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Original Article

Wuling capsules alleviate sleep disorders in patients receiving maintenance hemodialysis

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Abstract: Objective: To determine the clinical effect of Wuling capsules on sleep disorders in patients receiving maintenance hemodialysis. Methods: The data of 114 end-stage renal disease patients with sleep disorders who received maintenance hemodialysis in JiuJiang hospital of traditional Chinese medicine between February 2020 and January 2022 were retrospectively analyzed. Among them, 60 patients treated with Wuling capsule were assigned to a research group, and the other 54 patients treated with estazolam were enrolled into a control group. The two groups were compared in terms of clinical efficacy and adverse reactions after treatment, as well as Pittsburgh sleep quality index (PSQI), fatigue state, and negative emotions before and after treatment. Results: The research group showed a significantly higher overall response rate than the control group, and presented a significantly lower total incidence of adverse reactions than the control group. After treatment, the research group exhibited notably lower scores of PSQI, and physical as well as mental fatigue than the control group. In addition, after treatment, the research group demonstrated evidently lower anxiety and depression scores than the control group. No significant difference was found in prognosis between the two groups after 6 months of treatment. An older age, longer duration of dialysis, lower albumin level, higher serum phosphorus, and skin pruritus were independent risk factors for unfavorable prognosis. Conclusion: Wuling capsules exhibited good efficacy and safety in the treatment of sleep disorders in patients receiving maintenance hemodialysis as compared to estazolam, so this capsule is worthy of further clinical application.

Keywords: Wuling capsule, maintenance hemodialysis, sleep disorders, depression

Introduction

Chronic kidney disease (CKD) is a structural and functional disorder of the kidneys, which can be triggered by various causes. It affects approximate 10% of adult population worldwide and is among the top 20 leading causes of death globally [1]. The typical clinical features of CKD include increased serum creatinine, elevated uremic nitrogen, and decreased renal excretion function, which may eventually trigger end-stage renal disease (ESRD) [2]. Patients with ESRD are prone to various complications, such as cardiovascular diseases, infections, malnutrition, and metabolic diseases, most of which need dialysis treatment [3, 4]. Hemodialysis is a primary treatment method for renal replacement therapy and serves as a substitute for the kidney's excretion function to ensure normal metabolism in the body and prolong the lifespan of patients [5]. Sleep disorders are frequently seen in patients receiving hemodialysis. According to statistics, up to 80% of patients receiving hemodialysis suffer sleep disorders [6]. Sleep disorders not only trigger fatigue and lower the quality of life in patients, but also increase the risk of depression, low immune system and cardiovascular conditions, compromising their prognosis [7, 8]. Patients undergoing hemodialysis who experience sleep disorders are four times more likely to develop depression than those without sleep disorders [9]. Therefore, timely treatment and interventions are required to prevent unfavorable prognosis in these patients.

Currently, the treatment drugs for sleep disorders are mainly sedative and hypnotic drugs.

Long-term use of them will give rise to dependence and addiction, and withdrawal of them will trigger insomnia rebound, withdrawal symptoms and daytime residual effects, which may even result in cognitive impairment in severe cases [10, 11]. Wulingshen, a ginseng, is a kind of fungal sclerotia, with the effects of heart invigoration and diuresis, which can be adopted to treat diseases including insomnia and various types of bleeding. Wuling capsule is formulated using Wulingshen powder and possesses the effects of improving sleep, as well as combating anxiety, depression, and fatigue [12]. Wulingshen contains flavonoids, triterpenoids, saponins and polysaccharides, which can play a role by regulating neurotransmitters, exhibiting antioxidant and anti-inflammatory effects, as well as promoting sedation [13, 14]. Divate et al. [15] have reported that Wulingshen extract could restore mitochondrial membrane potential by inhibiting the release of lactate dehydrogenase and reducing DNA damage, prevent abnormal cell apoptosis by up-regulating Bcl-2 and down-regulating Bax and cystatin-3, scavenge DPPH free radicals, and inhibit lipid peroxidation and antioxidant activity, so as to play a neuroprotective effect.

Zhou et al. [16] pointed out that compared with benzodiazepine drugs, Wuling capsule substantially alleviated sleep disorders in adult patients with insomnia, without triggering obvious adverse reactions. However, the effect of Wuling capsule on sleep disorders is rarely studied in patients receiving maintenance hemodialysis.

