Iran Red Crescent Med J. 2019 September; 21(9):e96672. doi: 10.5812/ircmj.96672.

Published online 2019 September 30. **Research Article**

Pramipexole Versus Selegiline in Patients with Parkinson's Disease: An Effectiveness and Safety (EAS) Analysis

Zhonghai Tao [1, 2], Jiechun Chen [2], Lijie Xiao [3] and Chunfeng Liu [1, *]

[1]Department of Neurology, The Second Affiliated Hospital of Soochow University, Suzhou, China
[2]The Second People's Hospital of Lianyungang, Lianyungang, China
[3]Department of Neurology, The Second Affiliated Hospital of Xuzhou Medical College, Xuzhou, China

[*]*Corresponding author*: Department of Neurology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, 215004, China. Tel/Fax: +86-51268282030, Email: liuchunfeng@suda.edu.cn

Received 2019 July 28; **Revised** 2019 August 24; **Accepted** 2019 August 31.

Abstract

Background: Levodopa treatment is the gold standard in Parkinson's disease but has the risk of dyskinesias. Selegiline delays the introduction of levodopa and pramipexole is used as a symptomatic treatment in Parkinson's disease.
Objectives: This study aimed to compare the effectiveness of pramipexole with selegiline in Parkinson's disease patients.
Methods: Data regarding motor and cognitive impairments and plasma phospholipids of 500 Chinese patients with confirmed Parkinson's disease from medical records of 1 January 2015 to 1 June 2016 were retrospectively evaluated. Patients received either pramipexole (PP cohort, n = 250) or selegiline (SG cohort, n = 250). Also, data regarding hospitalization, adverse effects, and expenditure were collected and analyzed from records of the follow-up period.
Results: After 3-years of treatments, selegiline and pramipexole both improved motor and cognitive impairments and decreased plasma phospholipid levels ($P < 0.05$ for all). The intensity of improvement in motor and cognitive impairments and a decrease in the level of plasma phospholipids for pramipexole was higher than those of selegiline ($P < 0.05$ for all). Pramipexole caused muscle weakness ($P = 0.015$) and peripheral edema ($P = 0.0004$). While, selegiline caused cardiovascular disease ($P = 0.008$). Higher numbers of patients in the SG cohort were hospitalized during 3-years of treatment than those in PP cohort (11 vs. 1, $P = 0.009$). Selegiline treatment is more expensive than pramipexole (4,457 ± 345 ¥ vs. 3,649 ± 301 ¥/patient/year, $P < 0.0001$).
Conclusions: Pramipexole treatment may have better improvement in motor and cognitive impairments than selegiline with neuroprotective action and manageable side effects (Level of Evidence: III).

Keywords: Benzothiazoles, Cognitive Dysfunction, Dyskinesia, Levodopa, Motor, Muscle Weakness, Parkinson's Disease, Pramipexole, Selegiline, Phospholipids

1. Background

Parkinson's disease affects about 1.7 % of Chinese older individuals and is the second most common age-related neurodegenerative condition in China (1). The prevalence of Parkinson's disease increases with age. Also, the incidence of Parkinson's disease is higher in Chinese women and men than in the other developed countries (2). The symptoms of Parkinson's disease include motor manifestations, e.g., muscular rigidity, resting tremor, postural instability, and bradykinesia (1). Balance disorders, pain, and gait in Parkinson's disease have therapeutic challenges because they are related to the risk of physical decline, disability, and falls (3). The clinical symptoms of Parkinson's disease can be alleviated by drugs that increase dopamine function like levodopa, dopamine receptor agonists (e.g., pramipexole), type B monoamine oxidase inhibitors (e.g., selegiline and rasagiline), and catechol O-methyl transferase inhibitors (e.g., entacapone) (1).

Levodopa is the 'gold standard' pharmacological therapy, but has the risk of dyskinesias in long treatment (4). In the initial stage of Parkinson's disease, selegiline (L-deprenyl)) and rasagiline are commonly used (4) but rasagiline increases the cost of treatment (5). Pramipexole has a longer half-life than levodopa and is used in the progress of the disease when symptoms have appeared (6). Therefore, there is a necessity of retrospective analysis to compare the effectiveness and associated risk factors of pramipexole with selegiline before randomized trial.

