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The Effect of Ropinirole on the Quality of Life in Patients with Restless Legs Syndrome in Korea: An 8-Week, Multicenter, Prospective Study

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Background and Purpose Dopamine agonists are first-line drugs for treating the symptoms of restless legs syndrome (RLS). However, few studies have investigated the effect of dopamine agonists on the quality of life (QoL) in RLS patients. We conducted a study to determine whether ropinirole exerts positive effects on the QoL in RLS patients and to analyze the underlying factors.

Methods Primary RLS patients from eight medical centers were recruited in the study. They were evaluated in the baseline phase using various questionnaires including the Korean versions of the International Restless Legs Scale (K-IRLS), RLS QoL questionnaire (K-RLSQoL), and the Short Form 36 Health Survey (SF-36). After taking ropinirole for 8 weeks the same questionnaires were again completed as a re-evaluation. We analyzed the statistical difference using a paired *t*-test, a Pearson's correlation, and a stepwise multiple regression in order to identify the factors associated with the QoL change.

Results A total of 107 subjects, including 65 (60.7%) females, completed this study. They were aged 51.68±14.80 years (mean±SD) and had a symptom duration of 8.8±9.0 months. After treatment with ropinirole, there were significant improvements on the K-RLSQoL, SF-36, and K-IRLS. The Pearson's correlation analysis showed that the improvement of QoL in RLS patients was significantly correlated with the severity of RLS (r=0.236, p<0.014) at baseline.

Conclusions The results from this study suggest that treatment with ropinirole can improve the QoL in RLS patients. The improvement in the QoL is more related with the improvement of RLS symptoms. **J Clin Neurol 2013;9:51-56**

Key Words restless legs syndrome, dopamine agonists, quality of life, sleep.

Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor neurological disorder[1,2] with a reported prevalence of 3.9-11.5% in the general population.[3-9] It is characterized by leg discomfort with nocturnal aggravation, and the symptom severity aggravates with age.[10] Therefore, RLS patients commonly complain of both sleep disturbance and somatic symptoms. Due to these clinical characteristics the quality of life (QoL) of RLS patients is worse than that of healthy controls, and even worse than that of patients with chronic medical diseases, such as hypertension and type 2 diabetes.[3,11]

L-dopa has been prescribed for RLS symptoms since Akpanir reported the effects of L-dopa in RLS.[12] However, its strong association with the augmentation of RLS symptoms.[13] Thus, there has been an interest in the use of dopamine agonists for RLS patients. Ergot-derived dopamine agonists such as pergolide and cabergoline have been shown to improve RLS symptoms,[14] but they have potential risks of fibrotic side effects with cardiac valvulopathy.[15] The non-ergot-derived dopamine agonists ropinirole and pramipexole are not associated with such complications, which have made them the first-line treatment of RLS.[16]

Ropinirole exhibits a high affinity for D_2 and D_3 receptors, and controls nigrostriatal and mesolimbic-mesocortical dopaminergic activity.[17] Clinical trials have shown that ropinirole significantly improves symptoms of RLS,[18,19] producing scores on the mean International Restless Legs Scale (IRLS) that are 29-37% lower than those in placebo groups, and reducing periodic limb movements during sleep relative to baseline or placebo.[20] Furthermore, ropinirole significantly improved the QoL in RLS patients compared to placebos. However, the effects on the QoL in RLS patients have not been fully elucidated, and all of these studies were performed only in Western countries.[18-21]

The purpose of this study was to elucidate the effect of ropinirole on the QoL in Korean patients with RLS and the underlying factors.

