Comparing Effects of Clonazepam and Zolpidem on Sleep Quality of Patients on Maintenance Hemodialysis

Simin Dashti-Khavidaki,[1] Nastaran Chamani,[1] Hossein Khalili,[1] Azita Hajhossein Talasaz,[1] Farokhlegha Ahmadi,[2] Mahboob Lessan-Pezeshki,[2] Padideh Ghaeli,[1] Shirin Dalili,[3] Abbas Alimadadi[4]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy and Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Nephrology, Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3]Dialysis Unit, Imam-Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Psychology, Tehran University of Medical Sciences, Tehran, Iran

Keywords. hemodialysis, sleep disorders, clonazepam, zolpidem

Introduction. Poor sleep quality is very common among maintenance hemodialysis patients and has negative impacts on patients' quality of life. Benzodiazepines have traditionally been used in this population; however, they may induce physical dependence and sleep apnea. Nonbenzodiazepine hypnotic medications with less side effects are introduced as alternatives. This study was designed to compare the effect of zolpidem and clonazepam on sleep quality of hemodialysis patients.

Materials and Methods. In a randomized crossover study on 23 hemodialysis patients, sleep quality was assessed using the Pittsburgh Sleep Quality Index at baseline, at the initiation of a 1-week washout period after a 2-week treatment with zolpidem (1 mg) and clonazepam (5 mg to 10 mg), and after the second 2 weeks of treatment. Patients who suffer from any concurrent situations that may affect sleep quality or psychiatric disorders and those on medications affecting sleep quality were excluded.

Results. The prevalence of poor sleep quality was 87.8% of the 88 hemodialysis patients who were initially approached. There was a significant negative correlation between iron deficiency and poor sleep quality. Both clonazepam and zolpidem significantly improved sleep quality; however, clonazepam was more effective in decreasing the Pittsburgh Sleep Quality Index scores ($P = .03$). Zolpidem was better tolerated in the hemodialysis patients.

Conclusions. Clonazepam was more effective than zolpidem in the improvement of sleep quality of hemodialysis patients, while zolpidem was better tolerated in these patients.

IJKD 2011;5:404-9
www.ijkd.org

Original Paper

INTRODUCTION

Sleep disorders, in particular poor sleep quality, are widespread problems in maintenance hemodialysis patients.[1,2] The prevalence of poor sleep quality in hemodialysis patients was estimated to be 41% to 83%.[3-7] Poor sleep quality has negative impacts on patients' quality of life. After a while, these sleep disturbances may lead to "day-night reversal," ie, insomnia at night and sleepiness during the day; headache; depression; and declined functional capacity. Moreover, it has recently been shown that poor-quality sleep caused by periodic limb movements and their related arousals is an important predictor of mortality in patients with end-stage renal disease.[8]

Different strategies have been applied to

improve patients' sleep quality, among which physical activity in the form of intradialytic aerobic training showed to have a positive influence on the sleep disorder of hemodialysis patients.[9] Benzodiazepines, especially clonazepam, have been widely used to treat sleep disorders, including restless leg syndrome, in hemodialysis patients.[10] Clonazepam exerts its action by binding to the benzodiazepine site of the gamma-aminobutyric acid receptors that result in inhibition of synaptic transmission across the central nervous system.[11] Its onset of action is within 1 to 2 hours in healthy individuals. Clonazepam has an elimination half life of 20 to 80 hours, and it does not produce any pharmacologically active metabolites[12]; however, its potential to induce physical dependence and sleep apnea remains a matter of concern.[10]

Nonbenzodiazepine hypnotics, zaleplon and zolpidem, exert their hypnotic effects through selective affinity for benzodiazepine type 1 receptor,[12] with less physical dependence and less inducing sleep apnea or still conversely improving sleep apnea compared with benzodiazepine medications.[12-16] Zolpidem has rapid onset of action, with mean elimination half-life of 2.5 to 2.8 hours, and is metabolized to inactive metabolites primarily via cytochrome P450. These metabolites are eliminated by the kidney.[13] This study was designed to compare zolpidem with clonazepam, the widely used benzodiazepine, in terms of on sleep quality of patients on hemodialysis to gain important clinical insight into this major problem of patients.