Accordingly, through retrospective analysis, this study explored the clinical efficacy and safety of Wuling capsule in the treatment of sleep disorders in patients receiving maintenance hemodialysis.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria: Patients who were diagnosed with ESRD according to the results of clinical, pathological and imaging examinations [17]; patients who had received maintenance hemodialysis for over 3 months; patients with a Pittsburgh sleep quality index (PSQI) score of greater than 7 points; patients who met the diagnostic criteria of insomnia, and patients with detailed medical records.

Exclusion criteria: Patients with mental illness or cognitive impairment according to examinations; patients with cardiovascular or respiratory diseases; patients with secondary insomnia due to diseases of the endocrine system or organic diseases of body or brain; patients who suffered sleep disorders before hemodialysis; patients who were allergic to the drugs adopted in this study; patients with poor compliance during therapy.

Research subjects

According to the above criteria, we retrospectively collected and studied the case data of 114 ESRD patients who underwent maintenance hemodialysis in JiuJiang hospital of traditional Chinese medicine from February 2020 to January 2022. Among them, 60 patients treated with Wuling capsule were assigned to a research group, and the other 54 patients treated with estazolam were enrolled into a control group. The study was approved by the medical ethics committee of JiuJiang hospital of traditional Chinese medicine (Ethnical approval number: 20190132).

Therapeutic regimens

All the subjects were treated with regular hemodialysis with a Germany Fresenius 4008s hemodialysis machine, with dialysate flow maintained at 500 mL/min, blood flow maintained at 250 mL/min-300 mL/min, and unfractionated heparin (Ma'anshan Fengyuan Pharmaceutical Co., Ltd. Approval number: 20191108) or low molecular weight heparin (shenzhen SCIPROGEN Bio-pharmaceutical Co., Ltd. Approval number: 20191216) as the anticoagulant, for 4 hours each time, three times a week. The control group was given estazolam (Shanghai Sine Pharmaceutical Laboratories Co., Ltd., Approval number: 2020-0102) before going to bed, 1 mg each day. The research group was given oral Wuling capsules (Zhejiang Jolly Pharmaceutical Co., Ltd., Approval number: 20191014, specification: 0.33 g), 3 capsules each time, 3 times a day. Patients in both groups were treated for 4 consecutive weeks.

Data collection

The clinical information, laboratory test results and blood transfusion information of patients were collected from the Hospital Information System and Laboratory Information System, including age, gender, duration of dialysis, serum creatinine, urea nitrogen, hemoglobin, albumin, serum calcium, serum phosphorus, comorbid skin pruritus, primary disease, clinical symptoms, as well as scores of PSQI, fatigue scale-14 (FS-14), Hamilton anxiety and depression scale (HAMA), and Hamilton depression scale (HAMD).

Evaluation criteria of efficacy

The treatment efficacy in the patients was evaluated after 4 weeks of treatment. Markedly effective: the insomnia symptoms were greatly relieved, and the PSQI score was reduced by 50% or more. Effective: the insomnia symptoms were alleviated, and the PSQI score was reduced by 25%-49%. Ineffective: the insomnia symptoms were not alleviated, and the PSQI score was reduced by less than 24%. Overall response rate = markedly effective rate + effective rate.

Evaluation criteria for prognosis

The prognosis was evaluated according to the PSQI score of all patients after 6 months of treatment. Unfavorable prognosis: PSQI score > 7 points after 6 months of treatment; favorable prognosis: PSQI score ≤ 7 points after 6 months of treatment. All patients were followed up through outpatient clinic data or telephone.

Outcome measures

Primary outcome measures: (1) The efficacy was compared between the two groups. (2) The adverse reactions in the two groups were counted and analyzed.

Secondary outcome measures: (1) The PSQI was adopted to evaluate the sleep status of patients before and after intervention. PSQI covers 7 dimensions (sleep quality, time before falling asleep, sleep time, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction) with 19 items, with a total score of 21 points, and a higher score indicates worse sleep quality [18]. (2) The FS-14 was used to evaluate the fatigue of patients before and after treatment. The scale covers two dimensions: physical fatigue and mental fatigue, with a total score of 14 points, 0-8 points for physical fatigue and 0-6 points for mental fatigue. A higher score indicates more serious fatigue [19]. (3) HAMA and HAMD scales were adopted for evaluating the patients' anxiety and depression, respectively, before and after intervention. The HAMA scale includes 14 items, and the results are classified into normal situation (< 7 points), possible anxiety (8-13 points), affirmed anxiety (14-20 points), obvious anxiety (21-28 points) and severe anxiety (≥ 29 points) [20]. The HAMD covers 24 items, and the results are classified into normal situation (< 8 points), mild depression (8-19 points), moderate depression (20-34 points) and severe depression (≥ 35 points) [21]. (4) The prognosis of the patients 6 months after treatment was evaluated, and the risk factors impacting the prognosis were explored through multivariate logistics regression analysis.

