META-ANALYSIS

Efficacy and Safety of Gabapentin in Improving Sleep Quality of Patients with Sensory Nervous System Diseases: A Meta-Analysis

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ABSTRACT

Context • Sensory nervous-system diseases are chronic diseases that injury or disease of the somatosensory nervous system causes. Sleep disorders usually accompany these diseases, and in turn, worsen their conditions and form a vicious circle that brings great difficulties in clinical treatment.

Objective • The study intended to systematically evaluate the clinical efficacy and safety of gabapentin in improving the sleep quality of patients with sensory nervous-system diseases using a meta-analysis, so as to provide evidence-based medical evidence for clinical treatment.

Design • The research team performed a comprehensive narrative review by searching the China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal (VIP), WANFANG, Chinese Biomedical Database (CBM), PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases. The search terms included gabapentin, 1-(aminomethyl)-cyclohexaneacetic acid, gabapentin hexal, gabapentin-ratiopharm, sleep, and insomnia.

Setting • The review took place in the Department of Neurology at the First People's Hospital of Linping District in Hangzhou, China.

Outcome Measures • The research team extracted the data from the studies meeting the inclusion criteria and then transferred them into the Review Manager 5.3 software for meta-analysis. The outcome measures included scores: (1) for the improvement in the degree of sleep interference score; (2) for the improvement in sleep quality; (3) for the rate of poor sleep quality; (4) for the rate awakenings of >5 per night; and (5) for the incidence of adverse reactions.

Results • The research team found eight RCTs with 1269 participants, including 637 participants in a gabapentin test group and 632 participants in the placebo control group. The meta-analysis showed that the decrease in the degree of sleep interference [mean deviation (MD) = -0.86, 95% CI: (-0.91, -0.82), $P < .00001$] and the improvement in sleep quality [odds ratio (OR) = 2.64, 95% CI: (1.90, 3.67), $P < .00001$] in gabapentin group were significantly higher than those in placebo group ($P < .05$), while the rate of poor sleep quality [OR = 0.43, 95% CI: (0.23, 0.79), $P = .007$] and the rate of > 5 night awakenings [OR = 0.01, 95% CI: (0.05, 0.70), $P = .01$] in gabapentin group were significantly lower than those in placebo group ($P < .05$). No statistically significant differences existed in the incidence of adverse reactions between the two groups.

Conclusions • Gabapentin is safe and effective in improving the sleep quality of patients with sensory nervous-system diseases. Due to the limitations of sample size and types of diseases in the current study, the field needs multicenter, large-sample, and high-quality RCTs for further validation in the future. (*Altern Ther Health Med.* 2023;29(5):380-385).

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Sleep and wakefulness alternate with each other under the human body's normal physiological conditions. Sleep is an essential physiological necessity for people's lives and plays a crucial role in restoring physical strength, building cognitive ability, and regulating digestion. Sleep disorders have long been a troubling public-health issue, affecting not only patients' quality of life but also raising the risk of cardio-cerebrovascular diseases, increasing the medical burden.[1-3]

Sensory nervous-system diseases are chronic diseases that injury or disease of the somatosensory nervous system causes and primarily manifest as spontaneous pain, touch-induced pain, burning pain, and paresthesia. Some studies have found that sleep disorders usually accompany sensory nervous-system diseases, and in turn, worsen the disease's condition and form a vicious circle that brings great difficulties in clinical treatment.[4-6]

The higher an individual's score on the Pittsburgh Sleep Quality Index (PSQI), the poorer his or her sleep quality is.[7] Two studies found that 80% of participants with sensory nervous-system diseases had poor sleep quality, manifested as higher scores on the PSQI for sleep latency, sleep time, and sleep efficiency than normal people.[8,9] Buysse found that both poor sleep quality and sleep deprivation can increase pain sensitivity and paresthesia, which can further worsen the disease condition.[10]

Gabapentin

Clinicians widely use gabapentin in the treatment of epilepsy, neuropathic pain, and restless legs syndrome, and it can enhance slow-wave sleep, reduce night awakenings, and improve sleep efficiency in patients with primary sleep disorders.[11,12]

