COMPARISON OF PRAMIPEXOLE VERSUS ROPINIROLE IN THE TREATMENT OF PARKINSON'S DISEASE

Onur Serdar GENCLER[1], Nese OZTEKIN[2], Mehmet Fevzi OZTEKIN[3]

[1]Department of Neurology, Medical Park Ankara Hospital, Yuksek Ihtisas University, Ankara, Turkey
[2]Department of Neurology, Ministry of Health Ankara Numune Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[3]Department of Neurology, Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital, University of Health Sciences, Ankara, Turkey

English | https://doi.org/10.18071/isz.75.0039 | www.elitmed.hu

Background and purpose – Parkinson's disease is a progressive neurodegenerative disease characterized by motor and non-motor symptoms. Levodopa is the most effective drug in the symptomatic treatment of the disease. Dopamine receptor agonists provide sustained dopaminergic stimulation and have been found to delay the initiation of levodopa treatment and reduce the frequency of various motor complications due to the long-term use of levodopa. The primary aim of this study was to compare the efficacy of potent nonergoline dopamine agonists pramipexole and ropinirole in both "dopamine agonist monotherapy group" and "levodopa add-on therapy group" in Parkinson's disease. The secondary aims were to evaluate the effects of these agents on depression and the safety of pramipexole and ropinirole.
Methods – A total of 44 patients aged between 36 and 80 years who were presented to the neurology clinic at Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey and were diagnosed with idiopathic Parkinson's disease, were included into this randomized parallel-group clinical study. Dopamine agonist monotherapy and levodopa add-on therapy patients were randomized into two groups to receive either pramipexole or ropinirole. The maximum daily dosages of pramipexole and ropinirole were 4.5 mg and 24 mg respectively. Patients were followed for 6 months and changes on Unified Parkinson's Disease Rating Scale, Clinical Global Impression-severity of illness, Clinical Global Impression-improvement, Beck Depression Inventory scores, and additionally in advanced stages, changes in levodopa dosages were evaluated. Drug associated side effects were noted and compared.

A PRAMIPEXOL ÉS A ROPINIROL ÖSSZEHASONLÍTÁSA A PARKINSON-KÓR KEZELÉSÉBEN

Gencler OS, MD, PhD; Oztekin N, MD, PhD; Oztekin MF, MD, PhD

Ideggyogy Sz 2022;75(1–2):39–49.

Háttér és cél – A Parkinson-kór motoros és nem motoros tünetekkel járó, progresszív neurodegeneratív betegség. A betegség tüneti kezelésében a levodopa a leghatékonyabb gyógyszer. A dopaminreceptor-agonisták tartós dopaminerg stimulációt biztosítanak, és a tapasztalatok szerint késleltetik a levodopakezelés bevezetésének szükségességét, valamint csökkentik a hosszú távú levodopakezelés következtében kialakuló motoros mellékhatások gyakoriságát. A jelen vizsgálat elsődleges célja az volt, hogy összehasonlítsa két potens nem ergolin dopaminagonista, a pramipexol és a ropinirol hatékonyságát dopaminagonista monoterápiás csoportokban, valamint hozzáadott levodopa terápiás csoportokban. A másodlagos cél a pramipexol és a ropinirol depresszióra gyakorolt hatékonyságának és biztonságosságának megállapítása volt.
Módszerek – A randomizált, párhuzamos csoportos klinikai vizsgálatba 44, 36 és 80 éves kor közötti, idiopathiás Parkinson-kórral diagnosztizált beteget vontunk be a török egészségügyi minisztérium ankarai Diskapi Yildirim Beyazit Oktató- és Kutatókórház neurológiai klinikáján. A betegek két csoportba randomizálva dopaminagonista pramipexol- vagy ropinirol-monoterápiában, vagy hozzáadott levodopa terápiában is részesültek. A pramipexol, illetve a ropinirol maximális napi dózisa 4,5 mg, illetve 24 mg volt. A betegek utánkövetése 6 hónapig tartott, ezalatt rögzítésre kerültek az Egységesített Parkinson-kór Pontozó Skála, a Betegségsúlyosságra Vonatkozó Klinikai Összbenyomás és a Klinikai Összbenyomás javulása értékeiben történő változások, valamint az előrehaladott állapotú betegeknél a levodopadózisokban történő változás. Rögzítésre és összehasonlításra kerültek a gyógyszeralkalmazással összefüggő nemkívánatos események is.

