ORIGINAL ARTICLE

Comparison of pramipexole and citalopram in the treatment of depression in Parkinson's disease: A randomized parallel-group trial

Ehsan Ziaei, Parisa Emami Ardestani, Ahmad Chitsaz
Department of Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Depression is one of the most common neuropsychiatric symptoms in Parkinson's disease (PD). There is little evidence to guide depression treatment in these patients. The aim of this study was to compare citalopram and pramipexole in reducing depressive symptoms in patients with PD. **Materials and Methods:** In the present 8-week randomized trial, we compared the efficacy of pramipexole versus citalopram in the treatment of depression in PD patients. For this purpose, 44 PD patients with depression randomly received open-label oral citalopram tablets or pramipexole and their depression, quality of life, and daytime sleepiness scores were evaluated at baseline and after the 8-week trial period. **Results:** The median age of the patients was 64 years, and about 85% of them were male in both groups. The Beck Depression Inventory score, Parkinson's disease summary index (PDSI), and Epworth Sleepiness Scale were significantly decreased ($P < 0.05$) in both citalopram and pramipexole groups throughout this period and without significant difference ($P > 0.05$) between these two groups, except for PDSI score which showed significant improvement in pramipexole group compared with citalopram group ($P < 0.0001$, $r = 0.319$). There were neither serious adverse effects nor treatment discontinuation due to the adverse effects. **Conclusion:** The results indicated that both citalopram and pramipexole were effective in the alleviation of depression and improving the quality of life in PD patients; however, pramipexole was seemed to be slightly more beneficial on quality of life in these patients. Therefore, pramipexole seems to be an effective treatment for depression in addition to its benefits for motor symptoms of PD patients.

Key words: Citalopram, depression, Parkinson disease, pramipexole

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INTRODUCTION

Depression is a common nonmotor symptom in patients with Parkinson's disease (PD). The mean prevalence of depressive disorders in PD is 35%, although some studies estimated the mean prevalence to be up to 90%.[1] In addition to the patient suffering, it is associated with cognitive decline, reduced quality of life, and increased burden of caregivers.[2,3] It has also been associated with increased mortality in patients with PD.[4] Despite the relatively high prevalence of depressive disorders among patients with PD and its significance on patient's quality of life, there is little evidence to guide the best treatment options. In addition, the clinical efficacy and safety of antidepressant therapies in patients with PD are still unknown. Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) such as citalopram are the most commonly used medications and have evidence of efficacy in patients with PD;[5,6] however, there is conflicting evidence that this group of antidepressants may exacerbate parkinsonism among these patients.[7-9]

There are some lines of evidence showing that dopamine receptor agonists, especially pramipexole, might be effective in the treatment of depression in PD patients.[10-16] In a randomized, double-blind, placebo-controlled trial, pramipexole improved

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Address for correspondence: Prof. Ahmad Chitsaz, Department of Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: chitsaz@med.mui.ac.ir
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depressive symptoms in patients with PD.[10] A Movement Disorder Society (MDS) evidence-based review showed that pramipexole had been a clinically useful treatment with acceptable risk for depression in PD patients.[17] Pramipexole is a nonergot dopamine agonist with a high binding specificity for the dopamine D_3 receptor subtype that is effective in the treatment of motor symptoms of PD.[18,19] Dopaminergic pathway dysfunction has been shown a role in the pathogenesis of depression.[20]

The aim of this study was to compare an SSRI antidepressant, citalopram, and a dopamine agonist, pramipexole in reducing depressive symptoms in patients with PD. To our knowledge, there is no published study that compared pramipexole with citalopram in depression in PD. For this purpose, we have conducted an 8-week open-label parallel-group randomized trial designed to evaluate these two treatments for the management of depression in patients with PD. As secondary outcomes, we evaluated the quality of life and daytime sleepiness with the 39-item Parkinson's Disease Questionnaire (PDQ-39) and Epworth Sleepiness Scale (ESS), respectively.