Gabapentin, a derivative of gamma-aminobutyric acid (GABA), may improve sleep disorders: (1) by inhibiting the alpha 2 delta (α2δ) protein subunit of voltage-dependent calcium ion (Ca2+) channels in the central nervous system, which reduces Ca2+ influx, weakens release of excitatory transmitters, restores overexcited neurons to normal,[13] inhibits Ca2+ channels in postsynaptic membranes, and blocks abnormal discharge of diseased nerves, thereby ameliorating sleep quality[14,15]; and (2) through antagonizing the *N*-methyl-D-aspartate (NMDA) receptor, which increases the concentration of GABA in the brain to block the transmission of excitatory neurotransmitters.[16,17] Somnolence, dizziness, and asthenia are common adverse reactions to gabapentin.[18]

Vazquez-DeRose et al found that all sleep-promoting neurons use GABA as a neurotransmitter.[19] Through proton magnetic resonance spectroscopy, Winkelman et al discovered that the level of GABA in the brain of patients with primary insomnia was 30% lower than that of the control group, and the researchers confirmed that GABA levels were negatively correlated with the time of awakening from sleep according to the finding of polysomnography.[20]

In addition, studies have also implicated GABA in the occurrence and development of neurosensory diseases.[24,25] Therefore, clinicians consider GABA to be a common neurotransmitter related to the occurrence of neurosensory diseases, such as postherpetic neuralgia, restless legs syndrome, and sleep disorders.[21,22] Thus, neurosensory diseases may cause sleep disorders by reducing the central GABA level.[23,24]

In recent years, multiple studies have explored ways to effectively treat sensory nervous-system diseases and found that some drugs can ameliorate sleep disorders while effectively controlling sensory symptoms.[9-16] At present, multiple studies have reported that gabapentin can improve the symptoms of sleep disorders from sensory nervous-system diseases.[25-32]

However, those studies have had small patient samples and inconsistent assessments. A systematic evaluation is necessary to evaluate the efficacy and safety of gabapentin in improving the sleep disorders of sensory nervous-system diseases.

Current Study

The current study intended to systematically evaluate the clinical efficacy and safety of gabapentin in improving the sleep quality of patients with sensory nervous-system diseases using a meta-analysis, so as to provide evidence-based medical evidence for clinical treatment.

METHODS

Procedures

The review took place in the Department of Neurology at the First People's Hospital of Linping District in Hangzhou, China. The research team performed a comprehensive narrative review by searching the China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal (VIP), WANFANG, Chinese Biomedical Database (CBM), PubMed, Embase, and Cochrane Library and ClinicalTrials.gov databases. The research team retrieved studies from the establishment of a database to September 28, 2021. The research team screened titles and abstracts according to the inclusion and exclusion criteria, further reviewed full texts, and manually searched the references of the literature found.

Inclusion criteria. The review included studies if: (1) they were randomized controlled trials (RCTs), regardless of the use of a blinding method; (2) the participants were patients with sensory nervous-system diseases, regardless of disease type, race, nationality, age, or gender; (3) they treated participants in the intervention group with gabapentin and those in the control group with a placebo, without limitations on the dosage and course of treatment; and (4) they evaluated the improvement in the sleep quality.

Exclusion criteria. The review excluded studies if: (1) they weren't written in Chinese or English; (2) they were duplicates, experience summaries, case studies, reviews, literature with little or incomplete information, or conference minutes; (3) they had fewer than 20 participants in total; (4) they didn't use a placebo for the control group; or (5) they used combined medications.

Search terms. The search terms included gabapentin, 1-(aminomethyl)-cyclohexaneacetic acid, gabapentin hexal, gabapentin-ratiopharm, sleep, and insomnia.

Data extraction. From the included literature, the research team collected: (1) basic data, which included the first author, year of publication, type of disease, intervention measures, number and age of participants, duration of treatment, and follow-up time; and (2) the data from the outcome measures, which included scores for the improvement in the degree of sleep interference, the improvement in sleep quality, the rate of poor-sleep quality, the rate of awakenings of >5 times per night, and the incidence of adverse reactions.

If the outcome measures in the literature were unclear or missing, the investigators contacted the corresponding author as often as possible to obtain accurate original data and eliminated literature for which they couldn't obtain data or information.