Methods

This was a multicenter, national trial lasting 8 weeks that was conducted in eight university hospitals in Korea. We enrolled all consecutive primary RLS patients over 18 years old who consented to participate in the study. RLS was diagnosed by neurologists based on diagnostic standards set by the National Institutes of Health workshop on RLS during face-to-face interviews using the validated Korean-language version of the John Hopkins Telephone Diagnostic Questionnaire.[1,22] After excluding any mimic diseases through a direct physical examination and laboratory tests, the remaining patients were diagnosed with RLS. All patients had a score of at least 15 on the Korean version of the IRLS (K-IRLS) at baseline.[23] We excluded other comorbid sleep disorders through analysis of sleep questionnaires, comorbidities to RLS, or secondary RLS caused by pregnancy or by other diseases such as chronic kidney disease, peripheral polyneuropathy, and iron-deficiency anemia. However, subjects with only peripheral iron deficiency without definite cause were included.

Patients received ropinirole once daily at 2 hours before bedtime, with treatment starting at a dose of 0.25 mg. The dose was then titrated upwards over 4 weeks until they were judged to have reached their optimal dose or until they were receiving the maximum dosage (4.0 mg/day). Down-titration was allowed during the titration period if patients experienced adverse events. Patients were maintained on a constant dose of ropinirole from weeks 4 to 8. We assessed adverse effects of ropinirole and regularly checked blood pressure, heart rate, and vital signs whenever they visited a clinic.

QoL was evaluated based on two questionnaires: the Korean version of the RLS QoL questionnaire (K-RLSQoL) and the Short Form 36 Health Survey (SF-36).[22,24] The K-RLSQoL is a validated translated version of the RLS QoL questionnaire. Scores are from 0 to 100 points, with a lower score indicating a worse QoL. The SF-36 health questionnaire is currently a widely used tool to assess health-related QoL that also has been validated.[24] It comprises eight domains: physical function, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores are from 0 to 100 points, with a lower score indicating a worse QoL. The symptom severity was measured using the K-IRLS.[23] We also evaluated the sleep quality and mood based on the Korean version of the Pittsburg Sleep Quality Index (PSQI-K),[25] the Insomnia Severity Index, the Korean version of the Epworth Sleepiness Scale,[26] the Hospital Anxiety Scale,[27] and the Beck Depression Inventory-2 (BDI-2),[28] in addition to the demographic variables. Most of the questionnaires used in this study underwent a validation process involving Korean populations, and they were completed at baseline and at week 8. The patients were divided into two groups, responders and nonresponders, based on whether or not the K-IRLS score had decreased at week 8, respectively. During the survey, research coordinators who received training were available to help subjects who experienced difficulty completing the questionnaires. The study was approved by the institutional ethics committee at each university hospital.

Statistical analysis

Continuous and categorical variables are presented as mean± SD and frequency values, respectively. The significance of the

QoL and other scale changes between the baseline and after treatment were analyzed using the paired *t*-test. Correlations between QoL score changes and related factors, such as age, age at symptom onset, symptom duration, RLS severity, sleep quality, insomnia severity, and depression, were assessed using Pearson's correlation. Stepwise multiple regression analysis was used to select the significant predictors for the QoL changes in RLS patients, and at each step independent variables were entered if there were factors significantly correlated with the QoL. Differences in QoL changes between the baseline and after treatment were tested by analysis of covariance using baseline scores as covariates. Statistical analyses were performed using the statistical software package SPSS 19.0 for Windows. A probability value of $p<0.05$ was considered indicative of statistical significance.

Table 1. Demographic and clinical characteristics of the restless legs syndrome (RLS) patients

Characteristic	Value (*n*=107)
Age (years)	51.68±14.80
Gender (female), % (*n*)	60.7 (65)
BMI (kg/m^2)	23.80±2.98
History of alcohol consumption, % (*n*)	33.6 (36)
PSQI-K	10.6±4.4
BDI-2	12.4±8.6
Duration of symptoms (years)	8.8±9.0
Symptom severity (K-IRLS)	23.4±7.5
Mild (*n*=6, 5.6%)	
Moderate (*n*=31, 29.0%)	
Severe (*n*=50, 46.7%)	
Very severe (*n*=20, 18.7%)	
Total SF-36	63.0±19.9
K-RLSQoL	64.5±17.9

Data are mean±SD values except where stated otherwise.
BDI-2: Beck Depression Inventory-2, BMI: body mass index, K-IRLS: Korean version of the International Restless Legs Scale, K-RLSQoL: Korean version of the RLS quality of life questionnaire, PSQI-K: Korean version of the Pittsburg Sleep Quality Index.