MATERIALS AND METHODS

This study was conducted at Imam Khomeini Dialysis Center, affiliated to Tehran University of Medical Sciences. Eighty patients on maintenance hemodialysis (hemodialysis for more than 3 months) were assessed for sleep quality using the Persian edition of the Pittsburgh Sleep Quality Index (PSQI).[17] All of the PSQI questionnaires were filled out by one of the researchers. The PSQI is a 9-question, 19 item self-report instrument designed to measure sleep quality and disturbance over a 1-month period. It consists of 7 components of subjective sleep quality, sleep latency (ie, the amount of time that it takes to fall asleep), sleep duration, habitual sleep efficiency (ie, hours between bedtime and getting up time), sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. Each of these areas is self-rated by the patient. Scoring of answers is based on a zero-to-3 scale, on which 3 reflects the negative extreme. The total sum of scores above 5 indicate clinically meaningfully disturbed or poor sleep.[17]

Of the 80 patients, 23 further agreed to be enrolled in the randomized crossover trial phase of the study. The study protocol was approved by ethics committee of Tehran University of Medical Sciences and all the patients signed informed consent. Patients who suffer from any concurrent situations that may affect sleep quality including cancer, congestive heart failure, connective tissue disease, and psychiatric disorders were excluded from the study. Concurrent medications prescribed in these patients were also documented and if there were any medications administered within the 2 weeks prior to the study that might have effects on the sleep quality or interact with clonazepam or zolpidem, the patient would be excluded from the study. The sample size was determined based on a similar study that evaluated the effect of zaleplon on the sleep quality of hemodialysis patients,[18] in which the mean values of the PSQI before and after the administration of zaleplon were 11.7 ± 2.1 and 6.5 ± 2.8, respectively. Therefore, we considered the least difference between the PSQI scores in before and after phases of our study as 2 scores. With the confidence level of 0.05 and the power of 80%, the sample size of our study was calculated to be 15.

Permuted block randomization with a block size of 4 was used to randomized patients to receive zolpidem (10 mg for patients younger than 60 years old and 5 mg for older participants) or clonazepam (1 mg), nightly for the 1st two weeks (phase 1 of the study) and vice versa for another 2 weeks (phase 2 of the study) with a 1-week washout period between the two phases. Patients were blinded to the drug administered in each group. Sleep quality was re-assessed using the PSQI after the completion of each study phase. Patients' adherence to the treatment was checked in each visit by the researcher by checking the number of medications left and their blisters.

Data was analysis was performed using the SAS (Statistical Analysis System, version 9.1, SAS, Cary, NC, USA). Nonparametric tests were used to compare PSQI scores at baseline and at the end of research. The independent sample *t* test was used

to compare patients' age and PSQI score at baseline and after the first phase of the study between the two groups. The paired *t* test was used to compare the baseline and PSQI scores after phase 1 in each group. The PROC GLM and PROC MIXED procedures were used to evaluate the treatment, period, and carryover effects. The PROC GLM permits fitting both fixed effect regression models and fixed effect analysis of variance models. The PROC MIXED allows testing of both fixed effects and variance (covariance) components. The Pearson correlation test was used to estimate the correlations of age and baseline PSQI score with treatment effect and also correlations between baseline PSQI score and patients' laboratory findings, including anemia parameters, serum electrolytes, and intact parathyroid hormone. *P* values less than .05 were considered significant.

RESULTS

Sleep quality was assessed in 80 hemodialysis patients (55 men and 25 women) with a mean age of 53.7 ± 15.9 years old at baseline. The median of PSQI scores in these patients was 9, and 71 patients (87.7%) had a PSQI score greater than 5 (poor sleep quality).

Twenty-three patients (7 women and 16 men) enrolled in the controlled trial and completed the first phase of treatment (12 received zolpidem and 11 received clonazepam). The mean age of these patients was 60.0 ± 14.0 years (range, of 36 to 79 years). The most prevalent cause of end-stage renal disorder in these patients were diabetes mellitus (9 patients) and hypertension (6 patients), and all of the patients suffered from hypertension and/or diabetes mellitus as comorbidities. The mean time on dialysis in these patients was 6.7 ± 4.4 years. Medications commonly prescribed in these patients were angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, β-1 blockers, vitamin D analogs, and phosphate binders.

