	10.36(7.83 to 12.88)			
Duration of REM sleep (min)	DS	72.45(23.69)	86.88(21.40)[a]	14.43(7.70 to 21.15)	0.87	0.03	0.000
	DE	73.58(21.58)	88.82(11.74)[a]	15.24(8.34 to 22.14)			
Percentage of REM sleep (%)	DS	28.64(10.58)	22.74(5.14)[a]	−5.89(−8.53 to −3.25)	0.53	0.40	0.005
	DE	27.74(7.20)	20.65(3.59)[ab]	−7.09(−9.80 to −4.38)			

Notes: DS Group (n = 40), DE Group (n = 38). Data are presented as the means (SD). Compared with D_0, [a]$P < 0.05$; compared with DS, [b]$P < 0.05$.
Abbreviation: REM, Rapid eye movement.

10.36%, 95% CI = 7.83% to 12.88%, $P < 0.001$). There was no difference in both duration ($P = 0.27$) and proportion of N3 sleep between the groups at baseline ($P = 0.38$). At D_3, patients in DE group had a significantly longer duration (mean difference = 47.28, 95% CI = 36.58 to 57.99, $P < 0.001$) and a significantly greater proportion (mean difference = 8.24%, 95% CI = 6.07% to 10.40%, $P < 0.001$) (Table 2).

Changes in REM Sleep at Different Time Points

Compared with D_0, the duration of REM sleep was significantly increased in both groups (DS group: mean difference = 14.43, 95% CI = 7.70 to 21.15, $P < 0.001$; DE group: mean difference = 15.24, 95% CI = 8.34 to 22.14, $P < 0.001$), and the proportion of REM sleep was significantly decreased in both groups (DS group: mean difference = −5.89%, 95% CI = −8.53% to −3.25%, $P < 0.001$; DE group: mean difference = −7.09%, 95% CI = −9.80% to −4.38%, $P < 0.001$). There was no difference in the duration and proportion of REM sleep between the two groups at D_0 (mean difference = 1.13, $P = 0.83$; mean difference = −0.90%, p = 0.67). There was no difference in the length of REM sleep between the two groups at D_3 (mean difference = 1.94, $P = 0.62$), but there was a decrease in the proportion of REM sleep in DE group compared with that of DS group (mean difference = −2.09%, 95% CI = −4.10% to −0.08%, $P = 0.04$) (Table 2).

Changes in Self-Reported Sleep Quality at Different Time Points

From baseline to the morning of day 4 (D_4), patients in DE group had a mean decrease in SNRS scores of 0.94 (95% CI = 0.15 to 1.73, $P = 0.007$) compared to the DS group. Compared with baseline (D_0), there was no significant improvement at D_2 in DS group ($P = 0.20$), and patients in DE group had a significant decrease at D_2 ($P = 0.004$). At day 30, both groups declined from baseline ($P < 0.001$), but the DE group decreased their scores more (95% CI = 0.37 to 1.91, $P < 0.001$). PSQI data showed no difference between the two groups at baseline (D_0) ($P = 0.48$), at D_{30} there was a significant decrease in DE group compared to DS group (mean difference = −2.82, 95% CI = −3.76 to −1.88, $P < 0.001$). Both groups showed a significant decrease from baseline at day 30 (DS group: mean difference = −2.23, 95% CI = −2.75 to −1.70, $P < 0.001$; DE group: mean difference = −5.32, 95% CI = −5.85 to −4.78, $P < 0.001$) (Table 3).

Table 3 Comparison of Scale Scores

	DS Group (n = 40)	DE Group (n = 38)	Group × Time		DS Group vs DE Group	
			P	χ^2/F	Mean Difference (95% CI)	*P*
MADRS scores, median (IQR)						
D_0	27.00(24.00–33.00)	28(24.00–33.00)	<0.001	16.942[d]	–	–
D_2	27.00(24.00–31.75)	21.00(19.00–24.25)[a]			5.99(3.18 to 8.81)	<0.001
D_4	26.50(23.25–31.00)	20.00(15.75–22.00)[a]			8.74(5.68 to 11.80)	<0.001
D_{30}	25.00(22.00–30.00)[abc]	18.00(13.75–20.00)[abc]			8.96(6.17 to 11.75)	<0.001
Sleep Numeric rating scale scores, median (IQR)						
D_0	8.00(8.00–9.00)	8.00(8.00–9.00)	0.086	4.909[d]	–	–
D_2	8.00(7.00–9.00)	7.00(6.00–8.00)[a]			0.69(−0.14 to 1.53)	0.22
D_4	7.00(6.25–8.00)[ab]	6.00(5.00–7.00)[ab]			0.94(0.15 to 1.73)	0.007
D_{30}	6.00(6.00–7.00)[abc]	5.00(4.00–6.00)[abc]			1.14(0.37 to 1.91)	<0.001
PSQI scores, means (SD)						
D_0	18.15(1.79)	18.42(1.57)	<0.001	66.994[e]	–	–
D_{30}	15.95(1.35)[a]	13.11(2.66)[a]			2.82(1.88 to 3.76)	<0.001

