Original Article

Evaluation of the Efficacy and Safety of Mirtazapine in the Treatment of Uremic Pruritus in Hemodialysis Patients: A Randomized, Double-blind, Placebo-controlled Clinical Trial

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ABSTRACT

Objective: Uremic pruritus (UP) is a prevalent and debilitating condition experienced by patients undergoing hemodialysis, influenced by multiple underlying mechanisms. Despite the availability of various treatment options, many patients still endure significant pruritus. This double-blind, placebo-controlled clinical trial aims to assess and compare the safety and efficacy of mirtazapine and hydroxyzine in treating UP and improving sleep quality in hemodialysis patients. **Methods:** Twenty-seven patients in the mirtazapine group received 15 mg/night (7.5 mg for the first two nights) with a hydroxyzine placebo, while 28 patients in the hydroxyzine group received 25 mg/night (12.5 mg for the first two nights) with a mirtazapine placebo for 2 weeks. UP was assessed using the 5D-itch scale, and sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) at baseline, weeks 2, 3, and 4. Adverse effects were recorded using the Antidepressant Side Effect Checklist at each visit from baseline to week 2. **Findings:** UP ratings based on the 5D-itch scale decreased for both groups, with a more significant reduction in the mirtazapine group ($P = 0.04$). The mirtazapine group also showed a significant improvement in the PSQI compared to hydroxyzine ($P = 0.01$). Dry mouth was the only notable adverse effect, occurring more frequently in the mirtazapine group ($P = 0.02$). **Conclusion:** This study suggests that short-term treatment with mirtazapine is more effective than hydroxyzine in reducing the severity of UP and improving sleep quality for patients undergoing hemodialysis.

KEYWORDS: *Hemodialysis patients, Hydroxyzine, Mirtazapine, uremic pruritus*

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Introduction

Uremic pruritus (UP) is a prevalent and debilitating complication experienced by 40%–60% of patients with end-stage renal disease (ESRD) undergoing hemodialysis. In moderate-to-severe instances, this condition not only impairs physical health but also significantly diminishes the quality of life.[1-3] UP refers to localized or generalized itching that is unrelated to other causes. Poor treatment adherence among many patients often results in persistent symptoms.[4] Despite its prevalence and significant impact on quality of life, UP is frequently underreported by patients and underestimated by physicians.[5] The mechanisms of UP are not fully understood; therefore, there are limitations in identifying effective treatments. Several factors have been implicated in its pathogenesis, including the accumulation of calcium, phosphorus, aluminum, and magnesium; hyperparathyroidism; xerosis (dry skin); hypervitaminosis A; elevated serum bile acids; the release of histamine and substance P; neuropathies of the central or peripheral nervous systems; dysregulation of immune system modulators (such as interleukins); inflammatory mediators from mast cells; and the endogenous opioid system.[6-9] Histamine, a key mediator of itching, primarily acts through H1 receptors, while serotonin also significantly contributes to the sensation of pruritus. Clinical studies show that patients with UP often have elevated serum serotonin levels that correlate with symptom severity, indicating the importance of both histamine and serotonin pathways in this condition.[10-12]

In recent years, various therapeutic approaches have been recommended for UP management, including H_1 histamine receptor antagonists, topical steroids and emollients, gamma-aminobutyric acid receptor modulators, mu-opioid receptor antagonists, kappa-opioid receptor agonists, phototherapy, immune system modulators (e.g., tacrolimus and cyclosporine), and others.[13] Various studies have shown conflicting results about the effectiveness of these treatments, leaving effective therapeutic approaches still unknown. Many patients, especially those with refractory symptoms, do not fully respond to conventional treatments such as antihistamines (e.g., hydroxyzine) due to the complex pathophysiology of UP. This highlights the need for more effective and safer alternatives. While hydroxyzine is often used as a first-line treatment for its antihistaminergic and sedative properties, its efficacy in refractory cases has been inconsistent.[7,14,15]

Recently, mirtazapine, an antidepressant known for its antihistaminergic, serotonergic, and noradrenergic properties, has demonstrated potential therapeutic benefits for UP. Its effects on histamine H_1 and serotonergic receptors may relieve itching and related sleep disturbances in patients. Previous studies have indicated that mirtazapine not only alleviates UP but also effectively reduces pruritus associated with advanced stages of cutaneous T-cell lymphoma, advanced breast carcinoma, metastatic adenocarcinoma, and kidney cancer in patients with end-stage renal failure and the incidence of pruritus following intrathecal morphine administration.[16-21] In addition, it improves sleep quality by reducing sleep latency, enhancing sleep duration and efficiency, and offering significant benefits for patients experiencing itching-related sleep.[22] Limited data on mirtazapine compared to traditional treatments such as hydroxyzine leaves the optimal choice for managing resistant pruritus unclear. This study aims to evaluate and compare the efficacy and safety of mirtazapine and hydroxyzine in treating UP and improving sleep quality in hemodialysis patients with ESRD through a randomized, double-blind clinical trial design.