There was no association between patients' sleep quality and the underlying cause of end-stage renal disease ($P = .47$), dialysis days per week ($P = .34$), or marital status ($P = .25$). After a 1 week of washout period between crossing process, 16 patients (12 men and 4 women) completed the second phase of the study. Seven patients failed to fulfill the second phase of evaluation (3 on zolpidem and 4 on clonazepam) due to the absence of positive properties (ie, there was not any subjective improvement in the sleep quality; 3 on zolpidem and 1 on clonazepam) or side effects of the administered agent including headache and sleepiness on the day after (3 on clonazepam). There was not any difference between the patients who completed the study and those who refused the second phase in age or baseline the PSQI score, but the latter group of patients were mostly women ($P = .04$).

The median baseline PSQI score in the 23 patients was 13, which showed a very poor sleep quality. No difference was detected between the two study arms in terms of gender, age, and baseline PSQI score. The findings of the phase 1 showed significant improvement in sleep quality in both groups; the median PSQI decreased from 13 to 10 ($P = .04$) in zolpidem group and from 12 to 8 ($P = .004$) in clonazepam group. Moreover, there was no significant difference in the progress of sleep quality between the two groups ($P = .09$). As presented in Table 1, in both phases of the study, the PSQI score was higher in the patients on zolpidem.

The tests for period and carry-over effects of the crossover design were not significant (Table 2),

Table 2. Test of Treatment, Period, and Carryover Effect Estimation in Crossover Design*

Parameter	Estimate	Standard Error	*t*	*P*
Treatment	-2.000	0.847	-2.360	.03
Period	-0.250	0.990	-0.205	.80
Carryover	0.194	1.209	0.160	.87

*Degree of freedom for carryover effect is 14 and for the two other effects is 1.

Table 1. The Pittsburgh Sleep Quality Index (PSQI) Scores

	Phase 1				Phase 2			
Treatment Order	Baseline PSQI	Participants	Second PSQI	*P*	Participants	Adjusted Phase 1 PSQI*	Third PSQI	*P*
Zolpidem-clonazepam	13.25 ± 4.00	12	10.33 ± 3.11	.04	9	10.56 ± 2.13	9.00 ± 3.71	.15
Clonazepam-zolpidem	12.73 ± 3.29	11	8.27 ± 2.37	.004	7	9.14 ± 2.54	11.71 ± 3.90	.15

*The mean PSQI score was calculated again because of the reduced number of patients after the completion of phase 1.

and our data showed that clonazepam improves sleep quality more significantly than does zolpidem; it reduced the mean PSQI score by an additional 2 scores (95% confidence interval, 0.195 to 3.805) compared with that of zolpidem (P = .03; Figures 1 and 2). There was no difference in treatment effects between the men and the women (P = .87). Furthermore, no correlation existed between treatment effects and age (P = .82) or baseline PSQI score (P = .63). The effect of treatments on sleep architecture showed a significant difference between clonazepam and zolpidem in the sleep quality (first) and latency (second) components of the PSQI (P = .01 and P = .04, respectively). However, there was not any significant difference in other sleep components between the two study arms (Figure 3).

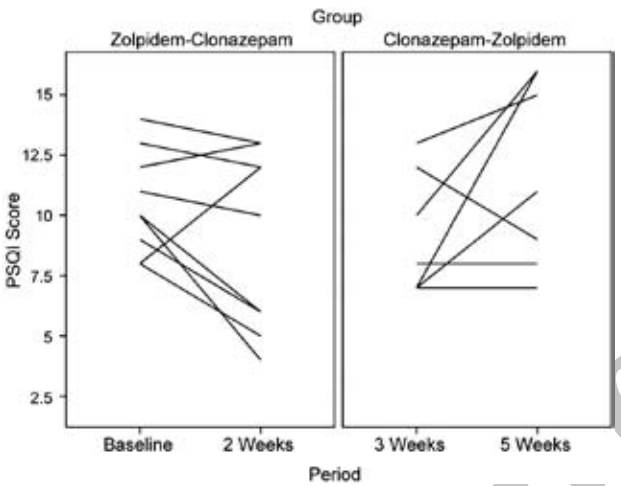

Figure 1. Profile plot of the Pittsburgh Sleep Quality Index (PSQI) score in each patient and sequence of treatment.