2. Objectives

The objectives of the retrospective analysis were to compare the effectiveness and the safety profile of

pramipexole with selegiline in patients with Parkinson's disease in a Chinese setting.

3. Methods

3.1. Ethics Approval and Consent to Participate

The original protocol of the study (SSU/CL/14/19 dated 28 June 2019) had been approved by the Second Affiliated Hospital of Soochow University review board. The study reporting adhered to the law of China, strengthening the reporting of observational studies in epidemiology (STROBE) statement: cohort studies, and the 2008 Helsinki Declaration (Chinese version). An informed consent form was signed by all participants or their relatives (legally authorized person) regarding interventions, pathology, radiology, and publication of the study irrespective of time and language during hospitalization. Being a retrospective analysis, the registration in the Chinese clinical trial registry was waived by the institutional review board.

3.2. Inclusion Criteria

From 1 January 2015 to 1 June 2016, a total of 678 patients, aged 18 years and more and of either sex were diagnosed and confirmed with Parkinson's disease as per UK Brain Bank criteria (7) and had declined motor and cognitive function at the department of psychiatry of the Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China (private hospital), the Second People's Hospital of Lianyungang, Lianyungang, Jiangsu Province, China (private hospital), and the Second Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu Province, China (private hospital).

3.3. Exclusion Criteria

Among the patients with confirmed Parkinson's disease, 75 patients were treated with advanced-stage therapies, 71 patients had other disorders that could cause cognitive function impairment, 12 patients had mental disorders (were taking psychotropic medications), 18 patients had dyskinesia, and two patients had drug abuse. Therefore, they were excluded from the study (n = 178). Also, patients who had missing data were excluded from the analysis.

Data regarding anthropological parameters, demographical characters, clinical parameters, interventions, and outcome measures were collected for 500 patients from institutional records and analyzed (Figure 1).

3.4. Cohort

For the purpose of evaluation of the effects of anti-Parkinson's drugs, patients were selected. The sample size was selected for the purpose of comparisons of means. The sample size was derived from PASS 16 (NCSS, LLC, Utah, USA) at 80 % of power ($\alpha = 1$ and $\beta = 0.05$). Patients who had been treated with selegiline for 3-years were included in SG cohort and those treated with pramipexole for 3-years were included in the PP cohort.

3.5. Interventions

Patients of SG cohort were treated with 2.5 mg/day (divided dose; twice in a day at morning and noon) selegiline and titrated up to 10 mg/day on a weekly basis. The maintenance dose was the dose which had satisfactory results. Patients of PP cohort were treated with 0.375 mg/day pramipexole (immediate release or sustained release; immediate release thrice in a day or sustained release once at noon) and titrated up to 4.5 mg/day on weekly bases. The maintenance dose was the dose which had satisfactory results.

3.6. Outcome Measures

3.6.1. Motor Impairment

The Unified Parkinson's Disease Rating Scale III (UPDRS III) was performed to measure the severity of daily living activities, non-motor symptoms, and motor impairment (8). It was evaluated before the start of interventions and after 3-years of treatment.

3.6.2. Cognitive Impairment

The Beijing version of the Montreal Cognitive Assessment (MoCA-BJ) was performed to evaluate mild cognitive impairment. The visuospatial/executive function, abstraction, naming, attention, delayed memory, language, and orientation domains were used to access cognitive impairment. It was evaluated before the start of interventions and after 3-years of treatment (9). The score was in the range of 0 - 30. 0: minimum and 30: maximum. If the subject was a graduate, then one point was added to the points to calibrate the bias of education levels (10).

The medical staff of institute (minimum 3-years of experience) were involved in the evaluation of impairments.

3.6.3. Plasma Phospholipids

A total of 4 mL of blood had been collected by a pathologist (minimum 3-years of experience) in sodium citrate cuvette before breakfast and was centrifuged for 20 min at 8,000 rpm. The upper layer of blood (plasma) was collected and phospholipid level was measured by using chromatography (10). Plasma phospholipids level was measured before the start of interventions and after treatment of 3-years.