Methods

This is a randomized, double-blind, placebo-controlled, parallel-arm clinical trial conducted in the two outpatient hemodialysis centers at Shahrvand Kidney Patients Center in Sari and Razi Hospital in Ghaemshahr (affiliated with Mazandaran University of Medical Science), northern Iran, from December 2023 to June 2024. Both centers followed the same treatment protocol to ensure consistency in the intervention and data collection procedures. Participants were divided into two groups: (a) Mirtazapine 15 mg/day[23] plus hydroxyzine placebo and (b) Hydroxyzine 25 mg/day[15] plus mirtazapine placebo. Patients enrolled were assessed at baseline, 2, 3, and 4 weeks. The study was conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and its amendment. The Ethics Committee of Mazandaran University of Medical Sciences approved the study protocol (ethical code: IR.MAZUMS.REC.1402.455). Informed consent was obtained from eligible patients, who were informed of their right to withdraw from the study without affecting their standard treatment (Clinical registration ID: IRCT20120314009297N9). The inclusion criteria were age over 18 years (both male and female) who had been diagnosed with ESRD on stable hemodialysis treatment (at least twice a week for a minimum of three months) and experiencing refractory UP, defined as a score above 8 on the 5D-itch scale despite adequate hemodialysis (Kt/V >1.2) and receiving standard treatments according to the dialysis center protocol.[24-26] Patients received standard hemodialysis (9–12 h per week), bicarbonate-based dialysate, and high-flux polysulfone membranes. Blood

and dialysate flows were 250–300 and 500 mL/min, respectively. Dialysis adequacy is evaluated using the urea reduction ratio (URR) and Kt/V_{urea}. K is the dialyzer clearance of urea (mL/min), t is dialysis time, and V is total body water. A hemodialysis session is considered effective with a URR of ≥0.65 or a Kt/V of >1.2.[27]

The exclusion criteria included (a) anemia (Hb <7 g/dL), (b) hyperparathyroidism (iPTH >600 pg/mL), (c) serum phosphorus >6 mg/dL, calcium >10.5 mg/dL or calcium × phosphorus >60, (d) individuals with chronic skin disorders unrelated to uremia (e.g., psoriasis, dermatitis, and lichen planus), (e) chronic liver failure or serum bilirubin levels more than 1.5 times the standard limit, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) levels exceeding 5 times the standard threshold, (f) untreated hypothyroidism, (g) psychiatric disorders, neurologic disease or the use of any psychoactive medications in the past month, (h) history of suicidal thoughts or actions, (i) inability to take oral medications, (j) recent corticosteroid or opiate use, (k) pregnancy and breastfeeding, (l) a known allergy to mirtazapine, (m) unwillingness to participate in or continue the study, and (n) any complications leading to intolerance or discontinuation of the medication, were also excluded.

The patients were randomized in a 1:1 ratio within four blocks using a computerized random number generator, with the intervention group receiving mirtazapine and the control group receiving hydroxyzine. The physicians, nurses, patients, evaluator, and statistician were all blind to the treatment allocation. The corresponding author securely maintained the study group allocation codes until the study and data analysis were completed.

Patients eligible for the study were taken off all antipruritic agents for a 1-week run-in period. Patients in the intervention group received mirtazapine tablets (Repizapine®, Tekaje Company, Tehran, Iran) plus a placebo (with the same shape, color, and taste as hydroxyzine) with an initial dose of 7.5 mg at bedtime for the first two nights, if tolerated; it increased to 15 mg on the third night and continued for the end of day 14. Patients in the control group received hydroxyzine tablets (Darou Pakhsh Company, Tehran, Iran) plus a placebo (with the same shape, color, and taste as mirtazapine) with an initial dose of 12.5 mg at bedtime for the first two nights, if tolerated; it increased to 25 mg on the third night and continued for the end of day 14. Treatment compliance was assessed by counting tablets at each visit. Placebo tablets were prepared at the Sari Faculty of Pharmacy in Mazandaran, Iran. After the intervention period, patients were assessed for 2 weeks to evaluate the persistence of the therapeutic effect.

The primary outcome was the difference in the total 5D-itch score and its variation during the study endpoints (baseline, weeks 2, 3, and 4). The 5D-itch score encompasses five dimensions of itching, and the total score for the five items ranges from 5 to 25. A score of 8 or lower indicates no pruritus, while scores of 9–11, 12–17, 18–21, and 22 or higher correspond to mild, moderate, severe, and very severe pruritus, respectively.[25,26] A positive response to treatment was defined as at least a 50% reduction from baseline.[28] Secondary outcomes included the Pittsburgh Sleep Quality Index (PSQI) score to evaluate sleep quality and treatment safety assessment. Scores of PSQI above 5 indicated poor sleep quality.[29,30] The 5D-itch scores and PSQI scores were measured at baseline and at the end of the 2nd, 3rd, and 4th weeks to evaluate the persistence of the therapeutic effect. The Persian versions of the 5D-itch scale[31] and PSQI score have been validated.[32]

The safety of the treatment was evaluated through laboratory assessments and monitoring of adverse effects using the Antidepressant Side Effect Checklist (ASEC).[33,34] Clinical laboratory tests, including complete blood count (CBC), serum creatinine, blood urea, ALT, AST, total bilirubin, and fasting serum glucose (FBS), were conducted at baseline. The CBC, FBS, and serum lipid profile (comprising triglycerides, low-density lipoprotein, and high-density lipoprotein) were assessed on day 14. Adverse effects were recorded at each visit using the ASEC checklist.