Quality evaluation The research team evaluated the quality of the included literature using the Cochrane Collaboration's tool for assessing risk of bias 5.3.0, mainly including the generation of random sequences, allocation concealment, blinding of subjects and operators, blinding of

Table 1. Basic characteristics of the RCTs. For the outcome measures, 1 = improvement in degree of sleep interference; 2 = improvement in sleep quality; 3 = rate of poor sleep quality; 4 = rate of awakenings of >5 per night; and 5 = incidence of adverse reactions

First Author, Publication Year	Type of Disease	Group	Intervention	Number of Participants N=1269 N (Male/ Female)	Age, y Mean ± SD	Treatment Duration	Follow-up Time	Outcome Measure
Backonja, 2011[9]	Postherpetic neuralgia	Intervention	Gabapentin 1200 mg	47 (22/25)	65.0 ± 12.32	14 d	33 d	1 and 5
		Control	Placebo	54 (27/27)	64.0 ± 12.69	14 d	33 d	
Bogan, 2010[10]	Restless legs syndrome	Intervention	Gabapentin 1200 mg	96 (62/34)	50.7 ± 11.68	12 wks	36 wks	2, 3, 4, and 5
		Control	Placebo	97 (52/45)	52.2 ± 12.13	12 wks	36 wks	
Irving, 2009[11]	Postherpetic neuralgia	Intervention	Gabapentin 1800 mg	52 (23/29)	68 ± 12.9	4 wks	8 wks	1 and 5
		Control	Placebo	51 (25/26)	69 ± 11.5	4 wks	8 wks	
Lee, 2011[12]	Restless legs syndrome	Intervention	Gabapentin 1200 mg	111 (52/59)	49.5 ± 12.67	12 wks	12 wks	2, 3, 4, and 5
		Control	Placebo	96 (59/37)	49.1 ± 12.19	12 wks	12 wks	
Wallace, 2010[13]	Postherpetic neuralgia	Intervention	Gabapentin 1800 mg	136 (60/76)	68 ± 11.8	10 wks	10 wks	1 and 5
		Control	Placebo	134 (79/55)	66 ± 12.6	10 wks	10 wks	
Walters, 2009[14]	Restless legs syndrome	Intervention	Gabapentin 1200 mg	33 (11/22)	50.2 ± 11.54	14 d	14 d	2, 3, 4, and 5
		Control	Placebo	33 (17/16)	49.4 ± 10.97	14 d	14 d	
Winkelman, 2011[15]	Restless legs syndrome	Intervention	Gabapentin 1200 mg	53 (unknown)	Unknown	12 wks	12 wks	2
		Control	Placebo	61 (unknown)	Unknown	12 wks	12 wks	
Gong Zhiyi, 2008[16]	Postherpetic neuralgia	Intervention	Gabapentin 1800 mg	109 (68/41)	67.49 ± 11.55	6 wks	6 wks	2 and 5
		Control	Placebo	106 (54/52)	65.25 ± 12.11	6 wks	6 wks	

outcome assessors, incomplete outcome data, selective reporting, and other biases. The team classified each item into low, unclear, or high risk of bias.[33] Two reviewers independently evaluated the quality of the studies. In the case of disagreements, they consulted a third reviewer.

Statistical Analysis

The research team extracted the data from the studies meeting the inclusion criteria and then transferred them into the Review Manager 5.3 software to conduct the meta-analysis. The team used: (1) the mean deviation (MD) for the effect analysis for the continuous variables, (2) the odds ratio (OR) for the effect analysis for categorical variables, and (3) a 95% confidence interval (CI) for interval estimation.

The team tested the included studies using the chi-squared (χ^2) test for heterogeneity. The team performed the meta-analysis using the fixed-effects model if no statistical heterogeneity existed among the studies' results ($P > .10$, $I^2 \leq 50\%$). Otherwise, the team performed the meta-analysis using the random-effects model and analyzed the source of heterogeneity.

The team repeatedly analyzed the same indicator, deleted one study each time to show its impact on the combined effect, and then evaluated the results using sensitivity analysis. Meanwhile, the team performed subgroup analysis and conducted heterogeneity analysis on the subgroups. $P < .05$ indicated statistically significant data. If the results included more than 10 studies, the team intended to evaluate publication bias using the inverted funnel plot.[34]

RESULTS

Included Studies

Figure 1 shows the literature screening process. The initial retrieval obtained 1761 relevant studies, and the research team retrieved three manually, for a total of 1764. Initial screening reduced that number to 1529, with the additional screening reducing that number to 10. Two of those studies had no outcome measures, and the meta-analysis included eight studies.[25-32]

The final studies included 1269 participants, including 637 participants in the gabapentin test groups and 632 participants in the placebo control groups. Table 1 shows the studies' basic characteristics.