Correspondent: Prof. dr. Onur Serdar GENCLER, Department of Neurology, Medical Park Ankara Hospital, Kent Koop quarter, 1868 street, Batikent Road. No: 15, 06680 Yenimahalle, Ankara. Yuksek Ihtisas University, Ankara, Turkey. Phone number: +905057992975. E-mail: serdargencler@gmail.com
https://orcid.org/0000-0002-1907-892X

Érkezett: 2020. augusztus 17. Elfogadva: 2021. január 30.

Results – In dopamine agonist monotherapy group all of the subsections and total scores of Unified Parkinson's Disease Rating Scale and Clinical Global Impression-severity of illness of the pramipexole subgroup showed significant improvement particularly at the end of the sixth month. In the pramipexole subgroup of levodopa add-on therapy group, there were significant improvements on Clinical Global Impression-severity of illness and Beck Depression Inventory scores, but we found significant improvement on Clinical Global Impression-severity of illness score at the end of the sixth month in ropinirole subgroup too. The efficacy of pramipexole and ropinirole as antiparkinsonian drugs for monotherapy and levodopa add-on therapy in Parkinson's disease and their effects on motor complications when used with levodopa treatment for add-on therapy have been demonstrated in several previous studies.
Conclusion – This study supports the effectiveness and safety of pramipexole and ropinirole in the monotherapy and levodopa add-on therapy in the treatment of Parkinson's disease.

Keywords: *Parkinson's disease, pramipexole, ropinirole, levodopa, depression*

Eredmények – A dopaminagonista monoterápiás csoportban szignifikánsan javult az Egységesített Parkinson-kór Pontozó Skála összes alcsoportjának pontszáma és összpontszáma, szignifikánsan javult továbbá a pramipexolcsoportban a Betegségsúlyosságra Vonatkozó Klinikai Összbenyomás, különösen a hatodik hónap végére.
A hozzáadott levodopa- és pramipexolkezelésben részesülő csoportban szignifikáns mértékben növekedett a Betegségsúlyosságra Vonatkozó Klinikai Összbenyomás- és a Beck Depresszió Kérdőív-pontszám, továbbá a 6. hónap végén szignifikáns javulás volt kimutatható a ropinirol-kezelésben részesülő alcsoport Betegségsúlyosságra Vonatkozó Klinikai Összbenyomás-pontszámában is.
Számos korábbi vizsgálat demonstrálta már a pramipexol és a ropinirol Parkinson-kór elleni hatékonyságát monoterápiában és hozzáadott levodopa kezeléssel, továbbá a hozzáadott levodopa kezelés hatékonyságát a motoros komplikációkkal kapcsolatban.
Következtetés – A vizsgálat támogatja a pramipexol- és a ropinirol-monoterápia, valamint a hozzáadott levodopa kezelés hatékonyságát és biztonságosságát Parkinson-kórban.

Kulcsszavak: *Parkinson-kór, pramipexol, ropinirol, levodopa, depresszió*

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by motor and non-motor symptoms with loss of dopaminergic neurons in the substantia nigra pars compacta[1]. Its cardinal motor symptoms are bradykinesia, rest tremor, rigidity, and postural instability. Among the non-motor symptoms, neuropsychiatric symptoms that cause severe disability have an important role in the PD phenomenology[2].

Although there are many treatment options for the treatment of dopamine deficiency and for the improvement of motor symptoms in PD, no medications have been found yet to reduce the rate of dopaminergic cell loss[1]. Levodopa (L-DOPA or LD) is the most effective drug in the symptomatic treatment of PD[3]. However, the long-term use of LD leads to motor complications due to the pulsatile stimulation of the dopamine receptors[4]. Dopamine receptor agonists (DA) provide sustained dopaminergic stimulation because of their long half-lives[5]. DAs have been found to delay the initiation of LD treatment and reduce the frequency of various motor complications such as wearing off and dyskinesia due to LD usage[6, 7]. Accordingly, DAs are used in monotherapy for the treatment of the early stage of PD and they are used adjunctively to the LD treatment in the advanced stage of PD[8, 9].

Pramipexole is a second-generation non-ergot derivative of synthetic amino-benzothiazole with strong agonistic activity on the D2, D3 and D4 dopamine receptors. Its affinity for the D3 receptor is higher than for the D2 receptor[10]. Ropinirole is a second-generation, non-ergot, indole-derivative dopamine receptor agonist, selective for the D2 receptor family, in the order of decreasing affinity as D3>D2>D4[11, 12].