Based on pilot study results, the mean (±standard deviation [SD]) 5D-itch scale scores at week 2 (postintervention) were 7.29 (±2.97) in the intervention group and 10.5 (±4.98) in the control group. The sample size was calculated as 30 participants per group, considering an effect size of 0.78, a 95% confidence level ($\alpha = 0.05$), a power of 80%, a two-tailed test, and a 10% attrition rate.

The normality of all data was assessed using the one-sample Kolmogorov–Smirnov test. Qualitative variables were reported as frequencies and percentages, while quantitative variables were expressed as means ± SD. Categorical variables between the two groups at baseline were compared using the Chi-square test or Fisher's exact test, and continuous variables were analyzed using the independent sample t-test or the Mann–Whitney U test, as appropriate. A generalized estimating equation (GEE) analysis was conducted to examine the effects of time, group, and the interaction between time and group for the total score of the 5D-itch scale and its subscales and for PSQI scores and their components. The independent sample t-test was utilized

to compare changes in PSQI scores from baseline to each time point, excluding week 2, between the two groups. The Mann–Whitney *U* test was employed to compare changes in PSQI components from baseline to each time point, along with the total PSQI score at week 2 between the two groups. Categorical variables, including qualitative scores of the 5D-itch scale and its subscales, treatment response, and frequency of side effects, were compared using the Chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed using SPSS Software (version 25; IBM SPSS Inc., Chicago, IL, USA), with $P < 0.05$ deemed statistically significant.

Results

The flow diagram in Figure 1 illustrates the selection process and the reasons for participant dropouts.

Table 1 shows the demographic and baseline data of the study population. No significant differences were found between the two groups at baseline ($P > 0.05$).

Table 2 presents the changes in the total score of the 5D-itch scale from baseline to week 4, along with its specific domains, analyzed using GEE. Throughout the study, both groups demonstrated a significant decrease in the total score of the 5D-itch scale and its domains. The GEE analysis revealed a significant effect of time ($P < 0.001$) and a time-by-treatment interaction ($P < 0.001$), indicating that the responses of the two treatment groups varied over time regarding the total score of the 5D-itch and its domains. In addition, a significant group effect on the total score of the 5D-itch scale, as well as the degree and distribution domains, was observed ($P < 0.05$) [Table 2]. The treatment response comparison derived from the 5D-itch scale in Table 3 indicates a significantly stronger response in the mirtazapine group than in the hydroxyzine group (odds ratio [OR] = 8.89, $P < 0.001$). Furthermore, the therapeutic response in the mirtazapine group was significantly higher at week 3 (OR = 5.13, $P = 0.005$) and approached significance at week 4 (OR = 3.67, $P = 0.049$).

Table 4 presents the mean difference in the global PSQI score and its components from baseline to week 4 as analyzed through GEE. The total PSQI score significantly decreased throughout the study in both