Results

One hundred and seven RLS patients were enrolled; their age was 51.68±14.80 years (range 19-75 years), and 65 (60.7%) were female. The demographic and clinical characteristics of RLS patients are listed in Table 1. The score for RLS symptom severity was 23.4±7.5, and the duration of symptoms was 8.8±9.0 years. The distribution of RLS symptom severity was as follows: 6 (5.6%) mild, 31 (29.0%) moderate, 50 (46.7%) severe, and 20 (18.7%) very severe; age and sex did not differ significantly between these four subgroups. The baseline QoL scores were 64.5±17.9 for K-RLSQoL and 63.0±19.9 for total SF-36 (Table 1).

All patients received ropinirole for 4 weeks and maintained a stable dosage for the following 4 weeks. The QoL of RLS patients was significantly improved after 8 weeks of ropinirole treatment, as measured by the K-RLSQoL (73.7±18.4 $p\leq 0.001$) and total SF-36 (67.5±19.8, $p=0.004$) scores. The individual domains of the SF-36 indicated significant differences between baseline and after treatment in bodily pain (52.4±25.3 vs. 63.6±23.8, $p\leq0.001$), general health (48.6±20.6 vs. 51.8±21.0, $p=0.025$), vitality (48.7±20.0 vs. 53.6±17.9, $p=0.008$), physical domains (57.7±20.3 vs. 63.2±20.5, $p\leq0.001$), and mental domains (62.7±19.2 vs. 65.8±18.1, $p=0.041$) (Fig. 1, Table 2). The K-IRLS score was significantly lower after ropinirole treatment (16.8±7.9) than the baseline (23.4±7.5, $p\leq 0.001$). The scores on the sleep-related scales were also improved from baseline to after treatment: PSQI-K (10.6±4.4 vs. 9.2±4.4, $p\leq0.001$), Insomnia Severity Index (14.5±7.1 vs. 10.5±6.5, $p\leq0.001$), and Korean version of the Epworth Sleepiness Scale (7.2±3.9 vs. 6.1±3.9, $p=0.007$); however, the

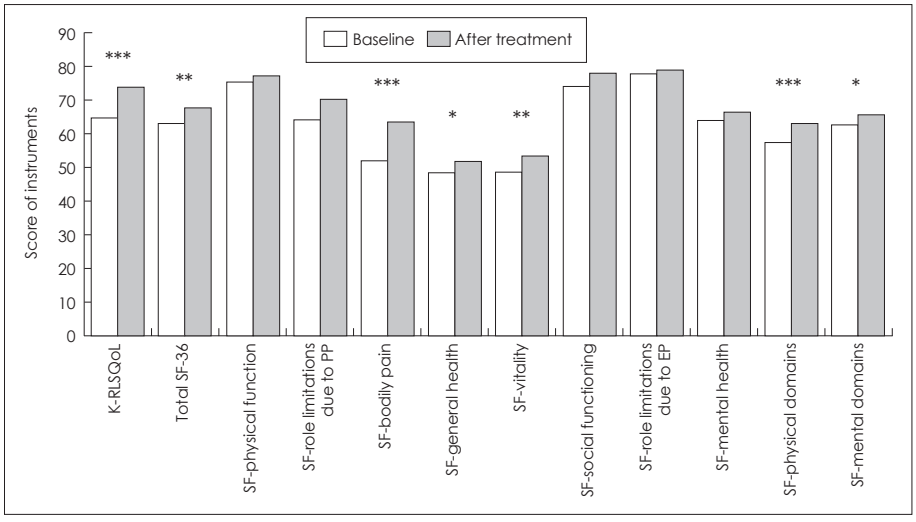

Fig. 1. Changes in the quality of life after ropinirole treatment. *$p<0.05$, **$p<0.01$, ***$p<0.001$. EP: emotional problems, K-RLSQoL: Korean version of the restless legs syndrome quality of life questionnaire, PP: physical problems, SF-: SF-36 subscale, SF-36: Short Form 36 Health Survey.