METHODS

This clinical trial was registered in the Iranian clinical trials registration website (http://www.irct.ir: IRCT20191111045407N1). In this 8-week open-label parallel-group, randomized trial, 44 patients between the ages of 35 and 80 years with clinically diagnosed PD, according to the MDS clinical diagnostic criteria,[21] and depressive disorders with depressed mood, according to Diagnostic and Statistical Manual of Mental Disorders V, were enrolled from two movement disorder clinics in Isfahan, Iran. Patients were included in the study if they were on levodopa monotherapy which makes their motor symptoms under satisfactory control without motor fluctuations as judged by the movement disorders specialist. Patients were excluded if they had serious or unstable medical conditions (includes the need for hospital admission for any reason and uncontrolled common medical diseases such as hypertension and diabetes mellitus), cognitive impairment (Mini–Mental State Examination <27), psychotic disorders, and suicidal thoughts and attempts, pregnancy, lactation and taking oral contraceptive pills, history of malignant melanoma and deep brain stimulation surgery, take any of antipsychotics, anticholinergics, and other psychotherapeutic medications and treatment. Patients with an "off" period >50% of the day were also excluded from the study. The study protocol was confirmed by the Isfahan University of Medical Sciences Research Ethics Committee (reference: IR.MUI.MED.REC.1398.403), and all patients provided informed consent at the first visit. After the eligibility assessment, in the next visit, patients were randomly assigned (1:1) to the citalopram or pramipexole group. Citalopram was started at 10 mg daily for a week and increased to 20 mg daily afterward for 7 weeks. Pramipexole was started at 0.7 mg orally daily (0.35 mg twice a day) for a week and further increased to 1.4 mg daily (0.7 mg twice a day) for another 7 weeks. The patients were evaluated at the first visit (baseline scoring) and demographic data were obtained. After the 8-week treatment, they were reevaluated (endpoint scoring). The primary outcome was a change in the Beck Depression Inventory (BDI) score between baseline and endpoint for each of the two groups (≥3 points are clinically significant).[22] The secondary outcome included changes in the Parkinson's disease summary index (PDSI) derivated from the 39-item PDQ-39 score between baseline and after 8-week treatment for each of the two groups to assess the patient's quality of life. This questionnaire consists of eight domains such as mobility, daily activities, and emotional well-being. PDSI is an overall single summarized index derivated from PDQ-39 (≥4.72 points are clinically significant).[23] Another secondary outcome was ESS score between baseline and after 8-week treatment for each of the two groups to assess the patient's daytime sleepiness changes after treatment with these two drugs due to their benefits and adverse effects (≥3 points are clinically significant).[24] All statistical analyses were performed using IBM SPSS Statistic Version 24.0 (IBM, Armonk, NY, United States of America). A per-protocol analysis was assessed to estimate the true efficacy of these two drugs. For primary and secondary variables, differences between treatment groups were analyzed by the ANCOVA model. In view of the nonnormal distribution of the parameters, Wilcoxon signed-rank test was used for changes in primary and secondary outcomes between baseline and endpoint in each group, and the Kruskal–Wallis test was used for detecting differences in general characteristics, levodopa daily dose, and duration of PD.

RESULTS

The trial profile is described in Figure 1. A total of 56 patients were assessed for eligibility, and finally, 44 patients with PD were randomized to receive citalopram[22] and pramipexole.[22] Three of the patients prematurely discontinued the trial due to loss of follow-up: One in the citalopram group and two in the pramipexole group. There was no treatment discontinuation due to adverse effects. Only one patient in the citalopram group and one patient in the pramipexole group had mild transient gastrointestinal symptoms (nausea) for few 1st days. They did not have any new motor symptoms or exacerbation in motor symptoms.