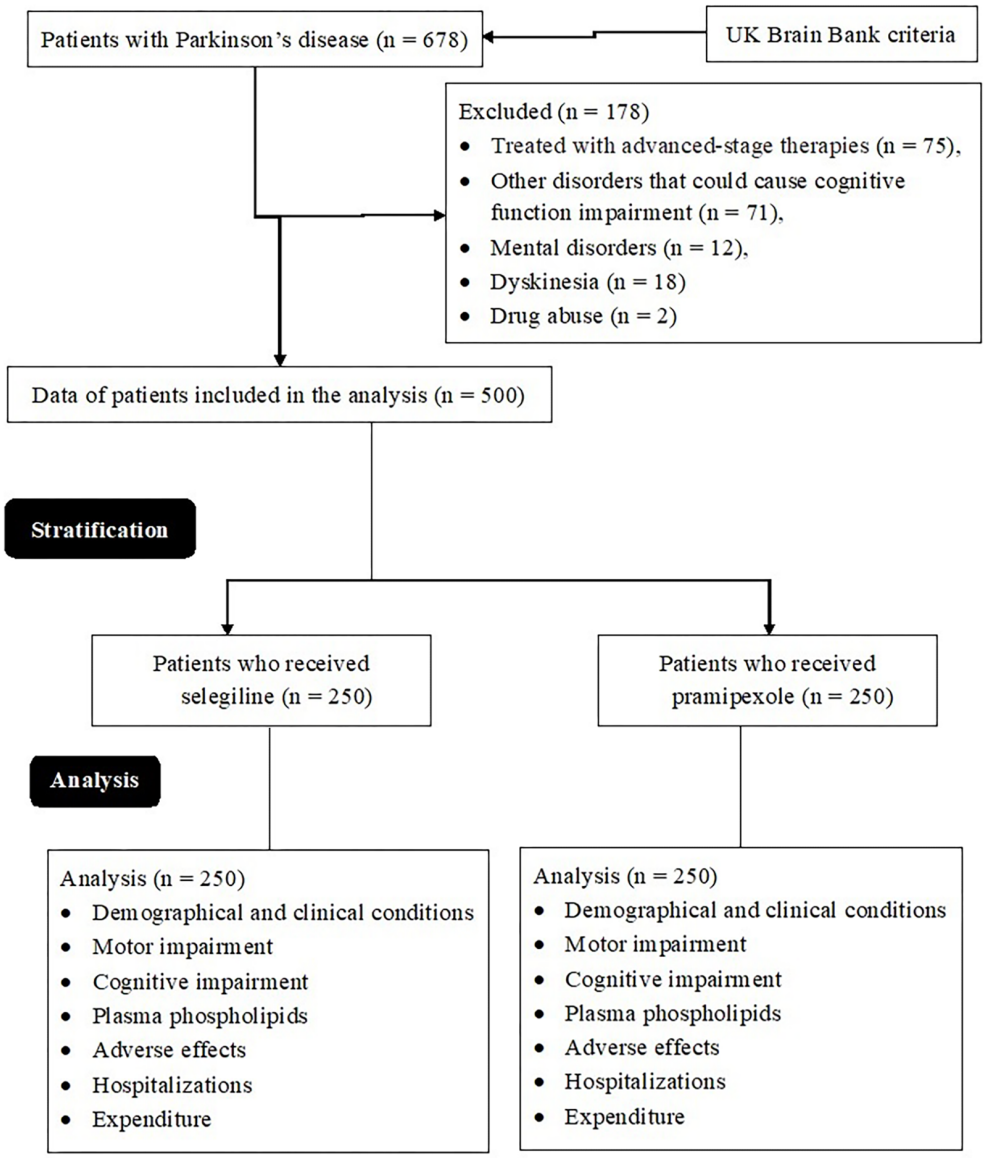

Figure 1. Flowchart of the study

3.7. Adverse Effects

Data of adverse effects were collected from the patients' record of institute.

3.8. Hospitalizations

Hospitalizations of patients due to Parkinson's disease, fracture, cardiovascular disease, or any other reasons were also extracted from the patients' record of institute. Minimum 1-day stay in the hospital was considered as hospitalization.

3.9. Expenditure

The expenditure was calculated considering the cost of treatment, cost of physicians, cost of pathology, and cost required to cover treatment-emergent adverse effects.