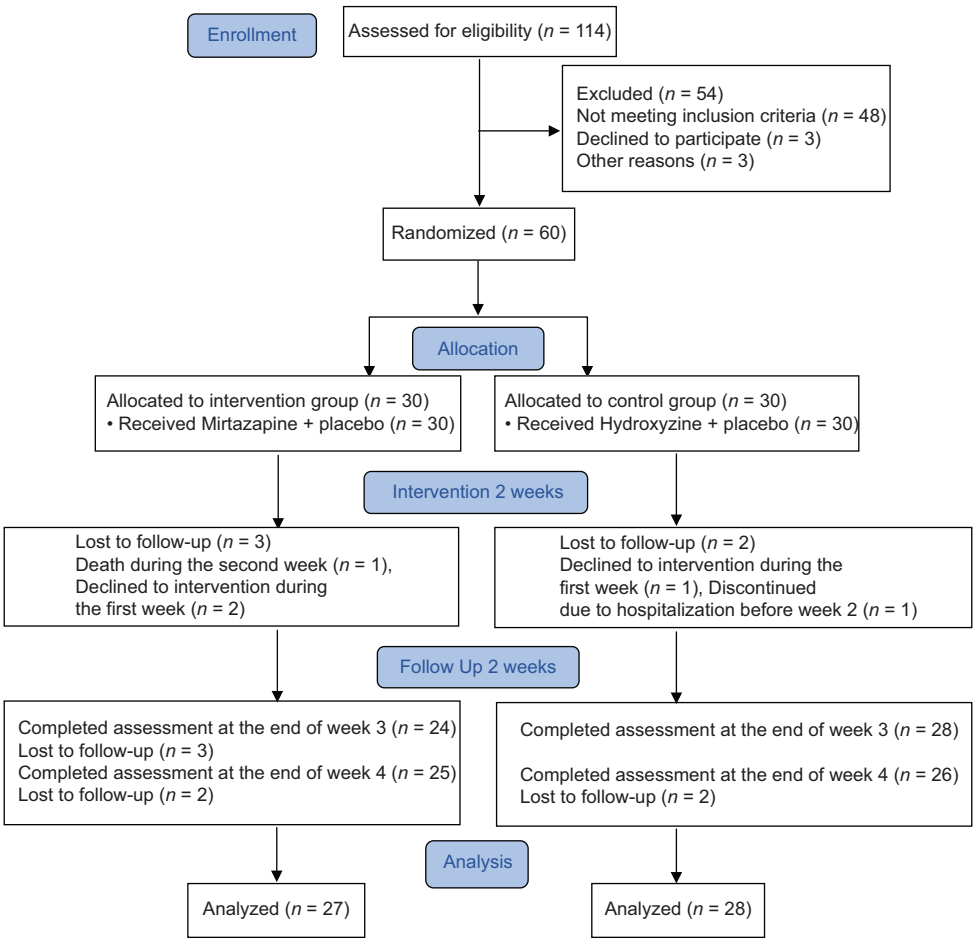

Figure 1: CONSORT flow diagram

Table 1: Demographic and baseline clinical data of all patients in both groups

	Mirtazapine group (*n*=27)	Hydroxyzine group (*n*=28)	P
Age (years)	60.7±15.1 (54.7–66.6)	61.8±15.1 (55.9–67.6)	t_{53}=−0.27, *P*=0.8[a]
Sex			
Male	15 (55.6)	16 (57.1)	0.9[b]
Female	12 (44.4)	12 (42.9)	
Cause of RF			
Diabetes mellitus	10 (37)	10 (35.7)	0.99[b]
Hypertension	11 (40.7)	12 (42.9)	
Infection	2 (7.4)	2 (7.1)	
Renal parenchymal disease	2 (7.4)	2 (7.1)	
Other	2 (7.4)	2 (7.1)	
Time of HD per week (h)	10.8±2.1 (9.9–11.6)	11.1±2 (10.3–11.9)	Z=−0.67, *P*=0.5[c]
Duration of pruritus (month)	4.76±3.9 (3.2–6.3)	4.55±4.3 (2.9–6.2)	Z=−0.89, *P*=0.4[c]
Dialysis adequacy			
KT/V	1.34±0.17 (1.27–1.4)	1.36±0.13 (1.31–1.41)	t_{53}=−0.57, *P*=0.6[a]
URR (%)	68±4 (67–70)	68±3 (67–69)	t_{53}=0.05, *P*=0.9[a]
5D-itch scale			
Mild	0	0	0.4[b]
Moderate	8 (29.6)	13 (46.4)	
Severe	10 (37)	8 (28.6)	
Very severe	9 (33.3)	7 (25)	
Global PSQI score	11.5±3.6 (10.1–12.9)	10.1±3.5 (8.8–11.5)	t_{53}=1.49, *P*=0.1[a]

[a]Independent sample *t*-test, [b]Chi-square or Fisher's exact test, [c]Mann–Whitney *U*-test. Data are presented as mean±SD (95% CI) or *n* (%), as applicable. SD=Standard deviation, CI=Confidence interval, RF=Renal failure, HD=Hemodialysis, KT/V=Ratio of urea clearance (K) × Dialysis time (T) to volume of distribution for urea (V), URR=Urea reduction ratio, PSQI=Pittsburgh Sleep Quality Index, 5D=Five-dimensional

treatment groups. In the mirtazapine group, the total PSQI score and all its components, except for the use of sleep medication, showed a significant reduction compared to the baseline. However, significant decreases were observed only in some scale components in the hydroxyzine group. The GEE analysis revealed a significant effect of time ($P < 0.001$) and a time-by-group interaction ($P < 0.001$), indicating that the patterns of change in the two treatment groups were not similar over time for the total PSQI score and its components. A significant group effect was found for the total PSQI score and its components, including objective sleep quality, latency, and duration ($P < 0.05$). At the end of the intervention, complete improvement in sleep quality (PSQI ≤5) was observed in 18 (66.7%) patients in the mirtazapine group versus 8 (28.6%) patients in the hydroxyzine group (OR = 5, $P = 0.005$). This difference remained significant in the 3rd week (16 [69.6%] vs. 7 [25.9%], OR = 6.5, $P = 0.002$) and the 4th week (13 [52%] vs. 5 [19.2%], OR = 4.5, $P = 0.01$). [Appendix 1, which provides additional information on the global PSQI score and its components at each point during the study].

Adverse effects reported by participants during the 2-week intervention were assessed using the ASEC checklist. The number of patients who reported adverse effects was 18 (66.7%) in the mirtazapine group and 7 (25%) in the hydroxyzine group, with a statistically significant difference between the two groups ($P = 0.002$). The most common adverse effects in the mirtazapine group were drowsiness ($n = 11$), dizziness ($n = 7$), and increased appetite ($n = 4$), while in the hydroxyzine group, drowsiness ($n = 6$) was the most frequently reported. A statistically significant difference between the two groups was observed only for dry mouth ($P = 0.02$). Laboratory tests, including CBC, FBS, and lipid profiles, showed no significant differences between groups at the end of the intervention ($P > 0.05$) or compared to baseline, particularly in the mirtazapine group ($P > 0.05$). All participants completed the study, and none discontinued due to adverse effects. [Appendix 2, which provides additional information on the frequency of adverse effects during the study].