score on the Depression Scale (BDI-2) did not differ after treatment (Fig. 2, Table 2). The daily dose of ropinirole at 8 weeks was 0.62±0.43 mg.

The patients were divided into two groups based on the efficacy of ropinirole (responders: *n*=86, 80%; nonresponders: *n*=21, 20%) to determine whether the improved QoL was purely associated with the change in symptom severity or with other treatment effects. The responders showed greater improvements ($p<0.05$) on all subscales except general health, vitality, and mental domain than nonresponders (Table 3).

The improvement of QoL in RLS patients was significantly correlated with the severity of RLS ($r=0.236$, $p<0.014$) at baseline. A stepwise multiple regression for factors affecting the K-RLSQoL score change was performed using the following independent factors: age, gender, age at symptom onset, symptom duration, depression (BDI-2), RLS severity (K-IRLS score), sleep quality (PSQI-K score), and total SF-36. The severity of symptoms was found to be significantly associated with the change in K-RLSQoL scores ($\beta=0.586$, $p=0.017$), with RLS patients with more severe RLS symptoms showing greater improvement in QoL after ropinirole treatment.

Adverse events were reported in nine patients (8.3%): dizziness (*n*=5, 4.6%), nausea (*n*=1, 0.9%), dry mouth (*n*=1, 0.9%), fatigue (*n*=1, 0.9%), and leg edema (*n*=1, 0.9%). Most of these adverse events were mild to moderate in intensity, and did not cause any patient to withdraw from the study.

Discussion

This study found improvement in the QoL as well as an improved symptom severity after short-term ropinirole treatment. The QoL was improved in terms of both physical and mental health. The QoL of patients with RLS is known to be considerably worse than that in healthy controls, and similar to that in patients with chronic medical diseases such as diabetes and Parkinson's disease.[3,11,29] Thus, the positive effect of ropinirole found in the present study represents further evidence that it is effective in the treatment of RLS. Ropinirole was generally tolerated well and there were no reported serious adverse events in our study.

The ropinirole-induced changes in the SF-36 scores for bodily pain, general health, and vitality domains indicated that patients using ropinirole experienced improvements in their bodily pain and general health, and had more energy and less fatigue. In particular, the responders showed greater improvements in most domains of the SF-36. The improvement of QoL in RLS patients was assessed using both the disease-specific K-RLSQoL and the SF-36. This finding that ropinirole improved the QoL of RLS patients was similar to that of a previous study.[19] The data presented here support the notion that treatment with ropinirole can lead to improvement in QoL in RLS patients. However, another study found that ropinirole was associated with a greater improvement in QoL when this was assessed using the disease-specific measure (i.e., RLS QoL questionnaire) than with generic measures (SF-36).[18] Western studies have produced different findings for QoL after ropinirole treatment when using the SF-36, which could be due to

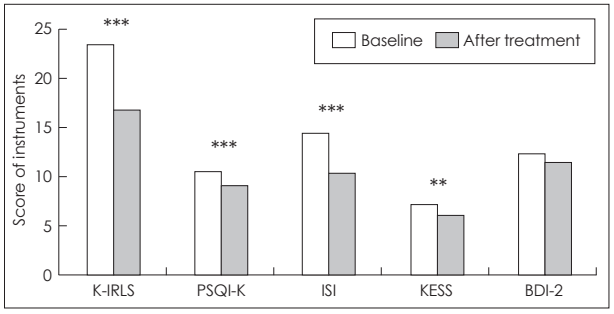

Fig. 2. Changes in the clinical characteristics after ropinirole treatment. BDI-2: Beck Depression Inventory-2, ISI: Insomnia Severity Index, K-IRLS: Korean version of the International Restless Legs Scale, KESS: Korean version of the Epworth Sleepiness Scale, PSQI-K: Korean version of the Pittsburg Sleep Quality Index. **$p<0.01$, ***$p<0.001$.