Baseline characteristics of the patients including age, sex, duration of PD, levodopa daily dose, the severity

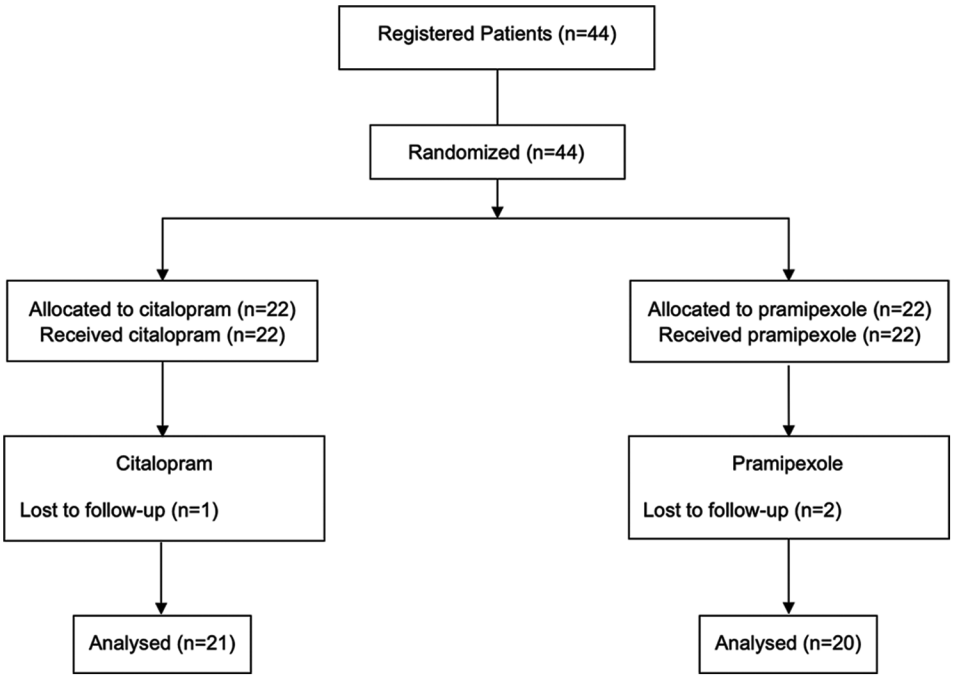

Figure 1: Trial profile

of depression (BDI score), quality of life (PDSI), and daytime sleepiness (ESS score) were not significantly different ($P > 0.05$) between two groups. The results are presented with medians and interquartile range due to nonnormal distribution of the parameters [Table 1].

In both the citalopram and pramipexole groups, the BDI score showed a highly significant decrease with a large effect size ($r \geq 0.6$) analyzed by a Wilcoxon signed-rank test ($Z = -4.018$, $P < 0.0001$, and $r = -0.877$ for citalopram group and $Z = -3.926$, $P < 0.0001$, and $r = -0.878$ for pramipexole group). The mean score change was − 8.48 ± 4.98 for the citalopram group and − 7.75 ± 5.36 for the pramipexole group [Table 2]. The difference between the two groups, analyzed by ANCOVA analysis, showed no statistical significance ($F = 1.392$ and $P = 0.245$).

As the secondary outcome, the PDSI was also significantly decreased in both groups with a large effect size ($r \geq 0.6$) analyzed by a Wilcoxon signed-rank test ($Z = -3.746$, $P < 0.0001$, and $r = -0.817$ for citalopram group and $Z = -3.921$, $P < 0.0001$, and $r = -0.877$ for pramipexole group). The mean score changes were − 3.09 ± 2.28 for the citalopram group and − 8.18 ± 4.83 for the pramipexole group [Table 2]. The difference between the two groups was statistically significant with a small-to-moderate effect size ($0.2 < r < 0.5$) by ANCOVA analysis ($F = 17.832$, $P < 0.0001$, and $r = 0.319$). The ESS score was decreased significantly in both treatment groups with moderate effect size ($0.4 < r < 0.6$) analyzed by a Wilcoxon signed-rank test ($Z = -2.301$, $P = 0.022$, and $r = -0.502$ for citalopram group and $Z = -2.293$, $P = 0.022$, and $r = -0.513$) but this decrease is not clinically significant (≥3 points are clinically significant[24]) in both groups. For the citalopram group, the mean score change was − 1.33 ± 2.56, whereas for the pramipexole group, it was − 0.95 ± 2.09 [Table 2]. For the ESS score, the difference between the two groups, analyzed by ANCOVA analysis, showed no statistical significance ($F = 1.332$ and $P = 0.256$).