There are not many head-to-head studies comparing the efficacy and safety of pramipexole and ropinirole. In addition, to our knowledge, previous studies have not evaluated them in a manner covering both monotherapy and levodopa add-on therapy in PD. Therefore, the primary aim of this study was to compare the efficacy of pramipexole and ropinirole in monotherapy and in levodopa add-on therapy of PD. The second aim was to evaluate the safety of these drugs through a head-to-head comparison of their side effects, as well as, of their effects on depression.

Methods

PATIENTS AND STUDY DESIGN

In this open-label, parallel-group, randomized study a total of 44 patients aged from 36 to 80 years, who were admitted to the Neurology Clinic at Ministry of Health Diskapi Yildirim Beyazit

Training and Research Hospital, Ankara, Turkey with the diagnosis of idiopathic PD according to the "UK Parkinson's Disease Society Brain Bank Diagnostic Criteria" were included. A total of 24 patients in the dopamine agonist monotherapy group (DAMG) and 20 patients in the levodopa add-on therapy group (LAG) were followed up for 6 months. This study was conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and its amendments. The study protocol was approved by the local Institutional Review Board and the Independent Ethics Committee. Written informed consent was obtained from each patient prior to the start of the study. Patients with severe dementia, epilepsy, serious psychiatric symptoms, symptomatic orthostatic hypotension, or severe cardiac, hepatic, or renal diseases; patients who used antipsychotic, anticholinergic, or MAO-B inhibitor medications, or amantadine; patients who had undergone surgical treatment for PD, and patients suspected of having secondary parkinsonism were excluded from the study.

Patients were divided into DAMG (Groups 1 or 2) and LAG (Groups 3 or 4) groups. The LAG patients had started levodopa/benserazide (LD/B) treatment prior to the study. Patients with a history of DA use underwent a one-month washout period and then were randomized to either pramipexole or ropinirole groups. Extended-release formulations were not used. 1 mg dihydrochloride monohydrate form of pramipexole equivalent to 0.7 milligram base was used. Levodopa Equivalent dose (LED) (mg/100 mg L-dopa) was determined to 1 for pramipexole and 4 for ropinirole. The randomization of the patients was performed by clinic nurses through simple randomization method using a 1:1 allocation scheme. The patients in Group 1 were started pramipexole 0.375 mg/day and the dose was increased to 0.750 mg/day in the second week, to 1.5 mg/day in the third week, and to 2.25 mg/day in the fourth week. Before each dose was increased, the patients attended a control visit. After the first month, the doses were adjusted based on the patients' scores of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Clinical Global Impression (CGI) Scales and on their tolerance to the medication and its side effects. The dose of the medication was increased to a maximum of 4.5 mg/day. The patients in Group 2 were started ropinirole 1.5 mg/day and the dose was increased to 3 mg/day in the second week, to 6 mg/day in the third week, and to 9 mg/day in the fourth week each time after the control visits. After the first month, the dose was increased to a maximum of 24 mg/day based on the patient outcomes. LAG patients were randomized to Group 3, who received pramipexole with the same dose scheme as Group 1, and to Group 4, who received ropinirole with the same dose scheme as Group 2. For these patients, the LD/B dosage was adjusted as needed. The DA dose of the patients was adjusted in the period from month 1 to month 3 and the patients received the maintenance dose in the period from the 4th to 6th months.

PATIENT MONITORING

Medical and family histories of all patients were examined before starting the treatments. They undergone detailed physical and neurological examinations. All patients undergone routine blood tests, electrocardiograms, and echocardiography before and after the six-month treatment and follow-up period; they undergone cranial MRI to exclude the causes of secondary parkinsonism. Patient follow-ups were performed once a week for the first month, every two weeks in the period from the 2nd to the 4th month, and once a month in the 4th month and afterwards.