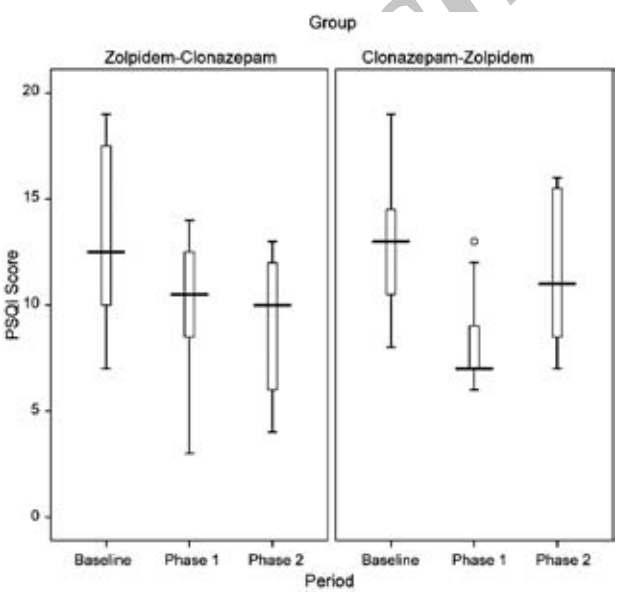

Figure 2. The Pittsburgh Sleep Quality Index (PSQI) scores in each period by sequence of treatments

In the 80 hemodialysis patients who were assessed at the initiation of the study, there was an insignificant negative correlation between baseline PSQI score and the time from the beginning of their dialysis program (P =.18). In these patients, the results showed a significant negative correlation of baseline PSQI score with transferin saturation (r = -0.27, P = .04), but not with serum hemoglobin, serum ferritin, or renal bone metabolism parameters (serum calcium, phosphate, and intact parathyroid hormone). Although all of the participants had serum sodium and potassium levels within normal range, there were significant negative correlations between baseline PSQI scores and serum concentrations of sodium (r = -0.25, P = .03) and potassium (r = -0.25, P = .04).

DISCUSSION

The prevalence of poor sleep quality among hemodialysis patients is reported to be from 41% to 83%.[3-7] However, our patients reported a higher frequency of sleep quality problems (88%). Patients on hemodialysis therapy have higher PSQI scores, less nocturnal sleeping hours, and more hours staying in bed.[19] Hence, the proper management of sleep disorders would be of great value in hemodialysis patients.

Long-acting benzodiazepines have been advised to be restricted in hemodialysis patients because of their side effects, including hangover, next-day residual effects, and sleep apnea.[10,20] Short-acting benzodiazepines may result in rebound insomnia and withdrawal symptoms.[17] Nonbenzodiazepine hypnotics may be good alternative hypnotic agents, particularly in dialysis centers, due to no physical dependence, no active metabolites, and good effects or at least no adverse effects regarding inducing sleep apnea.[14-16] In this study, zolpidem was not associated with undesirable sleep side effects such as daytime drowsiness, headache, or amnesia, at least during the short-term course of our study. Three patients refused to participate in the second phase of the study due to the perception that zolpidem might not be helpful in relieving insomnia. Meanwhile, the patients who received zolpidem did not complain of any particular side effects. In