3.10. Statistical Analysis

InStat, Windows version (GraphPad, San Diego, CA, USA) was used to perform statistical analysis. The Chi-square test was performed for constant data (9) and two-tailed paired t-test was performed for continuous data at

95 % of confidence level. Tukey test was performed for post hoc analysis (considering critical value [q] > 3.314 as significant).

4. Results

4.1. Demographical and Clinical Characteristics

UPDRS III, MoCA-BJ, and plasma phospholipid level had no significant differences between patients who had been treated with selegiline (SG cohort, n = 250) and those who were treated with pramipexole (PP cohort, n = 250) at baseline (P > 0.05 for all). Most of the enrolled patients had smoking habits. Male patients were more than female patients. All patients had an age of more than 50 years. The other demographical and clinical characteristics of the enrolled patients are reported in Table 1.

4.2. The Unified Parkinson's Disease Rating Scale III

After 3 years of interventions, selegiline (19.12 ± 9.81 vs. 17.25 ± 6.99, P = 0.035, q = 3.344) and pramipexole (18.89 ± 8.89 vs. 15.31 ± 9.46, P = 0.0005, q = 4.847) both improved motor impairment. The intensity of improvement in motor impairment was higher for pramipexole than selegiline (P = 0.016, q = 3.469, Figure 2).

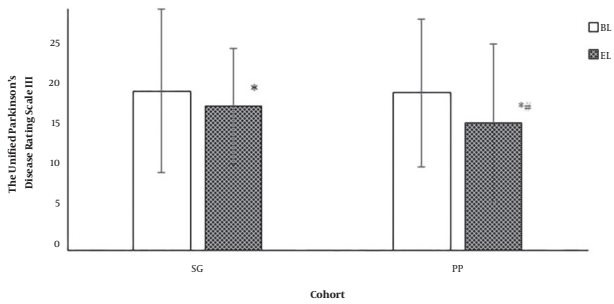

Figure 2. Motor activity evaluation. Data are shown as mean ± SD. A P value < 0.05 and q value > 3.314 were considered significant. BL: Baseline. EL: After 3 years of interventions. *Significant improvement than BL. #Significant improvement than SG cohort at EL.

Table 1. Anthropological, Demographical, and Clinical Characteristics of the Enrolled Patients[a, b]

Characteristics	Cohorts		P Value (Comparison Between Cohorts)
	SG	PP	
Patients included in the analysis	250	250	
Age, y			0.186
Minimum	58	59	
Maximum	73	74	
Mean ± SD	65.52 ± 7.57	64.59 ± 8.11	
Body mass index, kg/m²	24.49 ± 2.45	24.09 ± 2.12	0.052
Gender			0.647
Male	155 (62)	149 (60)	
Female	95 (38)	101 (40)	
Ethnicity			0.842
Han Chinese	233 (93)	230 (92)	
Mongolian	15 (6)	17 (7)	
Tibetan	2 (1)	3 (1)	
Education			0.235
Primitive	124 (50)	127 (51)	
Undergraduate	85 (34)	80 (32)	
Graduate to doctorate	41 (16)	43 (17)	
Smokers			0.76
No smokers	45 (18)	41 (16)	
Previous smokers	153 (61)	161 (65)	
Current smokers	52 (21)	48 (19)	
Disease duration, y	4.9 ± 1.25	5.15 ± 2.25	0.125
UPDRS III	19.12 ± 9.81	18.89 ± 8.89	0.784
MoCA-BJ	21.45 ± 3.09	21.01 ± 3.13	0.114
Plasma phospholipids, U	6.61 ± 0.69	6.57 ± 0.62	0.496

Abbreviations: MoCA-BJ, The Beijing version of the Montreal Cognitive Assessment; UPDRS III, The Unified Parkinson's Disease Rating Scale III; 0, minimum; 30, maximum.
[a] Categorical data are shown as frequency (percentage) and continuous data are shown as mean ± SD.
[b] A P value of less than 0.05 was considered significant.

4.3. The Beijing Version of the Montreal Cognitive Assessment

Selegiline (21.45 ± 3.09 vs. 20.54 ± 3.12, P = 0.011, q = 4.621) and pramipexole (21.01 ± 3.13 vs. 19.12 ± 3.89, P < 0.0001, q = 8.815) both improved MoCA-BJ after 3 years of interventions. Also, pramipexole improved MoCA-BJ in better way than selegiline (P < 0.0001, q = 6.629, Figure 3).