Statistical analyses

All the data were analyzed through SPSS 23.0 software. The quantitative data were described by mean ± SD, and their inter-group comparison and intra-group comparisons were conducted using independent sample t test and paired t test, respectively. Qualitative data were represented by percentage (%), and their inter-group comparison was conducted using the χ^2 test. Logistic regression test was adopted to analyze the risk factors affecting the prognosis of the patients. $P < 0.05$ indicates a significant difference.

Results

Baseline data

The two groups were not significantly different in terms of age, gender, duration of dialysis, serum creatinine, urea nitrogen, hemoglobin, albumin, serum calcium, serum phosphorus, comorbid skin pruritus, and primary diseases ($P > 0.05$, **Table 1**).

Comparison of efficacy between the two groups

The research group showed a significantly higher overall response rate than the control group (90.00% *vs.* 74.07%, $P < 0.05$, **Table 2**).

Table 1. Baseline data

	Research group (n=60)	Control group (n=54)	χ^2/t	*P* value
Age (year)	52.6±7.6	52.4±7.0	0.146	0.885
Gender			0.340	0.560
Male	38 (63.33)	37 (68.52)		
Female	22 (36.67)	17 (31.48)		
Duration of dialysis (months)	32.3±11.3	31.6±11.1	0.333	0.739
Serum creatinine (μmol/L)	635.73±68.72	631.45±67.79	0.334	0.739
Urea nitrogen (mmol/L)	17.43±4.92	18.04±4.22	0.707	0.481
Hemoglobin (g/L)	92.70±8.06	91.29±7.94	0.939	0.350
Albumen (g/L)	33.57±4.03	34.70±4.27	1.453	0.149
Serum calcium (mmol/L)	2.39±0.47	2.53±0.49	1.556	0.123
Serum phosphorus (mmol/L)	1.90±0.44	1.89±0.38	0.129	0.897
Comorbid skin pruritus			0.253	0.615
Yes	49 (81.67)	46 (85.19)		
No	11 (18.33)	8 (14.81)		
Primary diseases			1.504	0.681
Chronic nephritis	31 (51.67)	22 (40.74)		
Hypertensive nephropathy	9 (15.00)	9 (16.67)		
Diabetic nephropathy	13 (26.67)	14 (25.93)		
Others	7 (11.67)	9 (16.67)		

Table 2. Efficacy in the two groups

	Research group (n=60)	Control group (n=54)	χ^2	P
Markedly effective	33 (55.00)	16 (29.63)		
Effective	21 (35.00)	24 (44.44)		
Ineffective	6 (10.00)	14 (25.93)		
Overall response rate	54 (90.00)	40 (74.07)	4.983	0.026

Table 3. Adverse reactions

	Research group (n=60)	Control group (n=54)	χ^2	*P* value
Dizziness and headache	2 (3.33)	4 (7.41)		
Somnolence	0 (0.00)	2 (3.70)		
Nausea	1 (1.67)	2 (3.70)		
Mouth dryness	2 (3.33)	4 (7.41)		
Total adverse reactions	5 (8.33)	12 (22.22)	4.321	0.038

Comparison of safety between the two groups

The research group exhibited a significantly lower total incidence of adverse reactions than the control group (P < 0.05, **Table 3**).

Comparison of sleep quality between the two groups

Before treatment, the PSQI scores were not greatly different between the two groups in all 7 dimensions, while after treatment, the scores in the research group were significantly lower than those in the control group (P < 0.05, **Figure 1**).

Comparison of fatigue state between the two groups before and after treatment

The fatigue status of the two groups was compared before and after treatment by investigating the FS-14 scale score. Before treatment, the two groups were not greatly different in the scores of physical fatigue and mental fatigue, while after treatment, the scores of both physical and mental fatigue decreased notably in the two groups, with evidently lower scores in the research group than those in the control group (**Figure 2**).