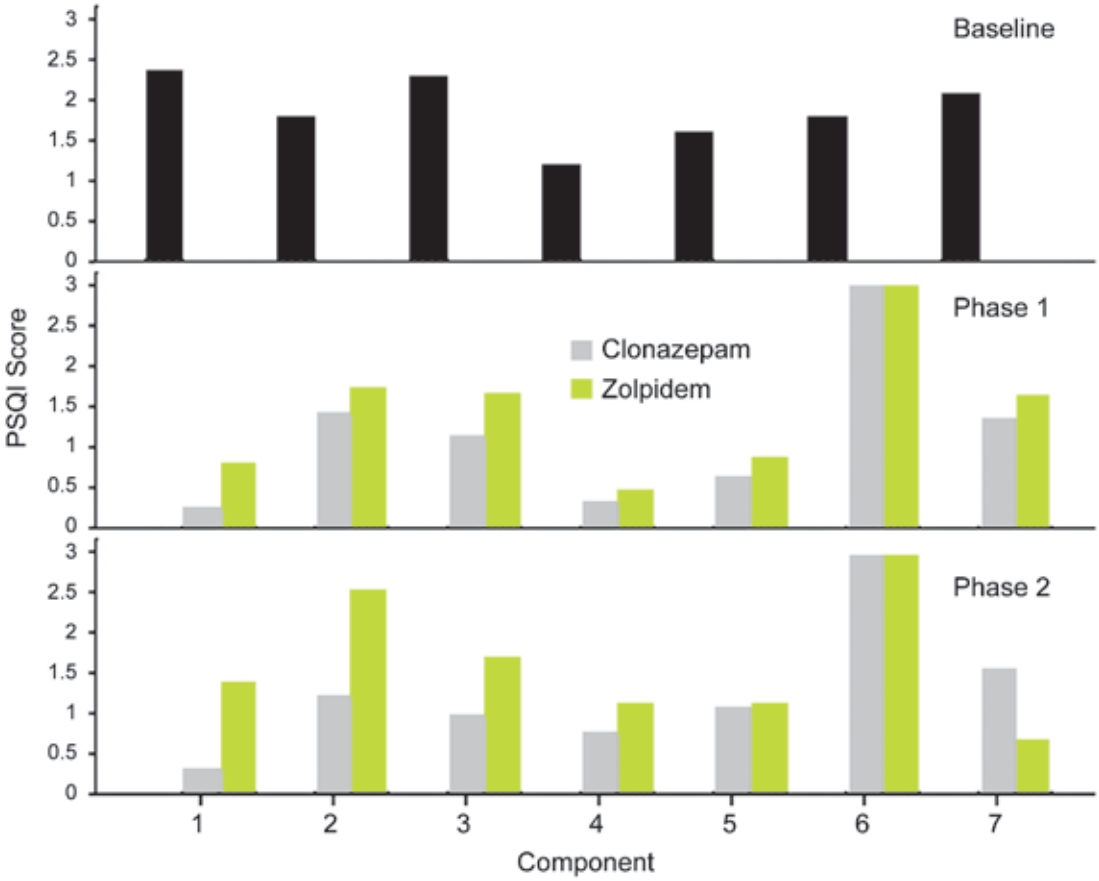

Figure 3. The mean Pittsburgh Sleep Quality Index (PSQI) scores of each component. Component 1 is subjective sleep quality; component 2, sleep latency; component 3, sleep duration; component 4, habitual sleep efficiency; component 5, sleep disturbances; component 6, use of sleeping medication; and component 7, daytime dysfunction over the last month.

contrast, patients on clonazepam experienced some adverse effects in the short course of treatment that discouraged them from continuing the study. However, clonazepam improved sleep disorders more effectively than zolpidem in the first and second components. Although clonazepam and zolpidem significantly improved sleep quality in hemodialysis patients; however, PSQI scores remained above 5 in our patients that showed poor sleep quality of our patients in spite of hypnotic administrations.

Several reasons have been suggested for the resistance to hypnotic medications, such as increased sympathetic tone of hemodialysis patients and the presence of dialysis-related symptoms including dry mouth and thirst during the night, pruritus, and the persistence of anxiety.[17,21] Hypnosis shifts the balance of the sympathovagal interaction toward an enhanced parasympathetic activity, parallel with a decrease of the sympathetic tone.[22] Therefore, the overactivity of sympathetic tone could reduce the effects of hypnotic medications. Although some studies suggest strong negative association between the longevity of hemodialysis therapy and the quality of sleep experienced by hemodialysis patients,[19] the large Dialysis Outcomes and Practice Patterns Study[7] in 7 countries showed no significant correlation between years on dialysis and poor sleep quality, with which the findings of our study is compatible.

Iron deficiency anemia was reported to be inversely related to sleep quality in hemodialysis patients.[23] We also found a significant negative correlation between sleep quality and serum transferring saturation. Although some researchers proposed disturbed bone metabolism, including hyperphosphatemia, hypercalcemia, or hyperparathyroidism, to be related to poor sleep quality,[7] we did not find any relationships between baseline PSQI scores and serum calcium,

phosphorus, or parathyroid hormone levels in our patients.

The main limitations of this study were the low number of participants and the short washout period between crossing processes, which were unavoidable due to poor compliance of these patients for a longer study, especially longer washout of any hypnotic agent, and also because of strict exclusion criteria of this study that made recruiting dropouts due to noncompliance almost impossible.