Discussion

To the best of our knowledge, this is the first randomized, double-blind, placebo-controlled clinical trial investigating the efficacy and safety of mirtazapine in the management of refractory UP and sleep quality in hemodialysis patients. The results of the present study demonstrated that a 2-week treatment with mirtazapine was associated with significant improvement in refractory UP severity and sleep quality, which persisted

Table 2: Comparison of quality score of five dimensional-itch and the domains at baseline, week 2, week 3, and week 4 between two treatment groups

Study time	5D-itch score and the domains												Group effect	Time effect	Group × time interaction
	Baseline			Week 2			Week 3			Week 4					
	Group 1	Group 2	*P**	Group 1	Group 2	*P**	Group 1	Group 2	*P**	Group 1	Group 2	*P**			
Quality score of 5Ditch															
No	0	0	0.4	21 (77.8)	11 (39.3)	0.03	15 (55.6)	9 (32.1)	0.1	9 (33.3)	5 (17.9)	0.4	χ_1^2: 4, *P*=0.04	χ_3^2: 39, *P*<0.001	χ_7^2: 108.8, *P*<0.001
Mild	0	0		3 (11.1)	7 (25)		3 (11.1)	6 (21.4)		4 (14.8)	6 (21.4)				
Moderate	8 (29.6)	13 (46.4)		3 (11.1)	6 (21.4)		5 (18.5)	7 (25)		8 (29.6)	6 (21.4)				
Severe	10 (37)	8 (28.6)		0	3 (10.7)		0	4 (14.3)		1 (3.7)	4 (14.3)				
Very severe	9 (33.3)	7 (25)		0	1 (3.6)		1 (3.7)	2 (7.1)		3 (11.1)	5 (17.9)				
Duration (h)															
<6	2 (7.4)	4 (14.3)	0.04	23 (85.2)	16 (57.1)	0.09	18 (66.7)	16 (57.1)	0.6	13 (48.1)	11 (39.3)	0.9	χ_1^2: 0.82, *P*=0.4	χ_3^2: 22.6, *P*<0.001	χ_7^2: 80, *P*<0.001
6–12	0	7 (25)		3 (11.1)	7 (25)		2 (7.4)	3 (10.7)		5 (18.5)	4 (14.3)				
12–18	10 (37)	7 (25)		1 (3.7)	1 (3.6)		3 (11.1)	4 (14.3)		2 (7.4)	3 (10.7)				
18–23	4 (14.8)	2 (7.1)		0	3 (10.7)		0	3 (10.7)		1 (3.7)	2 (7.1)				
All day	11 (40.7)	8 (28.6)		0	1 (3.6)		1 (3.7)	2 (7.1)		4 (14.8)	6 (21.4)				
Degree															
No	0	0	0.9	13 (48.1)	5 (17.9)	0.02	9 (33.3)	2 (7.1)	0.08	5 (18.5)	2 (7.1)	0.2	χ_1^2: 4.22, *P*=0.04	χ_3^2: 47.2, *P*<0.001	χ_7^2: 115.4, *P*<0.001
Mild	0	1 (3.6)		11 (40.7)	12 (42.9)		9 (33.3)	14 (50)		9 (33.3)	10 (35.7)				
Moderate	7 (25.9)	7 (25.0)		1 (3.7)	8 (28.6)		4 (14.8)	7 (25)		7 (25.9)	4 (14.3)				
Severe	10 (37)	12 (42.9)		2 (7.4)	2 (7.1)		2 (7.4)	4 (14.3)		2 (7.4)	8 (28.6)				
Unbearable	10 (37)	8 (28.6)		0	1 (3.6)		0	1 (3.6)		2 (7.4)	2 (7.1)				
Direction															
Completely resolved	0	0	0.3	12 (44.4)	1 (3.6)	0.001	9 (33.3)	1 (3.6)	0.03	4 (14.8)	1 (3.6)	0.7	χ_1^2: 3.86, *P*=0.05	χ_3^2: 15.8, *P*<0.001	χ_7^2: 181.3, *P*<0.001
Much better but still present	0	0		11 (40.7)	15 (53.6)		7 (25.9)	12 (42.9)		7 (25.9)	9 (32.1)				
Little bit better but still present	0	3 (10.7)		3 (11.1)	7 (25)		4 (14.8)	6 (21.4)		4 (14.8)	4 (14.3)				
Unchanged	13 (48.1)	14 (50)		1 (3.7)	5 (17.9)		2 (7.4)	6 (21.4)		4 (14.8)	4 (14.3)				
Getting worse	14 (51.9)	11 (39.3)		0	0		2 (7.4)	3 (10.7)		5 (18.5)	8 (28.6)				
Disability															
No effect	0	4 (14.3)	0.3	24 (88.9)	15 (53.6)	0.04	17 (63)	11 (39.3)	0.2	12 (44.4)	7 (25)	0.35	χ_1^2: 2.7, *P*=0.1	χ_3^2: 35.8, *P*<0.001	χ_7^2: 96.8, *P*<0.001
Very little impact	2 (7.4)	6 (21.4)		2 (7.4)	5 (17.9)		3 (11.1)	6 (21.4)		8 (29.6)	8 (28.6)				
Occasional impact	6 (22.2)	8 (28.6)		1 (3.7)	3 (10.7)		3 (11.1)	6 (21.4)		2 (7.4)	4 (14.3)				
Frequent impact	10 (37)	2 (7.1)		0	3 (10.7)		1 (3.7)	3 (10.7)		1 (3.7)	5 (17.9)				
Always	9 (33.3)	8 (28.6)		0	2 (7.1)		0	2 (7.1)		2 (7.4)	2 (7.1)				
Distribution															
0–2 areas	0	0	0.8	15 (55.6)	6 (21.4)	0.03	10 (37)	5 (17.9)	0.2	7 (25.9)	2 (7.1)	0.06	χ_1^2: 5.1, *P*=0.02	χ_3^2: 28.7, *P*<0.001	χ_7^2: 93.1, *P*<0.001
3–5 areas	3 (11.1)	2 (7.1)		7 (25.9)	9 (32.1)		6 (22.2)	8 (28.6)		4 (14.8)	10 (35.7)				
6–10 areas	11 (40.7)	11 (39.3)		5 (18.5)	9 (32.1)		6 (22.2)	9 (32.1)		10 (37)	5 (17.9)				
11–13 areas	9 (33.3)	8 (28.6)		0	1 (3.6)		2 (7.4)	2 (7.1)		2 (7.4)	6 (21.4)				
14–16 areas	4 (14.8)	7 (25)		0	3 (10.7)		0	4 (14.3)		2 (7.4)	3 (10.7)				