Comparison of negative emotions between the two groups before and after treatment

Before treatment, the two groups were not greatly different in HAMA and HAMD scores, while after treatment, the HAMA and HAMD

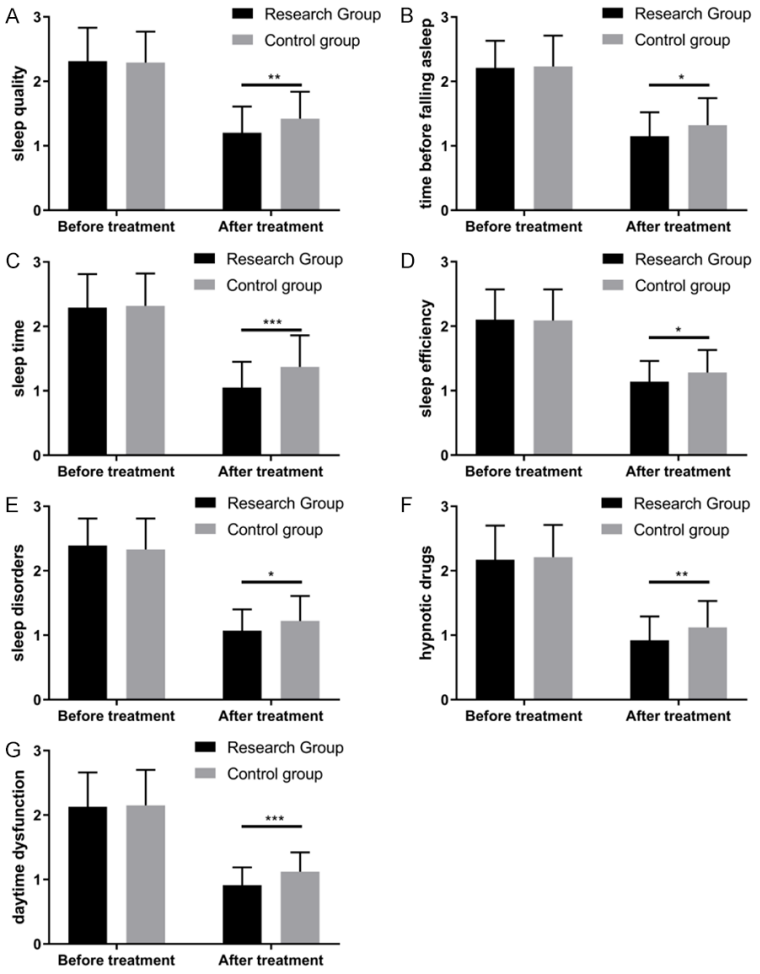

Figure 1. The changes in sleep quality before and after treatment. A-G. After treatment, the research group exhibited notably lower scores in sleep quality, time before falling asleep, sleep time, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction than the control group (P < 0.05). Note: *P < 0.05, **P < 0.01, ***P < 0.001.

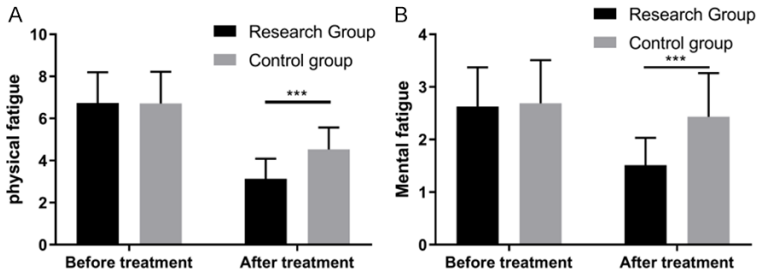

Figure 2. The fatigue state in the two groups before and after treatment. A. After treatment, the research group exhibited notably lower physical fatigue score than the control group (P < 0.001). B. After treatment, the research group showed notably lower mental fatigue score than the control group (P < 0.001). Notes: ***P < 0.001.

scores of both groups decreased notably, with significantly lower scores in the research group than those in the control group (**Figure 3**).

Univariate analysis of factors affecting the prognosis in the two groups

There were 48 patients (80.00%) with a favorable prognosis in the research group and 36 patients (66.67%) with a favorable prognosis in the control group, and the difference between them was not significant (P > 0.05). The patients were grouped into a favorable prognosis group and unfavorable prognosis group based on their prognosis. Univariate analysis revealed notable differences between these two groups in age, duration of dialysis, albumin, serum phosphorus and skin pruritus (**Table 4**).