4.4. Plasma Phospholipids

After 3 years of treatment, plasma phospholipids levels were decreased in SG (6.61 ± 0.69 U vs. 6.01 ± 0.67 U, P < 0.0001, q = 14.36) and PP (6.57 ± 0.62 U vs. 5.81 ±0.52 U, P < 0.0001, q = 19.572) cohorts. Also, pramipexole decreased plasma phospholipid levels more effectively than

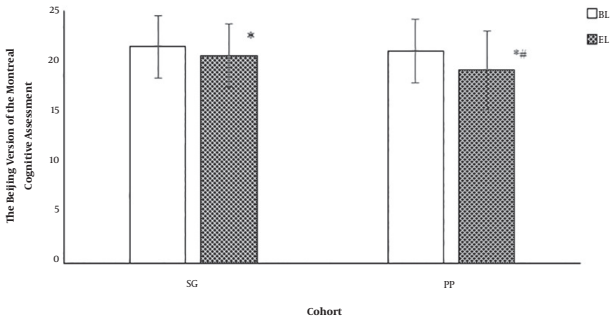

Figure 3. Cognitive activity evaluation. Data are shown as mean ± SD. A P value < 0.05 and q value > 3.314 were considered significant. BL: Baseline. EL: After 3 years of interventions. *Significant improvement than BL. #Significant improvement than SG cohort at EL. 0: minimum and 30: maximum.

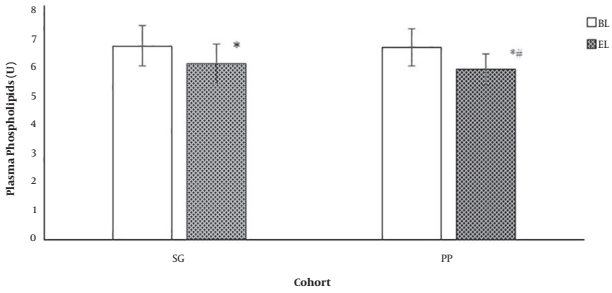

Figure 4. Plasma phospholipids levels. Data are shown as mean ± SD. A P value < 0.05 and q value > 3.314 were considered significant. BL: Baseline. EL: After 3-years of interventions. *Significant improvement than BL. #Significant improvement than SG cohort at EL.

selegiline (P = 0.0002, q = 5.01, Figure 4).

4.5. Adverse Effects

Higher numbers of patients were hospitalized for Parkinson's disease or any other reason during the 3-years of treatment for SG cohort than PP cohort (11 vs. 1, P = 0.009, Figure 5).

Dry mouth, nausea, headache, stomach upset, and drowsiness were commonly reported by patients of SG cohort and PP cohort. Pramipexole caused muscle weakness (P = 0.015), peripheral edema (P = 0.0004), and back pain (P < 0.0001). While, selegiline caused cardiovascular disease (P = 0.008). Also, two patients from the SG cohort and three patients from the PP cohort had reported melanoma (Table 2).

4.6. Expenditure

Per year expenditure to treat Parkinson's disease was higher for SG cohort patient than PP cohort patient (4,457 ± 345 ¥ vs. 3,649 ± 301 ¥/patient/year, P < 0.0001, Figure 6).

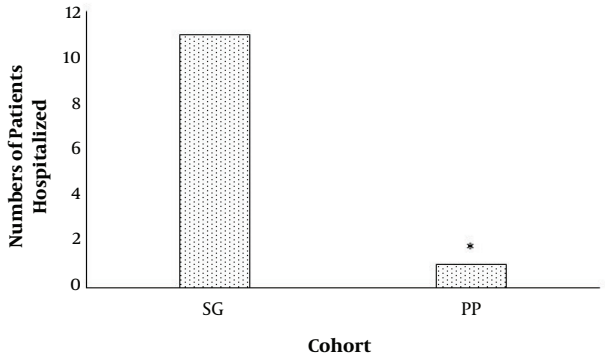

Figure 5. Hospitalization of the patient during the treatment period. Minimum 1-day stay in the hospital was considered as hospitalization. A P value < 0.05 was considered significant. *Significant fewer number than SG cohort.