*Fisher's exact test. Data are presented as n (%). Group 1=Mirtazapine, Group 2=Hydroxyzine, 5D=Five-dimensional

after discontinuing the treatment during the 2-week follow-up. At the end of week 2, treatment responses in patients with UP were 85.2% in the mirtazapine group compared to 39.3% in the hydroxyzine group, which were maintained at 70.8% versus 32.1% by week 3 and further declined to 40% versus 15.4% by week 4, respectively. In addition, sleep quality improved for 66.7% of participants in the mirtazapine group, compared to 28.6% in the hydroxyzine group, which were maintained at 69.6% versus 25.9% at week 3 and 52% versus 19.2% at week 4, respectively.

The effects of mirtazapine on managing UP severity in hemodialysis patients have been investigated in three studies.[23,35,36] The results of the current research on the management of UP align with their findings. However, these studies had limitations, necessitating cautious interpretation of their results. Mehrpooya *et al*. conducted an open-label clinical trial in which 30 eligible patients received 15 mg of mirtazapine daily for 2 weeks. The results significantly improved UP severity based on the visual analog scale (VAS). In addition, the study evaluated the effectiveness of mirtazapine in improving sleep quality. However, the investigator limited sleep assessment to a single verbal question regarding the patients' sleep status.[35] Gholyaf *et al*. conducted a pilot, open-label, crossover study to evaluate the efficacy of mirtazapine in 77 patients with refractory UP. In this study, mirtazapine at a dose of 15 mg daily compared with gabapentin at 100 mg daily for 2 weeks showed a significant improvement in the severity of UP in patients based on the VAS scale.[23] The most commonly reported adverse effects in these two studies included drowsiness, dry mouth, and dizziness. Similarly, in our study, drowsiness and dry mouth were among the most frequently reported adverse effects. However, none of the patients discontinued the study due to the adverse effects, and the treatment was tolerated throughout the intervention. Miyahara *et al*. reported in a case report that treatment with mirtazapine at a dose of 7.5 mg daily for 14 days in a hemodialysis patient who also suffered from refractory UP and depression was associated with improvement in the severity of UP based on the VAS scale.[36] The two clinical trials conducted in this field have limitations, including the absence of a control group, lack of double-blinding, and the use of low-specificity and low-sensitivity measures for assessing pruritus severity. While the VAS scale is a valid tool for evaluating itching intensity, it does not account for other aspects of

Table 3: Comparison of treatment response based on five-dimensional -itch score between groups at week 2, week 3, and week 4

Time	Group	Responders, *n* (%)	OR (95% CI)	*P**
Week 2	Mirtazapine (*n*=27)	23 (85.2)	8.89 (2.41–32.76)	<0.001
	Hydroxyzine (*n*=28)	11 (39.3)		
Week 3	Mirtazapine (*n*=24)	17 (70.8)	5.13 (1.6–16.8)	0.005
	Hydroxyzine (*n*=28)	9 (32.1)		
Week 4	Mirtazapine (*n*=25)	10 (40)	3.67 (0.97–13.9)	0.049
	Hydroxyzine (*n*=26)	4 (15.4)		

*Fisher's exact test. CI=Confidence interval, OR=Odd ratio

Table 4: Comparison of mean difference in the global Pittsburgh Sleep Quality Index score and its components from baseline to week 4 between two treatment groups