Multivariate analysis

According to multivariate logistics regression analysis, an older age, longer duration of dialysis, lower albumin level, higher serum phosphorus, and skin pruritus were independent risk factors for unfavorable prognosis in patients (**Table 5**).

Discussion

Sleep disorders in patients undergoing continuous hemodialysis can be influenced by various factors, including the dialysis treatment procedure, medications, melatonin levels, and metabolic disorders [22]. The disorder can disrupt the normal sleep-wake cycle and contribute to changes in sleep patterns and arousal rhythms in the patients. It also has various other manifestations, including insomnia, sleep apnea syndrome, daytime sleepiness, periodic body movement, restless sleep, and dreaminess, among which insomnia is seen the most [23]. Lack of sleep and insomnia may accelerate the

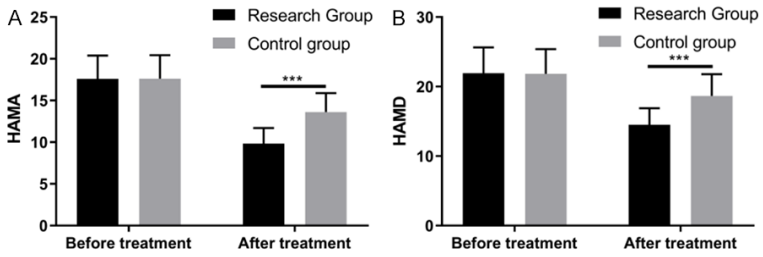

Figure 3. The negative emotions in the two groups before and after treatment. A. After treatment, the research group exhibited notably lower HAMA score than the control group ($P < 0.001$). B. After treatment, the research group exhibited notably lower HAMD score than the control group ($P < 0.001$). Notes: ***$P < 0.001$. HAMA: Hamilton anxiety rating scale, HAMD: Hamilton depression rating scale.

progression of ESRD and increase the mortality in patients undergoing maintenance dialysis [24]. Eloot et al. [25] evaluated the sleep treatment in patients undergoing different dialysis methods, and found no significant difference in sleep quality between them. It indicates that it is difficult to alleviate patients' sleep disorders by changing dialysis methods, so other measures are required for the treatment of sleep disorders.

In this study, the application effects of Wuling capsule and estazolam on sleep disorders were compared. According to the results, Wuling capsule was associated with a notably higher overall response rate than estazolam. After treatment, the PSQI scores in 7 dimensions and the FS-14 scores in physical and mental fatigue were significantly lower in patients given Wuling capsule than in patients given estazolam. The results suggest a better effect of Wuling capsule on improving sleep quality and fatigue state. Estazolam is a short-acting benzodiazepine, which takes a hypnotic effect by strengthening glutamate and γ-aminobutyric acid (GABA) receptors in the central nervous system. Estazolam has the characteristics of quick action and strong hypnotic effect, but the development of drug resistance is a concern [26]. The main component of Wuling capsule, Wulingshen powder, contains various amino acids, adenosine, polysaccharides, vitamins, and trace elements. Reportedly, Wuling capsule increased the content of GABA in the brain, promoted the activity of glutamate dehydrogenase, the synthesis of inhibitory neurotransmitter GABA and the binding activity of GABA receptor in the cerebral cortex, thus enhanced central sedation and regulated the central nervous function [27]. A multicenter randomized controlled study by Lin et al. [28], revealed that Wuling capsule significantly improved the quality of sleep and quality of life in patients, which is similar to our results.

Patients who received estazolam may have adverse reactions such as drowsiness, fatigue, head distension and mouth dryness, and a small number of patients suffered from them in this study, while a notably lower total incidence of adverse reactions was observed in patients taking Wuling capsules. Our results indicate the safety profile of Wuling capsules. The reason may be that estazolam produces sedation, hypnosis and anti-anxiety effects by inhibiting the activity of the central nervous system, but its influence on the central nervous system may cause adverse reactions in the course of its use [29]. In contrast, Wuling capsule plays a therapeutic effect through glycoside, adenosine, amino acids and other bioactive components, so patients have better tolerance and milder adverse reactions [30].