DISCUSSION

This randomized trial was designed to compare the efficacy of the dopamine agonist pramipexole with the SSRI antidepressant citalopram for treating depression in PD patients. It should be noted that this trial was designed to compare the effect of citalopram (as an antidepressant) and pramipexole (as a clinically useful treatment for depression) in PD patients,[17] accordingly, this trial did not include a placebo group. Both pramipexole and citalopram improved depression significantly as indicated by a significant decrease ($P < 0.0001$) in BDI score between baseline and endpoint evaluations. There was no significant difference between these two treatments in depression improvement. In the evaluation of the quality of life, both of these treatments also improved the quality of life of the patients as demonstrated by a significant decrease in PDSI score between baseline and endpoint evaluations. Our results also indicated that pramipexole was significantly more efficient than citalopram in terms of quality-of-life improvement in these patients. Both treatments showed a statistically significant decrease in ESS score between baseline and endpoint evaluations but it was not a clinically

Table 1: Baseline characteristics and demographics

	Citalopram (*n*=21)	Pramipexole (*n*=20)	*P*
Age (years), median (IQR)	64 (13)	64 (13)	0.60
Men, *n* (%)	18 (85.7)	17 (85)	0.95
Duration of PD, median years (IQR)	2 (2)	2 (2)	0.51
Levodopa dose (mg), median daily dose (IQR)	300 (200)	400 (175)	0.18
BDI score, median (IQR)	17 (18)	18 (13)	0.62
PDSI score, median (IQR)	16.67 (29.81)	20.25 (22.44)	0.18
ESS score, median (IQR)	6 (7)	7.5 (7)	0.37

IQR=Interquartile range; PD=Parkinson's disease; BDI=Beck Depression Inventory; PDSI=Parkinson's disease summary index; ESS=Epworth Sleepiness Scale

Table 2: Score change of outcomes parameters at the endpoint in the two treatment groups and the difference between these two groups

	Citalopram			Pramipexole			Difference	
	Mean±SD	*P*	ES	Mean±SD	*P*	ES	*F*	*P*
BDI score	−8.48±4.98	<0.0001	0.877	−7.75±5.36	<0.0001	0.878	1.392	0.245
PDSI	−3.09±2.28	<0.0001	0.817	−8.18±4.83	<0.0001	0.877	17.832	<0.0001
ESS score	−1.33±2.56	0.022	0.502	−0.95±2.09	0.022	0.513	1.332	0.256

BDI=Beck Depression Inventory; PDSI=Parkinson's disease summary index; ESS=Epworth Sleepiness Scale; ES=Effect size; SD=Standard deviation

significant change. No significant difference in ESS scores between these treatments was observed.

The result of this trial is consistent with earlier investigations on the antidepressant effect of pramipexole in PD patients.[10-15] A double-blind, randomized placebo-controlled trial of pramipexole compared with placebo in 296 patients with PD using BDI and PDQ-39 scores showed significant improvement of depressive symptoms mainly through a direct antidepressant effect (80%) and less due to improving motor symptoms (20%).[10] Another randomized open-label study comparing dopamine receptor agonists pramipexole and pergolide on depression in 41 patients using the Montgomery–Asberg Depression Rating Scale and the Unified Parkinson's Disease Rating Scale (UPDRS) demonstrated the antidepressant effect of pramipexole.[11] The results of a meta-analysis of seven placebo-controlled studies involving 1296 patients in mood and motivational symptoms in PD, suggested the beneficial effect of pramipexole on mood and motivational symptoms in PD patients who did not have a major depressive disorder.[25]

The only comparative study between pramipexole and an SSRI antidepressant was designed by Barone and his colleagues. In this open-label, comparative, randomized, parallel-group study, they compared pramipexole versus sertraline for the management of depressive symptoms in 67 PD patients without motor complications and under stable levodopa treatment using Hamilton Depression Rating Scale and UPDRS score. They found pramipexole ameliorated depressive symptoms in PD.[26]