Notes: Data are presented as the median (interquartile range)/means(SD).Compared with D_0, [a]$P < 0.05$; compared with D_2, [b]$P < 0.05$; compared with D_4, [c]$P < 0.05$. [d] Wald χ^2 statistic from generalized estimating equations; [e] F statistic from repeated measures analysis of variance (ANOVA).
Abbreviations: PSQI, Pittsburgh Sleep Quality Index; MADRS, Montgomery-Asberg Depression Rating Scale.

Changes in Depressive States at Different Time Points

In the morning of day 2 (D_2), patients in DE group showed a mean decrease in MADRS scores by 5.99 (95% CI = 3.18 to 8.81, $P < 0.001$) compared to DS group, after which there was a significant difference between both groups ($P < 0.001$). Compared with baseline (D_0), the DS group showed a significant difference on day 30 ($P < 0.001$), and patients in the DE group showed significant improvement in their MADRS scores after the first day of treatment (D_2) ($P < 0.001$) (Table 3).

Changes in BDNF Concentration

A significant interaction between group allocation and time point was detected for serum BDNF ($F = 37.219$, $P < 0.001$). Patients' serum BDNF concentrations were not statistically different between the two groups at D_0 ($P = 0.79$). At D_4, patients in DE group showed a significant increase from baseline (mean difference = 2.99, 95% CI = 2.39 to 3.59, $P < 0.001$) and were significantly higher than those in DS group (mean difference = 2.30, 95% CI = 0.16 to 4.45, $P = 0.04$) (Table 4).

Correlations

As shown in Table 5, after three days of treatment, there was a positive correlation between the mean changes in the depression rating scale and the sleep rating scale ($r = 0.597$, $P < 0.001$). The average change in MADRS demonstrates a negative correlation with total sleep time, continuity of deep sleep, duration and proportion of N3 sleep, as well as BDNF levels ($P = 0.025$, <0.001,

Table 4 Comparison of Serum BDNF Levels (ng/mL)

	DS Group (n = 40)		DE Group (n = 38)		Group × Time		
	D_0	D_4	D_0	D_4	*P*	*F*	Partial η^2
BDNF	23.12(4.69)	23.54(4.74)	22.85(4.36)	25.84(4.77)[ab]	<0.001	37.219	0.329

Notes: Data are presented as the means(SD). Compared with D_0, [a]$P < 0.05$; compared with DS, [b]$P < 0.05$.
Abbreviation: BDNF, brain-derived neurotrophic factor.

https://doi.org/10.2147/NDT.S530265

Table 5 Correlation Between the Average Differences in the Different Variables (Pre- to Post-Treatment)

Variables	MADRS		SNRS		BDNF	
	r	P	r	P	r	P
MADRS	1.000	–	0.597	<0.001[a]	−0.774	<0.001[a]
SNRS	0.597	<0.001[a]	1.000	–	−0.573	<0.001[a]
TST (min)	−0.254	0.025[a]	−0.183	0.109	0.286	0.011[a]
SOL (min)	0.042	0.713	0.072	0.533	−0.049	0.671
The deep sleep continuity score	−0.522	<0.001[a]	−0.501	<0.001[a]	0.478	<0.001[a]
N2 sleep (min)	0.020	0.861	−0.043	0.705	−0.059	0.609
Percentage of N2 sleep (%)	0.227	0.045[a]	0.127	0.267	−0.318	0.005
N3 sleep (min)	−0.593	<0.001[a]	−0.371	0.001[a]	0.622	<0.001[a]
Percentage of N3 sleep (%)	−0.411	<0.001[a]	−0.196	0.085	0.469	<0.001[a]
REM sleep (min)	−0.031	0.789	−0.033	0.772	0.171	0.135
Percentage of REM sleep (%)	0.098	0.394	0.081	0.480	−0.011	0.921
BDNF	−0.774	<0.001[a]	−0.573	<0.001[a]	1.000	–

Notes: [a]$P < 0.05$.
Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; SNRS, Sleep Numeric rating scale; TST, total sleep time; SOL, sleep onset latency; REM, Rapid eye movement; BDNF, brain-derived neurotrophic factor.