Depression and anxiety are common psychological disorders in patients receiving blood dialysis. Reportedly, depression and anxiety are strongly associated with insomnia and fatigue, and increased fatigue score and insomnia score in depressed patients will aggravate their depression. So, depression and anxiety also need to be concerned in dialysis patients [31]. This study compared the HAMA and HAMD scores of the two groups before and after treatment, and found significantly lower HAMA and HAMD scores in patients treated with Wuling capsule than in those treated with estazolam after treatment. This indicates that Wuling capsules can better alleviate depression and anxiety in dialysis patients. The reason for the better alleviation of depression and anxiety may be attributed to the relief of sleep disorder symptoms. Zheng et al. [32] revealed that Wuling capsule effectively enhanced the effect of antidepressants possibly through anti-inflammation. Li et al. [33] found that Wuling capsule effectively alleviated the helplessness and depression in mouse models of acquired help-

Table 4. Univariate analysis

	Favorable prognosis group (n=84)	Unfavorable prognosis group (n=30)	χ^2/t	P
Age (years)	51.4±6.9	55.4±7.7	2.643	0.009
Gender			0.109	0.741
Male	56 (66.67)	19 (63.33)		
Female	28 (33.33)	11 (36.37)		
Duration of dialysis (months)	30.0±10.7	37.4±10.8	3.244	0.002
Serum creatinine (μmol/L)	631.96±72.56	638.59±54.07	0.457	0.649
Urea nitrogen (mmol/L)	17.84±4.83	17.38±3.89	0.470	0.640
Hemoglobin (g/L)	92.76±8.29	90.00±6.82	1.635	0.105
Albumin (g/L)	34.79±3.92	32.18±4.30	3.051	0.003
Serum calcium (mmol/L)	2.44±0.50	2.51±0.44	0.678	0.499
Serum phosphorus (mmol/L)	1.84±0.43	2.06±0.30	2.583	0.011
Skin pruritus			6.584	0.010
Yes	48 (57.14)	25 (83.33)		
No	36 (42.86)	5 (16.67)		
Primary			1.856	0.603
Chronic nephritis	38 (45.24)	15 (50.00)		
Hypertensive nephropathy	13 (15.48)	5 (16.67)		
Diabetic nephropathy	19 (22.62)	8 (26.67)		
Others	14 (16.67)	2 (6.67)		
Treatment mode			2.606	0.107
Wuling capsule	48 (57.14)	12 (40.00)		
Estazolam	36 (42.86)	18 (60.00)		

Table 5. Multivariate analysis

Factors	B	S.E	Wald	Sig.	Exp (B)	95% CI of EXP (B).	
						Lower limit	Upper limit
Age	0.076	0.037	4.238	0.04	1.079	1.004	1.159
Duration of dialysis	0.072	0.026	7.615	0.006	1.075	1.021	1.131
Albumin	-0.213	0.068	9.664	0.002	0.808	0.707	0.924
Serum phosphorus	1.511	0.697	4.703	0.030	4.529	1.156	17.738
Skin pruritus	1.554	0.632	6.045	0.014	4.732	1.371	16.335

lessness and depression. This mechanism of action may be associated with the improvement of mitochondrial autophagy.

We evaluated the prognosis of the two groups after 6 months. According to the results, the research group had a slightly higher rate of favorable prognosis than the control group, but the difference was not significant. According to multiple logistics regression analysis, an older age, longer duration of dialysis, lower albumin level, higher serum phosphorus, and skin pruritus were independent risk factors for unfavorable prognosis. Accordingly, more attention should be paid to patients with these risk factors to reduce the risk of unfavorable prognosis.

This study also has some limitations. First of all, there was no blank control group, so it is difficult to ascertain the specific impact of the disease itself on the study outcomes. Secondly, no treatment plan involving the combination of drugs was adopted, so it is not possible to determine whether the combination of the two drugs has a synergistic effect on the therapy of sleep disorders. We hope to conduct a combination therapy in future research to explore

whether the combination is feasible. Finally, because of the short treatment cycle, the effects and adverse reactions of long-term use of Wuling capsules remain unclear.

To sum up, this study compared Wuling capsules and estazolam in the treatment of sleep disorders in patients receiving maintenance hemodialysis, and found that Wuling capsules demonstrated good efficacy and safety in the therapy of insomnia. Therefore, Wuling capsules hold promise for further clinical application in the management of sleep disorders in this patient population.

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Disclosure of conflict of interest

None.

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