The result of this study was also comparable with earlier findings of SSRI antidepressants' efficacy in treating depression in PD patients. SSRIs were the most commonly used drugs for the treatment of depression in PD and considered the first-line treatment in 63% of patients in depression in PD.[27]

Extrapyramidal symptoms such as drug-induced parkinsonism are one of the side effects of SSRI antidepressants that potentially can be troublesome for PD patients. In a pharmacoepidemiological study, the most common SSRI-induced extrapyramidal symptoms were akathisia, dystonia, parkinsonism, myoclonus, and tremor.[8] In another review, 6.6% of reported cases with SSRI-induced extrapyramidal symptoms were PD patients and 20.9% of all cases with SSRI-induced extrapyramidal symptoms were parkinsonism.[9] These side effects may be due to the inhibitory effects of serotonin on dopamine neurotransmission in basal ganglia. Few reports and studies are suggesting that SSRIs may exacerbate the motor symptoms in PD.[7-9] Our patients treated with citalopram did not have any exacerbation in motor symptoms.

Pramipexole also has adverse events such as sleep disturbance, gastrointestinal symptoms, and neuropsychiatric symptoms (hallucinations and impulse-control disorders) that most of them are dose-dependent. In general, pramipexole with a total daily dose of 4.5 mg is well tolerated.[28] Our patients in the pramipexole group also did not have any troublesome adverse events.

Depression is a common complaint in PD and has the greatest influence on the quality of life in these patients and their caregivers.[2,3] More studies need for choosing effective, well-tolerated, and safe treatment for depression in these patients. In the present study, pramipexole was as effective as citalopram in depressive symptoms in PD patients. Furthermore, we found that pramipexole was

made more impact on the quality of life than citalopram. It might be due to the pramipexole effects on motor symptoms that affect the PDSI as an overall single index derivated from the PDQ-39.

This study was a small open-label parallel-group randomized trial with limitations. The gender distribution in each group (predominantly male) may have influenced the result but there is no statistical difference in gender between the two groups. The present study aimed to compare pramipexole as a drug for PD motor symptoms with citalopram as an antidepressant drug. Therefore, this study did not include a placebo arm. Recent studies in depression suggested a placebo effect mediated by the dopaminergic reward mechanisms in the prefrontal cortex and it may be unavoidable.[29] In the present trial, we cannot exclude the placebo effect. Despite these limitations and the relatively small sample size, the outcome results of this trial were highly significant in each group.