<0.001, <0.001, and <0.001, respectively), while showing a positive correlation with the proportion of N2 sleep ($P = 0.045$). Additionally, the average variation in the sleep numerical rating scale is negatively correlated with the continuity of deep sleep, N3 sleep duration, and BDNF levels ($P < 0.001$, 0.001, and <0.001, respectively). The mean change in BDNF was negatively correlated with the change in MADRS, SNRS scores ($P < 0.001$; $P < 0.001$), and significantly positively correlated with the total sleep duration, deep sleep continuity scores, and the duration and proportion of N3 sleep ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively).

AEs

The adverse events experienced by the patients during treatment are shown in Table 6. Most of the adverse events were mild to moderate and could be tolerated by patients or relieved themselves. Oral dryness was the most common adverse event experienced by 13 (32.5%) patients in DS group and 10 (26.32%) patients in DE group, followed by nausea. Additionally, 1 person in DE group experienced a separation sensation during treatment with esketamine, but the symptom was mild and did not require an emergency injection of benzodiazepine; and 2 people experienced nightmares during the therapy.

Table 6 Adverse Events

Adverse Events	DS Group (n = 40)	DE Group (n = 38)
Oral dryness	13(32.5)	10(26.32)
Nausea	2(5.00)	4(10.53)
Vomit	1(2.50)	1(2.63)
Bradycardia	2(5.00)	1(2.63)
Hypotension	2(5.00)	1(2.63)
Dissociation	0(0.00)	1(2.63)
Nightmare	0(0.00)	2(5.26)

Notes: Data are presented as the n(%).

Discussion

Our findings revealed that ESK significantly enhanced the clinical efficacy of DEX in patients with insomnia and depression. The combination therapy reduced depression scores and improved sleep quality, characterized by increased total sleep time, elevated N3 sleep proportion, decreased N2 and REM sleep proportions, and enhanced deep sleep continuity. The mechanism may involve the upregulation of BDNF.

DEX has been reported to improve sleep quality by modulating circadian rhythms, reducing sleep latency, prolonging N2 and N3 sleep duration, and extending total sleep time.[5,6,11,12] Consistent with these reports, our data showed that DEX monotherapy shortened sleep latency, increased total sleep duration, and elevated N2 sleep proportion compared to pretreatment baselines. Nevertheless, patients continued to report subjectively poor sleep quality, likely reflecting depression-related cognitive distortions and impaired deep sleep continuity. While Moon et al demonstrated that six-day intraperitoneal DEX ameliorated depressive behaviors in sleep-deprived mice,[13] our clinical observations revealed some differences. In patients receiving dexmedetomidine monotherapy, MADRS scores showed a numerical decline during the first three days of treatment, though this reduction failed to reach statistical significance. The observed decrease was primarily attributable to improvements in sleep-related items, while mood symptoms exhibited minimal improvement. Discernible mood improvement only emerged at the 30-day assessment. Moreover, MADRS reductions were significantly more modest in the DEX-monotherapy group than in the combination cohort. These results indicate that while DEX monotherapy demonstrates partial benefits for comorbid depression and insomnia, its efficacy is constrained in both magnitude and time course. This supports adjunctive use of rapid-onset antidepressants, particularly in acute care settings requiring therapeutic response.

Patients with comorbid insomnia and depression frequently exhibit limited REM sleep suppression, disrupted sleep continuity, and alterations in NREM sleep, as evidenced by EEG studies.[14] Esketamine, a novel drug approved by the US FDA for treatment-resistant depression,[15] was evaluated in our study using polysomnography (PSG) to assess its potential for improving sleep quality in these patients. Our results demonstrate that ESK treatment not only reduced MADRS scores but also improved sleep architecture, especially when combined with DEX. Moreover, several other studies have since highlighted the sleep-improving effects of ESK. A clinical trial reported that intraoperative low-dose ESK infusion reduced postoperative sleep disruption incidence in patients undergoing gynecological laparoscopic surgery.[16] Furthermore, post-hoc analysis of depressed patients correlated improved sleep metrics after initial ESK infusion with subsequent depressive symptom amelioration.[17]