Figure 1. Flow Diagram of Literature Screening Process

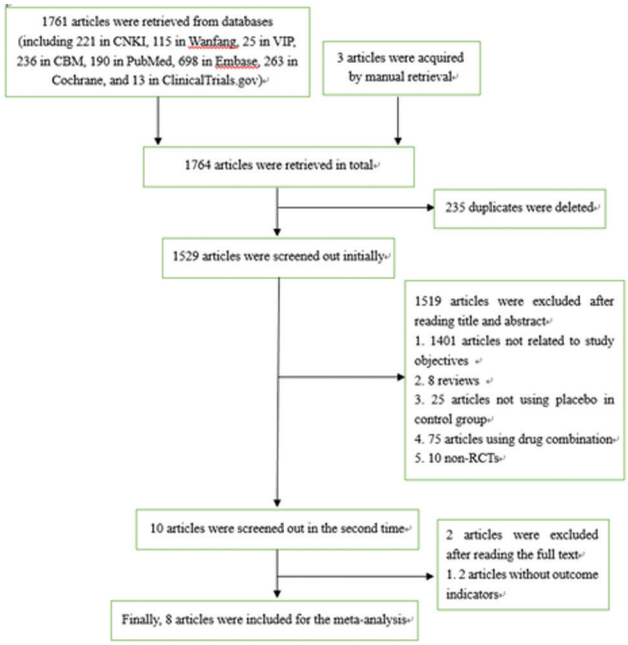


Figure 2. Risk of Bias

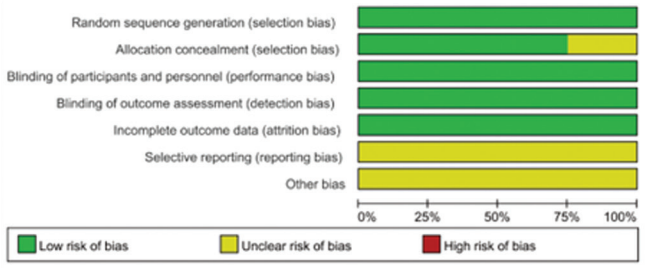
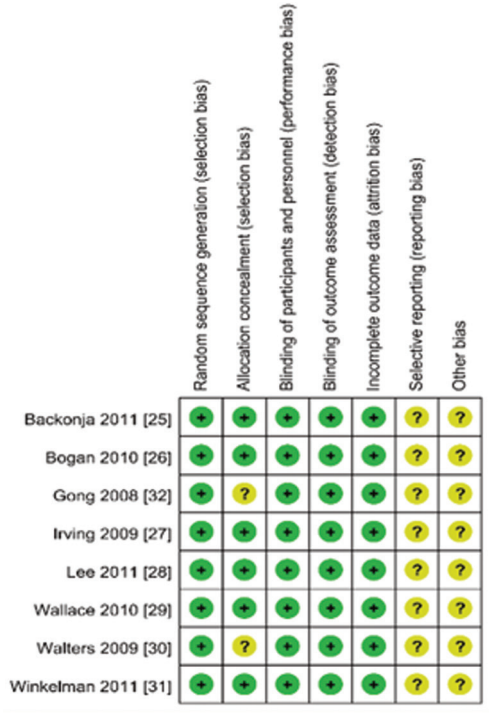


Figure 3. Summary for Risk of Bias



Quality Evaluation

All eight included studies were RCTs with complete data (Figures 2 and 3). Six studies described allocation concealment,[25-29,31] but two studies didn't.[30,32] None of the studies mentioned selective reporting or other sources of bias.[25-32]

Degree of Sleep Interference

Three studies with 474 participants reported the scores for the changes in the degree of sleep interference postintervention (Figure 4).[25,27,29] No statistically significant heterogeneity existed among the studies ($P = .42$, $I^2 = 0\%$). The results of the fixed-effects model, combined with effect sizes, showed that the decrease in the degree of sleep interference was significantly higher for the gabapentin group than that of the placebo group [MD = -0.86, 95% CI: (-0.91, -0.82), $P < .00001$].

Sleep Quality

Four studies with 794 participants reported the sleep quality postintervention (Figure 5).[26,28,30-32] No statistically significant heterogeneity existed among the studies ($P = .15$, $I^2 = 40\%$). The results of the fixed-effects model, combined with effect sizes, showed that the sleep quality was significantly lower in the gabapentin group than that in the placebo group [OR = 2.64, 95% CI: (1.90, 3.67), $P < .00001$].

Rate of Poor Sleep Quality

Three studies with 465 participants reported the changes in the rate of poor sleep quality postintervention (Figure 6).[26,28,30] No statistically significant heterogeneity existed among the studies ($P = .14$, $I^2 = 48\%$). The results of the fixed-effects model, combined with effect sizes, showed that the rate of poor sleep quality was significantly lower in the gabapentin group than that in the placebo group [OR = 0.43, 95% CI: (0.23, 0.79), $P = .007$].