CONCLUSIONS

Clonazepam improved sleep quality more effectively than zolpidem; however, zolpidem was better tolerated in our hemodialysis patients.

ACKNOWLEDGEMENTS

This study was part of a PharmD thesis supported by Tehran University of Medical Sciences. The Authors thank Ms Aseah Ashouri for her valuable help in this study.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sabbatini M, Minale B, Crispo A, et al. Insomnia in maintenance haemodialysis patients. Nephrol Dial Transplant. 2002;17:852-56.
2. Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. Am J Kidney Dis. 1995;26: 751-56.
3. Holley JL, Nespor S, Rault R. A comparison of reported sleep disorders in patients on chronic hemodialysis and continuous peritoneal dialysis. Am J Kidney Dis. 1992;19:156-61.
4. Stepanski E, Faber M, Zorick F, et al. Sleep disorders in patients on continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 1995;6:192-97.
5. Hui DS, Wong TY, Ko FW, et al. Prevalence of sleep disturbances in Chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 2000;36:783-8.
6. De Vecchi A, Finazzi S, Padalino R, et al. Sleep disorders in peritoneal and haemodialysis patients as assessed by a self administered questionnaire. Int J Artif Organs. 2000;23:237-42.
7. Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from dialysis outcome and practice patterns study (DOPPS). Nephrol Dial Transplant. 2008;23:998-1004.
8. Benz RL, Pressman MR, Hovick ET, et al. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis. 2000;35:1052-60.
9. Afshar R, Emany A, Saremi A, et al. Effects of Intradialytic Aerobic Training on Sleep Quality in Hemodialysis Patients. Iran J Kidney Dis. 2011;5:119-23.
10. Molnar MZ, Novak M, Mucsi I. Management of restless leg syndrome in patients on dialysis. Drugs. 2006;66:607-24.
11. Skerritt JH, Johnston GA. Enhancement of GABA binding by benzodiazepines and related anxiolytics. Eur J Pharmacol. 1983;89:193-8.
12. Greenblatt DJ, Miller LG, Shader RI. Clonazepam pharmacokinetics, brain uptake, and receptor interactions. J Clin Psychiatr. 1987;48 Suppl: 4-11.
13. Terzano MG, Rossi M, Palomba V, et al. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem, and zaleplon. Drug Saf. 2003;26:261-82.
14. Berry RB, Patel PB. Effect of zolpidem on the efficacy of continuous positive airway pressure as treatment for obstructive sleep apnea. Sleep. 2006;29:1052-56.
15. Quadri S, Darke C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. J Clin Sleep Med. 2009;5:122-9.
16. Grimaldi D, Provini F, Vetrugno R, et al. Idiopathic central sleep apnoea syndrome treated with zolpidem. Neurol Sci. 2008;29:355-57.
17. Buysse DJ, Reynolds CF, Monk YH, et al. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.
18. Sabbatini M, Crispo A, Pisani A, et al. Zaleplon improves sleep quality in maintenance hemodialysis patients. Nephron Clin Pract. 2003;94:c99-103.
19. Yoshioka M, Ishii T, Fukunishi I. Sleep disturbance of end-stage renal disease. Jpn J Psychiatry Neurol. 1993;47:847-51.
20. Maczaj M. Pharmacological treatment of insomnia. Drugs. 1993;45:44-55.
21. Converse RL, Jacobsen TN, Toto RD, et al. Sympathetic over activity in patients with chronic renal failure. N Eng J Med. 1992;327:1912-8.
22. DeBenedittis G, Cigada M, Bianchi A, et al. Autonomic changes during hypnosis: a heart rate variability power spectrum analysis as a marker of sympatho-vagal balance. Int J Clin Exp Hypn. 1994;42:140-52.
23. Gul A, Aoun N, Trayner EM Jr. Why do patients sleep on dialysis. Semin Dial. 2006;19:152-7.

Correspondence to:
Simin Dashti-Khavidaki, PharmD
Faculty of Pharmacy and Nephrology Research Center, Tehran University of Medical Sciences, PO Box: 14155/6451 Tehran, Iran
Tel: +98 912 247 1998
Fax: +98 21 6695 4709
E-mail: dashtis@sina.tums.ac.ir

Received January 2011
Revised May 2011
Accepted June 2011