Table 2. Treatment-Emergent Adverse Effects During 3 Years of Interventions[a, b]

Characteristics	Cohorts		P Value (Comparison Between Cohorts)
	SG	PP	
Patients included in the analysis	250	250	
Dyskinesias	3 (1)	0 (0)	0.247
Dry mouth	42 (17)	38 (15)	0.712
Abdominal pain	9 (4)	3 (1)	0.144
Dizziness	5 (2)	6 (2)	0.761
Nausea	23 (9)	21 (8)	0.875
Trouble sleeping	11 (4)	10 (4)	0.824
Stomach upset	14 (6)	15 (6)	0.848
Headache	15 (6)	13 (5)	0.846
Melanoma	2 (1)	3 (1)	0.653
Muscle weakness	2 (1)	12 (5)[c]	0.015
Confusion	2 (1)	9 (4)	0.067
Memory loss	2 (1)	7 (3)	0.179
Drowsiness	9 (4)	11 (4)	0.82
Cardiovascular disease	15 (6)[d]	3 (1)	0.008
Peripheral edema	2 (1)	19 (8)[c]	0.0004
Back pain	2 (1)	23 (9)[c]	< 0.0001

[a] Values are shown as frequency (percentage).
[b] A P value < 0.05 was considered significant.
[c] Significant pramipexole- related unwanted effect.
[d] Significant selegiline-related unwanted effect.

5. Discussion

5.1. Motor Impairment

After 3-years of treatment, UPDRS III indicated that daily living and motor activities of the patients of SG cohort had improved. The study results were parallel with

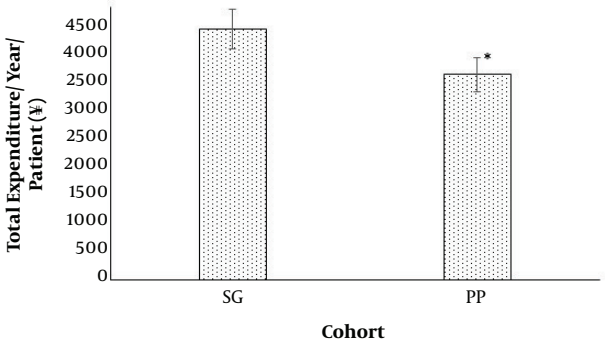

Figure 6. Total expenditure per year per patient of treatment. Expenditures included drug cost, follow-up cost, pathology cost, consultant charges, and charges of treatment of adverse effects. Data are shown as mean ± SD. A P value < 0.05 was considered significant. *Significant fewer value than SG cohort.

the results of the retrospective case-control study (4). Selegiline may delay the progression of disease in patients with confirmed Parkinson's disease.

After 3-years of treatment, in the same manner, motor and daily living tasks (UPDRS III scale) of the patients of PP cohort were also improved. The study results were parallel with the results of double-blind studies (11, 12). Pramipexole may also delay the progression of disease in patients with confirmed Parkinson's disease.

Selegiline did not improve the motor impairment as strongly as pramipexole (P = 0.016, q = 3.469) during treatment of 3-years. The results of the study were consistent with a retrospective case-control study (4). Motor impairment is attributed to decrease in dopamine level. The natural dopamine in the body could be more effective when pramipexole intervention is given than that of selegiline, (13) since pramipexole binds with higher affinity to D3 receptor (6) and natural dopamine binds with higher affinity to D2 receptor (13). Therefore, there is an additive effect. Pramipexole may have long-term benefits compared to selegiline in patients with confirmed Parkinson's disease.

5.2. Cognitive Impairment

Selegiline and pramipexole both improved cognitive impairment after 3-years of treatment. Also, pramipexole improved cognitive impairment more strongly than selegiline. Mild cognitive impairment is a major non-motor feature of patients with confirmed Parkinson's disease (14). Patients with mild cognitive impairment are at high risk of dementia (15). Pramipexole has negligible metabolism in the body and binds with higher affinity to D3 receptor than D2 and D4 (6). While selegiline is extensively metabolized in the liver and exerts selective inhibition of type B monoamine oxidase effect. Also, selegiline increases the level of phenylethylamine and dopamine but is not successful in the increase in the level of serotonin or noradrenaline, which decreases its action in the brain (16). Selegiline and pramipexole both delay disability, but pramipexole may delay the decline of cognitive function in a better way in patients with Parkinson's disease than selegiline.