Figure 4. Comparison of the Decreases in the Degree of Sleep Interference Postintervention Between the Intervention and Control Groups in the Meta-analysis

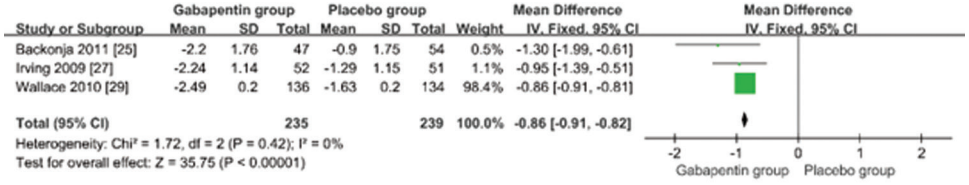
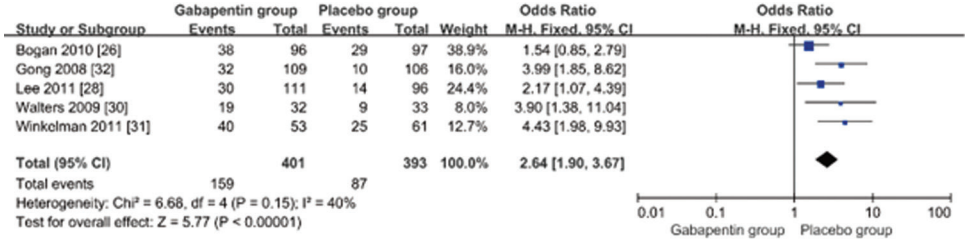


Figure 5. Comparison of the Sleep Quality Postintervention Between the Intervention and Control Groups in the Meta-analysis



Awakenings of >5 Per Night

Three studies with 465 participants reported the rate of awakenings of >5 per night (Figure 7).[26,28,30] No statistically significant heterogeneity existed among the studies (P = .64, I^2 = 0%). The results of the fixed-effects model, combined with effect sizes, showed that the rate of awakenings of >5 per night was significantly lower in the gabapentin group than that in the placebo group [OR = 0.01, 95% CI: (0.05, 0.70), P = .01].

Adverse Reactions

Seven studies with 1155 participants reported adverse reactions (Figure 8).[25-29,32] Statistically significant heterogeneity existed among the studies (P = .11, I^2 = 60.7%). The results of the random-effects model, combined with effect sizes, showed that no statistically significant difference existed in the incidence rate of adverse reactions between the gabapentin and placebo groups [OR = 1.17, 95% CI: (0.56, 2.45), P = .67].

Figure 8 1.1.1 shows a subgroup analysis based on the dosage of gabapentin that found that no statistically significant difference existed in the incidence rate of adverse reactions between the 1200 mg/d gabapentin group and the placebo group [OR = 0.68, 95% CI: (0.24, 1.98), P = .48].

In the sensitivity analysis, the combined effect had no directional changes after the research team excluded the included studies one by one, suggesting that the results of the subgroup analysis were basically stable.

In addition, Figure 8 1.1.2 shows that no statistically significant difference existed in the incidence rate of adverse reactions between the 1800 mg/d gabapentin and placebo groups [OR = 1.17, 95% CI: (0.56, 2.45), P = .11]. In the sensitivity analysis, the combined effect had no directional changes after the research team excluded the included studies one by one, indicating that the subgroup analysis results were basically stable.

Publication Bias

Because the review included fewer than 10 studies, the research team didn't analyze publication bias.

Figure 6. Comparison of the Rate of Poor Sleep Quality Postintervention Between the Intervention and Control Groups in the Meta-analysis

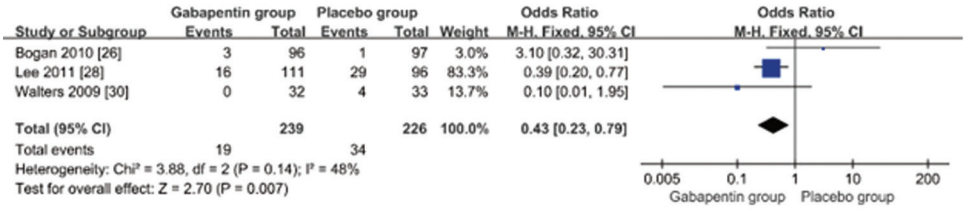


Figure 7. Comparison of the Rate for >5 Night Awakenings Postintervention Between the Intervention and Control Groups in the Meta-analysis