REM sleep represents a crucial phase within the sleep cycle. During this phase, heightened brain activity occurs alongside muscle relaxation, facilitating essential processes such as emotional regulation and creativity.[18] Nonetheless, an excessively high proportion of REM sleep may elevate the risk of nightmares and emotional instability. In the present study, we found that subanesthetic doses of ESK increased the REM sleep duration in patients while significantly reducing the proportion of REM sleep relative to total sleep duration. Research has established that REM sleep is often accompanied by a decrease in monoaminergic neurotransmitters and an increase in cholinergic tone.[19,20] In this regard, it is noteworthy that ESK can significantly inhibit cholinergic tone and increase monoaminergic neurotransmitters.[21,22] These neurochemical effects suggest that ESK may facilitate a shift from REM sleep towards other sleep stages.

Within the NREM sleep stages, our study found that ESK prolonged the duration of both N2 and N3 sleep, consequently increasing total sleep time (TST). Furthermore, ESK administration decreased the proportion of N2 sleep while increasing the proportion in N3 sleep and enhancing deep sleep continuity in patients. According to previous research, administering a subanesthetic dose of ketamine could increase delta oscillations and induce slow-wave activity (SWA) during NREM sleep.[23–25] The underlying neurobiology, as conceptualized in the "ketamine disinhibition hypothesis", suggests that low-dose ketamine primarily antagonizes NMDA receptors on GABAergic interneurons. This disinhibition leads to a burst of glutamatergic neurotransmission, activating downstream signaling pathways that promote the transcription and expression of BDNF.[26] A positive correlation exists between BDNF levels and SWA, which is considered a reliable EEG marker of NREM sleep intensity.[27] Supporting a causal role for BDNF in sleep homeostasis, unilateral microinjection of BDNF into the rat cortex resulted in higher SWA during NREM sleep specifically in the injected hemisphere.[28] Furthermore, combined pharmacological, optogenetic, and transcriptomic studies indicate that cortical BDNF, acting through tropomyosin receptor kinase B (TrkB) receptors and the cAMP

response element-binding protein (CREB), orchestrates the regulation of SWA.[27] These mechanisms collectively provide a plausible explanation for the NREM sleep enhancements observed in our patients following ESK administration. Regarding sleep latency, we did not observe significant differences between the groups in our study. In previous research, ESK was found to exert a stimulating effect, promoting wakefulness and reducing NREM sleep in mice within 1 hour of being administered. This impact, accompanied by a decrease in EEG δ-power, is thought to stem from NMDA receptor inhibition in the prefrontal cortex (PFC) and the subsequent release of wake-promoting neurotransmitters.[29,30]

Beyond its role in sleep regulation, BDNF plays a significant part in the pathogenesis of depression and the antidepressant mechanisms of ESK. These biological properties, combined with the convenience of clinical sampling and measurement procedures for BDNF, supported its selection as the primary biomarker in this study. The neurotrophic hypothesis of depression posits that disrupted neurotrophic support is a central mechanism underlying the synaptic and circuit alterations associated with major depressive disorder.[31] BDNF, a critical member of the neurotrophin family, is essential for synaptic formation, plasticity, and neuronal survival. The rapid antidepressant effects of ketamine involve an initial increase in BDNF synthesis, followed by activation of the BDNF-TrkB-mTORC signaling pathway. This cascade promotes synaptic protein synthesis and the formation of new dendritic spines, underpinning the sustained antidepressant response.[32] While dexmedetomidine is also known to promote BDNF expression and exert neuroprotective effects,[33] our data revealed significantly higher serum BDNF levels in patients receiving combination therapy (ESK + dexmedetomidine) compared to dexmedetomidine monotherapy. Correlation analyses demonstrated that increases in BDNF levels were associated with reductions in depressive and sleep scale scores, as well as improvements in total sleep time and deep sleep metrics. Collectively, these findings suggest that the upregulation of BDNF may contribute to the observed improvements in both sleep architecture and depressive symptoms in patients receiving the combination treatment.

Previous research has indicated a complex bidirectional relationship between sleep disorders and depression, where both conditions can mutually influence each other.[34] Correlation analysis revealed a significant association between the improvement of depressive symptoms and improvements in sleep quality, particularly in deep sleep quality, in this patient cohort. Emerging evidence also indicates that modifiable lifestyle behaviours-especially regular physical activity and balanced nutrition-can independently improve sleep quality and alleviate depressive symptoms, thereby potentially enhancing the overall efficacy of pharmacological interventions.[35,36] Therefore, it is plausible that for patients experiencing comorbid sleep disorders and depression, targeting depressive symptoms concurrently may produce superior outcomes.