5.3. Plasma Phospholipids

Selegiline and pramipexole both decreased plasma phospholipid levels and pramipexole had a higher ability to decrease plasma phospholipid levels than selegiline. Higher phospholipid levels may affect brain functions (17). By decreasing the plasma phospholipid level, both drugs provided neuroprotective action. The mechanism of actions for the decrease in plasma phospholipid level by selegiline and pramipexole are required to investigate.

5.4. Adverse Effects and Hospitalization

Selegiline caused cardiovascular diseases, and higher numbers of patients were hospitalized due to Parkinson's disease or any other reason (s) in SG cohort. The study results were parallel with the results of the historical cohort study (5). Meanwhile, pramipexole caused muscle weakness, peripheral edema, and back pain. The study results were parallel with the results of a double-blinded study (11). Unlike PP cohort, in SG cohort, patients with dyskinesias were reported. The results of the study were consistent with another retrospective case-control study (4) and PD-MED trial (13). Pramipexole has only 10 % metabolism in the kidney (6). While 60 % of selegiline is metabolized in the liver, which produces toxic products (16). Long term use of selegiline may have the risk of serious treatment-emergent adverse effects and need more hospitalization than pramipexole.

5.5. Expenditure

Patients of SG cohort had a higher cost of treatment than those of PP cohort. The study results were parallel with the results of the historical cohort study (5). Selegiline treatment may increase the burden over the patients' head.

5.6. Limitations

The study has several limitations, for example, the retrospective study has prescription bias, and a randomized controlled trial is required for authentic results. The study evaluated MoCA-BJ instead of the Mini-Mental State Examination, which is routinely used to evaluate psychiatric status in patients with confirmed Parkinson's disease (18). The possible justification for this is that MoCA-BJ has excellent performance in Chinese people especially in those with

primitive education levels (19) and MoCA-BJ has more sensitivity than the Mini-Mental State Examination in the longitudinal studies (20). The study used the UK Brain Bank criteria to define Parkinson's disease but did not use the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease (MDS-PD Criteria). The possible reason for using outdated criteria was that the Chinese neurology guideline of the parent institute had not recommended the MDS-PD Criteria. Also, olfactory and cardiac sympathetic criteria of MDS-PD Criteria are expensive, lengthy, and have not been well achieved in the Chinese population (7).

5.7. Conclusions

Although the motor and cognitive impairments were improved by pramipexole and selegiline, pramipexole had a higher activity to delay disease progression and disability with neuroprotective action in Parkinson's disease. Hospitalization, expenditures, and adverse effects were also fewer in pramipexole treatment. Pramipexole immediate release or sustained release therapy is recommended for Chinese patients who are diagnosed with Parkinson's disease in neurology clinics.

Footnotes

Authors' Contribution: All authors read and approved the manuscript for publication. Zhonghai Tao was the project administrator, contributed to data curation, resources, and literature review of the study. Jiechun Chen contributed to formal analysis, data curation, software, resources, and literature review of the study. Lijie Xiao contributed to the investigation, validation, resources, and literature review of the study. Chunfeng Liu contributed formal analysis and literature review of the study and draft, review, and edited the manuscript for intellectual content. All authors agree to be accountable for all aspects of work, ensuring integrity and accuracy.

Conflict of Interests: It is not declared by the authors.

Ethical Approval: The original protocol of the study (SSU/CL/14/19 dated 28 June 2019) had been approved by the Second Affiliated Hospital of Soochow University review board. The study reporting adhered to the law of China, strengthening the reporting of observational studies in epidemiology (STROBE) statement: cohort studies, and the 2008 Helsinki Declaration (Chinese version). Being a retrospective analysis, the registration in the Chinese clinical trial registry was waived by the institutional review board.

Funding/Support: None.

Patient Consent: An informed consent form was signed by all participants or their relatives (legally authorized person) regarding interventions, pathology, radiology, and publication of the study irrespective of time and language during hospitalization.

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