Global PSQI score and the components	Groups	Base to week 2; β±SE (95% CI)	Base to week 3; β±SE (95% CI)	Base to week 4; β±SE (95% CI)	Group effect	Time effect	Group × time interaction
Global PSQI score	1	−6.4±0.6; (−7.6–−5.3)**	−5.9±0.7; (−7.3–−4.4)**	−4.7±0.6; (−5.8–−3.5)**	χ_1^2: 6.3, *P*=0.01	χ_3^2: 52.1, *P*<0.001	χ_7^2: 147.5, *P*<0.001
	2	−1.8±0.5; (−2.9–−0.8)**	−2.1±0.4; (−3–−1.2)**	−1.6±0.5; (−2.7–−0.6)*			
Objective sleep quality	1	−3±0.7; (−4.3–−1.7)**	−2.4±0.7; (−3.7–−1.1)**	−2±0.5; (−3.1–−1)**	χ_1^2: 4.8, *P*=0.03	χ_3^2: 11.6, *P*<0.001	χ_7^2: 56.9, *P*<0.001
	2	−0.3±0.4; (−1–0.4)	−0.1±0.3; (−0.8–0.6)	−0.2±0.4; (−0.9–0.5)			
Sleep latency	1	−1.7±0.4; (−2.4–−1)**	−1.5±0.5; (−2.4–−0.5)*	−0.8±0.5; (−1.7–0.1)	χ_1^2: 6.7, *P*=0.01	χ_3^2: 10.2, *P*=0.001	χ_7^2: 45.4, *P*<0.001
	2	−0.4±0.2; (−0.8–0.06)	−0.3±0.3; (−1–0.4)	−0.1±0.4; (−0.9–0.6)			
Sleep duration	1	−2.8±0.5; (−3.7–−1.8)**	−2.4±0.5; (−3.5–−1.4)**	−2±0.5; (−3–−1)**	χ_1^2: 13.3, *P*<0.001	χ_3^2: 17.8, *P*<0.001	χ_7^2: 72, *P*<0.001
	2	−0.2±0.2; (−0.7–0.3)	−0.5±0.3; (−1.2–0.2)	−0.6±0.4; (−1.3–0.2)			
Habitual sleep efficiency	1	−1.4±0.4; (−2.2–−0.7)**	−1.3±0.5; (−2.3–−0.4)*	−0.8±0.5; (−1.7–0.2)	χ_1^2: 3.1, *P*=0.08	χ_3^2: 4.3, *P*=0.04	χ_7^2: 61, *P*<0.001
	2	−0.3±0.3; (−0.9–0.3)	−1±0.3; (−1.6–−0.2)*	−0.4±0.4; (−1.1–0.3)			
Sleep disturbance	1	−2.8±0.6; (−4–−1.7)**	−2.6±0.6; (−3.7–−1.5)**	−1.6±0.4; (−2.5–−0.8)**	χ_1^2: 2.9, *P*=0.09	χ_3^2: 14.4, *P*<0.001	χ_7^2: 68.7, *P*<0.001
	2	−1±0.4; (−1.7–−0.2)*	−1.1±0.4; (−1.8–−0.3)*	−1.2±0.4; (−2–−0.4)*			
Use of sleeping medication	1	−0.4±0.3; (−1.1–0.3)	−0.4±0.4; (−1.3–0.5)	−0.3±0.3; (−1–0.3)	χ_1^2: 0.16, *P*=0.7	χ_3^2: 0.4, *P*=0.5	χ_7^2: 8.5, *P*=0.3
	2	−0.007±0.4; (−0.7–0.7)	0.2±0.4; (−0.6–1)	−0.1±0.5; (−1.1–0.8)			
Daytime dysfunction	1	−1.8±0.4; (−2.6–−1)**	−2.7±0.6; (−3.8–−1.5)**	−2.3±0.6; (−3.5–−1.1)**	χ_1^2: 0.1, *P*=0.7	χ_3^2: 11.7, *P*<0.001	χ_7^2: 59.6, *P*<0.001
	2	−0.9±0.4; (−1.7–−0.2)*	−0.8±0.4; (−1.6–0.02)	−0.3±0.5; (−1.3–0.7)			

**P*<0.05, ***P*<0.001. Group 1=Mirtazapine, Group 2=Hydroxyzine, PSQI=Pittsburgh Sleep Quality Index

pruritus, such as its impact on disability, duration, and distribution.

Furthermore, patients may encounter difficulties accurately reporting itching intensity changes over time, often resulting in similar responses.[37] These limitations emphasize pruritus' subjective and multidimensional nature, highlighting the need for more comprehensive and sensitive assessment tools. In the present study, we employed the 5D-itch scale, a multidimensional instrument designed to evaluate various aspects of pruritus, including duration, intensity, direction, disability, and distribution. Our results demonstrated that mirtazapine treatment significantly reduced the number of affected areas and improved daily functioning. The overall 5D-itch Quality Score demonstrated that mirtazapine was more effective than hydroxyzine in alleviating severe-to-very severe pruritus. By the end of the 2nd week, an impressive 70.3% of patients in the mirtazapine group, who initially presented with severe-to-very severe pruritus, reported a reduction in the intensity of their symptoms. UP was found to be associated with poor sleep quality in hemodialysis patients. In contrast, among the hydroxyzine group, 53.6% initially experienced severe-to-very severe pruritus. By the end of the 2nd week, 14.3% of those patients continued to report this severity level. UP was found to be associated with poor sleep quality in hemodialysis patients.[38] Previous studies have not independently examined the effects of mirtazapine and hydroxyzine on sleep quality in hemodialysis patients. The only relevant research by Mehrpooya *et al*.[35] used a verbal question to evaluate sleep improvement in mirtazapine users, while our study employed the PSQI score, a more refined tool, to assess important aspects of sleep, such as latency, duration, and efficiency. In our study, all participants exhibited poor sleep quality at baseline, with the highest scores observed in sleep latency and duration in both groups. Mirtazapine significantly improved sleep latency, duration, efficiency, and sleep disturbance compared to hydroxyzine. Notably, these improvements were maintained in a higher proportion of patients in the mirtazapine group even after the intervention was discontinued.

Our study faced several limitations, mainly the small sample size and short follow-up period. While the sample size was adequate for comparing the two groups, the results need validation through more extensive and prolonged trials to be generalized to a broader population. In addition, our assessment of medication adverse effects was confined to the short term. However, specific adverse effects, such as disturbances in lipid profiles,[39] may develop weeks to months after the initiation of treatment. Consequently, a larger sample size and an extended follow-up period are necessary to identify these adverse effects accurately.