Finally, no serious AEs were observed. Common side effects included oral dryness, nausea, and vomiting. All participants tolerated these symptoms well, and they resolved within 1 hour. Additionally, although some patients experienced fluctuations in BP and HR during treatment, these manifestations were transient and rarely required intervention. This favorable safety profile may be attributable to pre-treatment drug titration, which excluded higher-risk patients and guided appropriate dosing. Lower dosages likely contributed to reduced AE incidence. In the DE group, one patient experienced dissociative symptoms that resolved spontaneously within hours without pharmacological intervention. Moreover, AEs such as Hypertension (HTN), persistent dissociation, and anxiety were not observed in this study. This absence may reflect the study protocol involving slow intravenous infusion of low-dose esketamine (ESK; 0.2 mg/kg) combined with the sedative drug DEX. The present findings provide preliminary evidence supporting the safety of the DEX + ESK combination therapy for patients with comorbid insomnia and depression.

This study has some limitations. Firstly, its single-center design and modest sample size constrain the generalizability and statistical power of the findings, necessitating future multicenter validation with larger cohorts. Secondly, the absence of sustained blinding and a placebo control group presents methodological constraints—while double-blinding was implemented during the initial three-day phase, the transition to an open-label design thereafter, coupled with reliance on patient-reported outcomes at the 30-day endpoint, precludes definitive exclusion of placebo effects, participant/investigator expectation biases, or nonspecific factors including natural disease progression. Future investigations should maintain full blinding protocols with placebo controls while incorporating objective measures such as polysomnography and serum biomarkers for comprehensive efficacy assessment. Thirdly, mechanistic exploration remains limited: although the observed correlation between BDNF and clinical improvement provides initial mechanistic direction, we have not tested causal theory. Furthermore, a single indicator is limiting, and in the future bioindicators could be enriched

to include unmeasured confounders for mechanistic studies through pathway analysis. Finally, the evaluation was restricted to single-treatment administration, leaving unresolved questions regarding sustained efficacy, long-term safety, and tolerability of chronic administration. Consequently, clinical trials assessing repeated and extended treatment regimens are imperative to fully characterize this combination's therapeutic utility.

Conclusion

In conclusion, our findings demonstrate that Esketamine augments the sleep-improving effects of dexmedetomidine in patients with comorbid insomnia and depression. The primary effects observed were included significant reductions in depression scores and enhanced N3 sleep quality. This therapeutic effect may involve upregulation of BDNF. This combination therapy potentially provides a promising novel treatment approach for managing this complex comorbidity.

Abbreviations

(DEX), Dexmedetomidine; (ESK), Esketamine; (PSG), Polysomnography; (BDNF), Brain-Derived Neurotrophic Factor; (AEs), Adverse Events; (REM), Rapid Eye Movement; (MADRS), Montgomery-Asberg Depression Rating Scale; (SNRS), Sleep Numeric Rating Scale; (NREM), Non-Rapid Eye Movement; (NMDA), N-methyl-D-Aspartate; (FDA), Food and Drug Administration; (BC), Breast Cancer; (HAMD), Hamilton Depression Rating Scale; (PSQI), Pittsburgh Sleep Quality Index; (ECG), Electrocardiogram; (BP), Blood Pressure; (EEG), Electroencephalogram; (HR), Heart Rate; (SpO2), oxygen saturation of the pulse; (EOG), Electrooculogram; (EMG), Electromyography; (ELISA), Enzyme-Linked Immunosorbent Assay; (SBP), Systolic Blood Pressure; (DBP), Diastolic Blood Pressure; (ANOVA), Analysis of Variance; (GEE), Generalized Estimating Equations; (TrkB), Tropomyosin receptor kinase B; (mTORC), mechanistic target of rapamycin; (PFC), Prefrontal Cortex; (HTN), Hypertension.

Data Sharing Statement

The data generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University (Ethics No. [2023] YLJSA066, date of approval: 2023-10-24). Informed consent was obtained from both patients and their family members.

Acknowledgments

We thank all the participants in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; 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.

Funding

This study was funded by the Research project of Changzhou Medical Center (NO. CMCC202214) and Changzhou Municipal Health Commission Science and Technology Program Fund (NO. ZD202318).

Disclosure

The authors declare no conflict of interest.

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