STUDY VARIABLES

The primary outcome variables of the study were the changes in the total and the section II, III, II+III scores of UPDRS from the beginning to the end of the study. Secondary outcomes were the changes in BECK Depression Inventory (BDI), the severity of illness (CGI-S) and global improvement (CGI-I) subscales of CGI, and the changes in LD/B doses in the levodopa add-on therapy subgroups. All patients were assessed for these variables at the end of the first, third, and sixth months. The median scores and the changes in the median scores of the scales were compared within and between the groups. Reliability and tolerability were assessed according to emergent side effects, vital signs (pulse and blood pressure/BP measurements), laboratory test results, and the evaluation of patients' electrocardiograms and echocardiography results. Patients underwent electrocardiography and echocardiography at the beginning and end of the study to evaluate valvular heart disease or fibrosis or heart failure that can be developed due to DAs. In order to detect any orthostatic hypotension due to drugs used in the study, BP was measured in the supine position and one minute after standing upright. Decreases of ≥20 mmHg systolic BP and of ≥10 mmHg in diastolic BP were accepted as ortho-

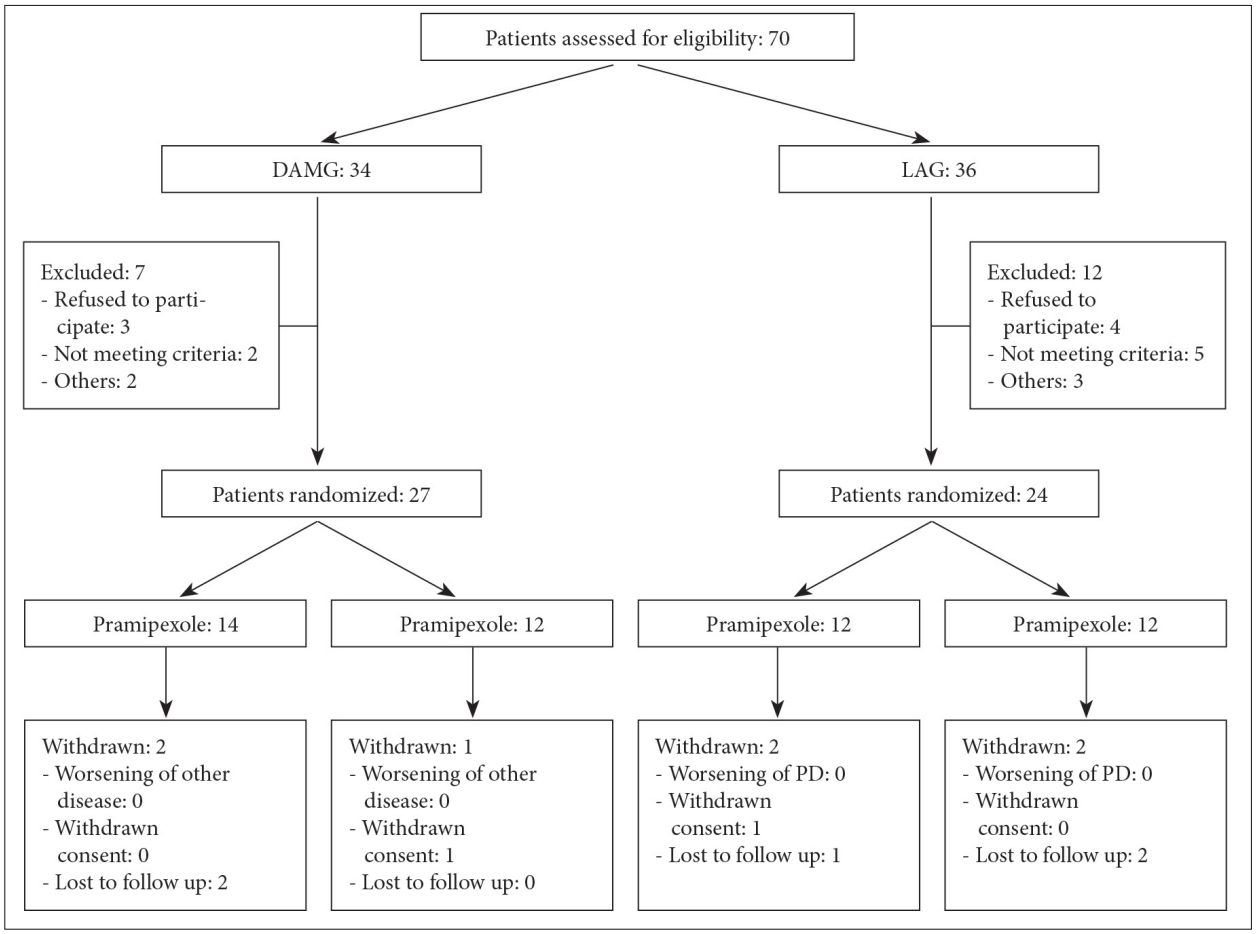

Figure 1. *Patient study flow diagram*

static hypotension. As laboratory tests, we examined complete blood count, creatinine, blood urea nitrogen, alanine transaminase, aspartate aminotransferase, gamma glutamyl transferase, sodium, potassium, calcium levels and thyroid function tests in blood.