Table 2. Clinical characteristics at baseline and after 8 weeks of ropinirole treatment

	Baseline	After treatment	*p*
K-RLSQoL	64.5±17.9	73.7±18.4	<0.001
Total SF-36	63.0±19.9	67.5±19.8	0.004
SF36_PF	75.4±23.8	77.3±23.8	0.255
SF36_RP	64.2±41.0	70.8±40.6	0.053
SF36_BP	52.4±25.3	63.6±23.8	<0.001
SF36_GH	48.6±20.6	51.8±21.0	0.025
SF36_V	48.7±20.0	53.6±17.9	0.008
SF36_SF	74.2±24.5	78.0±23.1	0.070
SF36_RE	77.6±37.7	79.1±37.6	0.635
SF36_MH	64.0±21.0	66.6±16.1	0.196
PH	57.7±20.3	63.2±20.5	<0.001
MH	62.7±19.2	65.8±18.1	0.041
K-IRLS	23.4±7.5	16.8±7.9	<0.001
BDI-2	12.4±8.6	11.5±10.1	0.191
PSQI-K	10.6±4.4	9.2±4.4	<0.001
ISI	14.5±7.1	10.5±6.5	<0.001
KESS	7.2±3.9	6.1±3.9	0.007

Data are mean±SD values.
BDI-2: Beck Depression Inventory-2, ISI: Insomnia Severity Index, K-IRLS: Korean version of the International Restless Legs Scale, K-RLSQoL: Korean version of the restless legs syndrome quality of life questionnaire, KESS: Korean version of the Epworth Sleepiness Scale, MH: mental domains, PH: physical domains, PSQI-K: Korean version of the Pittsburg Sleep Quality Index, SF36: Short Form 36 Health Survey, SF36_BP: bodily pain, SF36_GH: general health, SF36_PF: physical function, SF36_MH: mental health, SF36_RE: role limitations due to emotional problems, SF36_RP: role limitations due to physical problems, SF36_SF: social functioning, SF36_V: vitality.

Table 3. Changes in quality of life in responder and nonresponder groups

	Baseline		After treatment		*p*
	Nonresponders 21 (20%)	Responders 86 (80%)	Nonresponders 21 (20%)	Responders 86 (80%)	
K-RLSQoL	69.9±15.5	63.2±18.3	61.1±3.3	76.7±1.6	<0.001
Total SF36	66.2±21.8	62.2±19.5	56.0±2.9	70.3±1.4	<0.001
SF36_PF	79.8±20.8	74.4±24.5	66.7±3.4	79.9±1.7	0.001
SF36_RP	73.8±40.7	61.8±40.9	48.4±6.5	76.3±3.2	<0.001
SF36_BP	60.2±26.4	50.5±24.8	47.2±4.3	67.7±2.1	<0.001
SF36_GH	50.0±20.5	48.3±20.7	49.6±3.0	52.3±1.5	0.427
SF36_V	51.4±17.6	48.0±20.5	51.1±3.4	54.2±1.7	0.410
SF36_SF	73.4±30.4	74.5±23.1	67.3±4.0	80.7±2.0	0.003
SF36_RE	74.7±39.3	78.3±37.5	58.9±6.2	84.1±3.1	<0.001
SF36_MH	64.0±25.0	64.1±20.0	62.9±3.2	67.5±1.6	0.196
PH	62.9±20.5	56.3±20.2	51.8±2.9	66.0±1.4	<0.001
MH	63.2±21.1	62.6±18.8	57.8±2.9	67.9±1.4	0.003