CONCLUSION

We conclude that both citalopram and pramipexole could improve depression and quality of life in PD patients, even though pramipexole was seemed to be slightly more beneficial on quality of life. We suggest that pramipexole may be an effective treatment for treating depression in addition to its benefits on motor symptoms in PD patients. Further studies with a placebo arm are required to confirm the efficacy of pramipexole compared with other antidepressants on depression and quality of life (especially on motor symptoms and daily activities) in PD patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 2008;23:183-9.
2. Agüera-Ortiz L, García-Ramos R, Grandas Pérez FJ, López-Álvarez J, Montes Rodríguez JM, Olazarán Rodríguez FJ, *et al.* Focus on depression in Parkinson's disease: A Delphi consensus of experts in psychiatry, neurology, and geriatrics. Parkinsons Dis 2021;2021:6621991.
3. Frisina PG, Borod JC, Foldi NS, Tenenbaum HR. Depression in Parkinson's disease: Health risks, etiology, and treatment options. Neuropsychiatr Dis Treat 2008;4:81-91.
4. Hughes TA, Ross HF, Mindham RH, Spokes EG. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand 2004;110:118-23.
5. Zhuo C, Xue R, Luo L, Ji F, Tian H, Qu H, *et al.* Efficacy of antidepressive medication for depression in Parkinson disease: A network meta-analysis. Medicine (Baltimore) 2017;96:e6698.
6. Mills KA, Greene MC, Dezube R, Goodson C, Karmarkar T, Pontone GM. Efficacy and tolerability of antidepressants in Parkinson's disease: A systematic review and network meta-analysis. Int J Geriatr Psychiatry 2018;33:642-51.
7. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Gironell A, García-Sánchez C, Martínez-Corral M. Motor changes during sertraline treatment in depressed patients with Parkinson's disease. Eur J Neurol 2008;15:953-9.
8. Revet A, Montastruc F, Roussin A, Raynaud JP, Lapeyre-Mestre M, Nguyen TT. Antidepressants and movement disorders: A postmarketing study in the world pharmacovigilance database. BMC Psychiatry 2020;20:308.
9. Hawthorne JM, Caley CF. Extrapyramidal reactions associated with serotonergic antidepressants. Ann Pharmacother 2015;49:1136-52.
10. Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, *et al.* Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: A randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:573-80.
11. Rektorová I, Rektor I, Bares M, Dostál V, Ehler E, Fanfrdlová Z, *et al.* Pramipexole and pergolide in the treatment of depression in Parkinson's disease: A national multicentre prospective randomized study. Eur J Neurol 2003;10:399-406.
12. Lemke MR, Brecht HM, Koester J, Kraus PH, Reichmann H. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci 2005;17:214-20.
13. Lemke MR, Brecht HM, Koester J, Reichmann H. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. J Neurol Sci 2006;248:266-70.
14. Letvinenko IV, Odinak MM, Mogil'naia VI. Pain and depression in Parkinson's disease: New therapeutic possibilities of pramipexole. Zh Nevrol Psikhiatr Im S S Korsakova 2008;108:36-8.
15. Levin OS, Boĭko AN, Nesterova OS, Otcheskaia OV, Zhuravleva EIu, Artemova IIu, *et al.* Effect of dopamine agonist pramipexole (mirapex) on tremor, affective disorders and quality of life in patients with Parkinson's disease. Zh Nevrol Psikhiatr Im S S Korsakova 2010;110:39-44.
16. Rektorová I, Rektor I, Bares M, Dostál V, Ehler E, Fanfrdlová Z, *et al.* Cognitive performance in people with Parkinson's disease and mild or moderate depression: Effects of dopamine agonists in an add-on to L-dopa therapy. Eur J Neurol 2005;12:9-15.
17. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, *et al.* Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord 2019;34:180-98.
18. Perez-Lloret S, Rey MV, Ratti L, Rascol O. Pramipexole for the treatment of early Parkinson's disease. Expert Rev Neurother 2011;11:925-35.
19. Wilson SM, Wurst MG, Whatley MF, Daniels RN. Classics in chemical neuroscience: Pramipexole. ACS Chem Neurosci 2020;11:2506-12.
20. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007;64:327-37.
21. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, *et al.* MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-601.
22. Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ,

et al. Minimal clinically important difference on the Beck Depression Inventory – II according to the patient's perspective. Psychol Med 2015;45:3269-79.
23. Horváth K, Aschermann Z, Kovács M, Makkos A, Harmat M, Janszky J, *et al.* Changes in quality of life in Parkinson's disease: How large must they be to be relevant? Neuroepidemiology 2017;48:1-8.
24. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, *et al.* The Epworth sleepiness scale: Minimum clinically important difference in obstructive sleep apnea. Am J Respir Crit Care Med 2018;197:961-3.
25. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: A meta-analysis of placebo-controlled studies. Clin Ther 2009;31:89-98.
26. Barone P, Scarzella L, Marconi R, Antonini A, Morgante L, Bracco F, *et al.* Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: A national multicenter parallel-group randomized study. J Neurol 2006;253:601-7.
27. Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, *et al.* The movement disorder society evidence-based medicine review update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26 Suppl 3:S42-80.
28. Constantinescu R. Update on the use of pramipexole in the treatment of Parkinson's disease. Neuropsychiatr Dis Treat 2008;4:337-52.
29. de la Fuente-Fernández R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002;1:85-91.