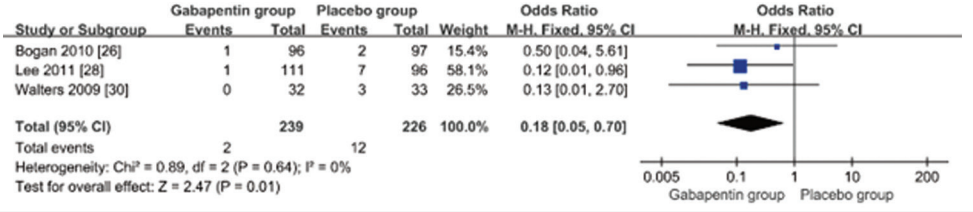
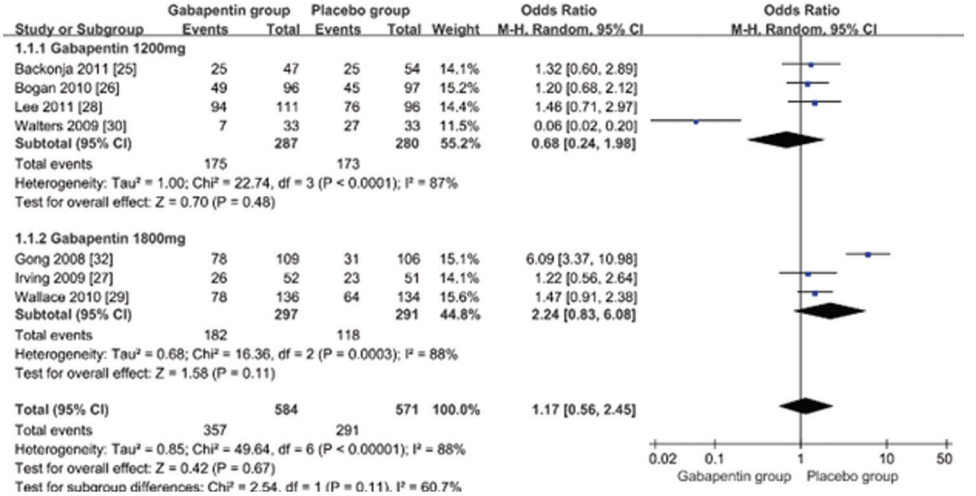


Figure 8. Comparison of Adverse Reactions in the Intervention and Control Groups in the Meta-analysis



DISCUSSION

The current study's research team hope to provide evidences for clinical treatment of sensory nervous system diseases. Postintervention, the gabapentin group's improve in the degree of sleep interference, sleep quality, rate of poor sleep quality and rate of awakenings of >5 per night were significantly better than those of the placebo group. Indicates that gabapentin can improves sleep quality by elevating sleep efficiency and decreasing spontaneous arousal, and then improving the quality of life of patients. However, due to the limited number of studies included, subgroup analysis of the efficacy of different doses of gabapentin was not possible. The incidence rate of adverse reactions wasn't significantly different for the 1200 mg/d and 1800 mg/d gabapentin groups from that of the control group. Seven studies were included in the analysis of adverse reactions. The incidence of adverse reactions in the gabapentin group was 61% (357/584), while the incidence of adverse reactions in the placebo group was 51% (291/571). It can be seen that the

incidence of adverse reactions in the gabapentin group was higher than that in the placebo group, and the adverse reactions showed an upward trend with increasing dosage. Although the difference in adverse reactions between the two groups was not statistically significant, However, it is still necessary to closely monitor adverse reactions when using the gabapentin group.

The study had some limitations: (1) the sample size was small in most studies; (2) the dosages of gabapentin, durations of treatment, and follow-up times were inconsistent among the studies; (3) the meta-analysis analyzed only two kinds of neurosensory diseases; (4) the types of diseases included in the 8 articles weren't the same, which may have affected the conclusions. All of the above factors may have affected the accuracy of the meta-analysis' conclusions.

CONCLUSIONS

Gabapentin is safe and effective in improving the sleep quality of patients with sensory nervous-system diseases. Due to the limitations of sample size and types of diseases in the current study, the field needs multicenter, large-sample, and high-quality RCTs for further validation in the future.

AUTHORS' DISCLOSURE STATEMENT

The authors had no potential conflicts of interest to report relevant to the review.

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