Baseline data are mean±SD (standard deviation) values, after-treatment data are mean±SE (standard error) values.
K-RLSQoL: Korean version of the restless legs syndrome quality of life questionnaire, MH: mental domains, PH: physical domains, SF36: Short Form 36 Health Survey, SF36_BP: bodily pain, SF36_GH: general health, SF36_MH: mental health, SF36_PF: physical function, SF36_RE: role limitations due to emotional problems, SF36_RP: role limitations due to physical problems, SF36_SF: social functioning, SF36_V: vitality.

this instrument not fully covering aspects of sleep in RLS patients.

RLS patients complain of both leg discomfort and sleep problems. Ropinirole effectively treats the symptoms of RLS as measured by the K-IRLS, improving sleep quality and reducing both sleep disturbance and daytime somnolence. These positive effects of ropinirole on sleep were similar to those found in previous studies,[18,30] and should prove beneficial in the management of RLS. However, the improvement of QoL in RLS patients is due to alleviating symptoms of RLS rather than improving sleep quality.

The mean ropinirole daily dosage was 0.62 mg, which is smaller than that found in Western studies (1.5-1.9 mg).[18,19] It seems that the symptoms of Korean RLS patients responded well to low-dosage ropinirole. The mean K-IRLS score in the present study was 23 at baseline and 17 after 8 weeks of ropinirole administration, while the mean adjusted change in IRLS scores between baseline and week 12 was -11.2 in a Western study.[19] The smaller improvement in the present study could be due to Korean doctors tending to prescribe the drug at a lower dosage; our results cannot be compared directly with those of Western studies due to differences in drug dosage and culture.

The prevalence of depression is higher among RLS patients than controls.[31,32] Treating depression in RLS is challenging since some antidepressants reportedly exacerbate or even trigger RLS symptoms.[31,33] In contrast to a previous study,[34] we found that ropinirole did not improve depression as measured by the BDI-2. This discrepancy could be due to that study using a different (immediate-release) ropinirole formula and a longer treatment duration (12 weeks). Therefore, the antidepressive effects of ropinirole in RLS patients remain unclear, and so future studies should attempt to clarify the antidepressive effects of dopamine agonists such as ropinirole in RLS patients.

Adverse events of ropinirole in the present study were milder in severity and had a lower incidence than those in Western studies.[18,19,21] This may be related to our mean dosage of ropinirole being lower than in the other studies. The adverse events were generally consistent with those known for this class of dopamine agonists.

The main weaknesses of our study are that it was not a randomized placebo-controlled trial and there was no long-term follow-up. However, it is significant in being a multicenter clinical trial and finding that Korean RLS patients using ropinirole showed improvement in their QoL as measured by both the K-RLSQoL and the SF-36. Ropinirole appeared to have a positive impact on QoL in our study, but future studies should evaluate long-term changes in larger populations in order to determine whether QoL improvements are sustained or further enhanced and whether high doses affect QoL to a greater degree than low doses.

In conclusion, this multicenter trial showed that short-term ropinirole is potentially beneficial for the QoL as well as alleviating symptom severity in Korean RLS patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