We recommend that future studies on mirtazapine use larger sample sizes, longer treatment durations, different doses, and the evaluation of other quality-of-life aspects using validated scales.

Short-term treatment with mirtazapine is more effective than hydroxyzine in reducing the severity of UP and improving sleep quality for patients undergoing hemodialysis. However, further research is needed to assess the long-term efficacy and safety of mirtazapine in these patients.

Authors' Contribution

Narjes Hendouei and Fatemeh Espahbodi contributed to the study's conception and design. Hamidreza Namvar prepared the materials and collected the data. Seyed Mobin Rahimnia prepared the placebo. Mahmood Moosazadeh performed the data analysis. Hamidreza Namvar wrote the first draft of the manuscript, which Narjes Hendouei critically revised. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Comparison of global Pittsburgh Sleep Quality Index score and its components (mean±standard deviation) between groups at baseline, week 2, week 3, and week 4

Variables	Groups	Baseline	*P*	Week 2	*P*	Week 3	*P*	Week 4	*P*
Global PSQI score	1	11.5±3.6 (10.1–12.9)	0.1	5.1±4 (3.5–6.7)	0.001	5.2±4 (3.5–6.9)	0.01	6.8±4.4 (4.9–8.6)	0.1
	2	10.1±3.5 (8.8–11.4)		8.3±3.6 (6.9–9.7)		7.8±3.2 (6.5–9)		8.5±3.5 (7.1–9.9)	
Objective sleep quality	1	1.9±0.9 (1.5–2.2)	0.08	0.5±0.7 (0.2–0. 8)	0.005	0.7±1 (0.3–1.2)	0.06	0.8±0.7 (0.5–1.1)	0.08
	2	1.5±0.9 (1.2–1.8)		1.2±0.9 (0.8–1.5)		1.2±0.9 (0.8–1.5)		1.3±0.9 (0.9–1.7)	
Sleep latency	1	2.2±0.8 (1.9–2.6)	0.4	1±1.2 (0.6–1.5)	0.02	1.2±0.9 (0.8–1.6)	0.05	1.4±1 (1–1.9)	0.1
	2	2±0.9 (1.6–2.4)		1.7±1.1 (1.3–2.2)		1.8±1 (1.4–2.2)		1.9±1.1 (1.5–2.4)	
Sleep duration	1	2.2±1 (1.8–2.6)	0.4	0.7±0.9 (0.3–1.1)	<0.001	0.8±0.9 (0.4–1.2)	0.004	1±0.96 (0.6–1.4)	0.04
	2	1.9±1.1 (1.5–2.3)		1.7±1.1 (1.3–2.2)		1.6±1 (1.2–2)		1.6±1.1 (1.2–2.1)	
Habitual sleep efficiency	1	1.1±1.2 (0.7–1.6)	0.7	0.5±0.8 (0.1–0.8)	0.03	0.3±0.7 (0.0–0.6)	0.07	0.7±0.8 (0.3–1)	0.4
	2	1.2±1.1 (0.8–1.7)		1±0.99 (0.6–1.3)		0.6±0.6 (0.3–0.8)		0.8±0.7 (0.5–1.1)	
Sleep disturbance	1	1.7±0.5 (1.5–1.9)	0.7	1±0.4 (0.8–1.2)	0.02	1±0.5 (0.8–1.2)	0.09	1.2±0.6 (1–1.5)	0.9
	2	1.6±0.6 (1.4–1.8)		1.3±0.5 (1.1–1.5)		1.3±0.5 (1.1–1.5)		1.3±0.5 (1–1.5)	
Use of sleeping medication	1	0.9±1.3 (0.4–1.4)	0.7	0.6±1.2 (0.1–1.1)	0.8	0.6±1.1 (0.1–1)	0.7	0.9±1.4 (0.3–1.4)	0.6
	2	0.7±1.2 (0.3–1.2)		0.6±1.1 (0.2–1.1)		0.7±1.1 (0.2–1.1)		0.6±1.2 (0.2–1.1)	
Daytime dysfunction	1	1.5±0.8 (1.2–1.8)	0.06	0.7±0.9 (0.4–1.1)	0.9	0.6±0.8 (0.2–0.9)	0.4	0.7±1 (0.3–1.1)	0.2
	2	1.1±0.7 (0.7–1.4)		0.7±0.8 (0.4–1)		0.7±0.7 (0.4–0.9)		0.9±0.8 (0.6–1.3)	

Data are presented as mean±SD (95% CI). SD=Standard deviation, CI=Confidence interval, Group 1=Mirtazapine, Group 2=Hydroxyzine, PSQI=Pittsburgh Sleep Quality Index

Appendix 2: Frequency of adverse effects during the study

Adverse effect	Mirtazapine group (*n*=27), *n* (%)	Hydroxyzine group (*n*=28), *n* (%)	*P**
Dry mouth	7 (25.9)	1 (3.6)	0.02
Drowsiness	11 (40.7)	6 (21.4)	0.1
Confusion	2 (7.4)	0	0.2
Headache	0	1 (3.6)	0.9
Increased appetite	4 (14.8)	0	0.05
Weight gain	3 (11.1)	1 (3.6)	0.3
Lightheadedness	2 (7.4)	1 (3.6)	0.6
Others	2 (7.4)	0	0.2

*Fisher's exact test