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REFERENCES

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101-119.
2. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med* 2010;11:807-815.
3. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286-1292.
4. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med* 2004;164:196-202.
5. Bjorvatn B, Leissner L, Ulfberg J, Gyring J, Karlsborg M, Regeur L, et al. Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. *Sleep Med* 2005;6:307-312.
6. Cho YW, Shin WC, Yun CH, Hong SB, Kim JH, Allen RP, et al. Epidemiology of restless legs syndrome in Korean adults. *Sleep* 2008;31:219-223.
7. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* 2004;5:237-246.
8. Högl B, Kiechl S, Willeit J, Saletu M, Frauscher B, Seppi K, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. *Neurology* 2005;64:1920-1924.
9. Tison F, Crochard A, Léger D, Bouée S, Lainey E, El Hasnaoui A. Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT Study. *Neurology* 2005;65:239-246.
10. Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med* 2007;120:S13-S21.
11. Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, et al. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther* 2004;26:925-935.
12. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol* 1982;39:739.
13. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* 1996;19:205-213.
14. Trenkwalder C, Hundemer HP, Lledo A, Swieca J, Polo O, Wetter TC, et al. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. *Neurology* 2004;62:1391-1397.
15. Andersohn F, Garbe E. Cardiac and noncardiac fibrotic reactions caused by ergot-and nonergot-derived dopamine agonists. *Mov Disord* 2009;24:129-133.
16. Hornyak M, Trenkwalder C, Kohnen R, Scholz H. Efficacy and safety of dopamine agonists in restless legs syndrome. *Sleep Med* 2012;13:228-236.
17. Cheer SM, Bang LM, Keating GM. Ropinirole: for the treatment of restless legs syndrome. *CNS Drugs* 2004;18:747-754; discussion 755-756.
18. Trenkwalder C, Garcia-Borreguero D, Montagna P, Lainey E, de Weerd AW, Tidswell P, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004;75:92-97.
19. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K, et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004;19:1414-1423.
20. Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep* 2004;27:907-914.
21. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY; TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006;81:17-27.
22. Cho YW, Lee MY, Yun CH, Shin WC, Hong SB, Kim JH. The reliability and validity of the Korean version of paradigm of questions for epidemiology studies of restless legs syndrome and the Johns Hopkins telephone diagnostic interview form for the restless legs syndrome. *J Korean Neurol Assoc* 2007;25:494-499.
23. Yang JG, Kim DH, Lee JH, Park KH, Jung KY, Shin WC, et al. The reliability and validity of the Korean versions of the international restless legs scale and the restless legs syndrome quality of life questionnaire. *J Korean Neurol Assoc* 2010;28:263-269.
24. Han CW, Lee EJ, Iwaya T, Kataoka H, Kohzuki M. Development of the Korean version of Short-Form 36-Item Health Survey: health related QOL of healthy elderly people and elderly patients in Korea. *Tohoku J Exp Med* 2004;203:189-194.
25. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. *Sleep Breath* 2012;16:803-812.
26. Cho YW, Lee JH, Son HK, Lee SH, Shin C, Johns MW. The reliability and validity of the Korean version of the Epworth sleepiness scale. *Sleep Breath* 2011;15:377-384.
27. Oh SM, Min KJ, Park DB. A study on the standardization of the hospital anxiety and depression scale for Koreans: a comparison of normal, depressed and anxious groups. *J Korean Neuropsychiatr Assoc* 1999;38:289-296.
28. Jo SA, Park MH, Jo I, Ryu SH, Han C. Usefulness of Beck Depression Inventory (BDI) in the Korean elderly population. *Int J Geriatr Psychiatry* 2007;22:218-223.
29. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, et al. Burden of restless legs syndrome on health-related quality of life. *Qual Life Res* 2007;16:617-624.
30. Bogan RK. Ropinirole treatment for restless legs syndrome. *Expert Opin Pharmacother* 2008;9:611-623.
31. Picchietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep, and depression. *Sleep* 2005;28:891-898.
32. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* 2006;7:545-552.
33. Rottach KG, Schaner BM, Kirch MH, Zivotofsky AZ, Teufel LM, Gallwitz T, et al. Restless legs syndrome as side effect of second generation antidepressants. *J Psychiatr Res* 2008;43:70-75.
34. Benes H, Mattern W, Peglau I, Dreykluft T, Bergmann L, Hansen C, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. *J Neurol* 2011;258:1046-1054.