STATISTICAL ANALYSIS

Analysis of the data was done with the SPSS package for Windows (version 11.5). Shapiro-Wilk test was used to determine whether the distribution of continuous variables was normal. Descriptive statistics were expressed as the mean ±standard deviation or median (25^{th} - 75^{th} percentiles) for continuous variables or as the number of cases and percentages for the categorical variables. The significance of the differences between the groups was investigated by the Student's *t*-test or by the Mann-Whitney U test based on the normality of distribution. Categorical variables were assessed with Pearson's Chi or Fisher's Exact Chi-Square test. Wilcoxon Signed-Rank Test was used to determine if there was any significant change in clinical measurements within the groups over time. Results were considered statistically significant at a *p-value* <0.05. Bonferroni correction was used in all multiple comparisons to control possible Type I errors.

Results

A total of 70 patients were enrolled in our study (34 for DAMG and 36 for LAG). Seven DAMG and 12 LAG patients were ineligible, so we randomized a total number of 51 patients (27 DAMG and 24 LAG patients) into groups. After the assignment, three patients with DAMG and four patients with LAG were withdrawn. Twenty-four and 20 patients were able to complete the study in the DAMG and LAG, respectively **(Figure 1)**.

Table 1A. *Demographic characteristics of the dopamine agonist monotherapy group*

Variables	Group 1 (n=12)	Group 2 (n=12)	P-value
Age (mean±SD)	60.9±13.7	62.6±11.5	0.750[a]
Gender (male/female)	3/9	6/6	0.400[b]
Duration of disease (month)	24.5 (7-104)	14.5 (3-48)	0.410[c]
Side (right/left)	7/5	8/4	1.000[b]
Family history	4 (33.3%)	3 (25.0%)	1.000[b]
Initial mH&Y	2 (1-2)	2 (1-2)	0.713[c]
DA dose (mg/day)	4.5 (1.5-4.5)	14.25 (6-24)	-

The results were considered statistically significant when P<0.05. [a]Student's t test, [b]Fisher's exact test, [c]Mann-Whitney U test. Side: The side of the body where illness began. Initial mH&Y: Modified Hoehn &Yahr stage at day 0. DA dose: the median dose of dopamine agonist given during the study. Initial LD dose: the median dose of levodopa patients have been taking at day 0.
SD: standard deviation

Table 1B. *Demographic characteristics of the levodopa add-on group*

Variables	Group 3 (n=10)	Group 4 (n=10)	P-value
Age (mean±SD)	69.8±5.9	66.0±10.6	0.335[a]
Gender (male/female)	4/6	7/3	0.370[b]
Duration of disease (month)	84.5 (60-218)	74.0 (31-214)	0.481[c]
Side (right/left)	0/10	2/8	0.474[b]
Family history	3 (30.0%)	2 (20.0%)	1.000[b]
Initial mH&Y	3 (2.5-4)	3.5 (2.5-4)	0.579[c]
DA dose (mg/day)	4.5 (3-4.5)	24 (6-24)	-
Initial LD dose (mg/day)	593.7 (375-875)	562.5 (375-875)	0.796[c]

The results were considered statistically significant when P<0.05. [a]Student's t test, [b]Fisher's exact test, [c]Mann-Whitney U test. Side: The side of the body where illness began. Initial mH&Y: Modified Hoehn &Yahr stage at day 0. DA dose: the median dose of dopamine agonist given during the study. Initial LD dose: the median dose of levodopa patients have been taking at day 0.
SD: standard deviation

FINDINGS FOR DAMGS

Baseline and Demographic Data

The study included a total of 24 DAMG patients: 9 (37.5%) males and 15 (62.5%) females. The patients were in the age range 36-80 years old, and the mean age was 61.75 ± 12.4 years. The patients were randomized to Group 1 and 2, each group consisting of 12 patients. The patients in Group 1 were in the age range 36-80 years and the mean age was 60.9 ± 13.7 years. The patients in Group 1 received a median pramipexole dose of 4.5 mg/day (1.5-4.5 mg/day). The patients in Group 2 were in the age range 44-77 years and the mean age was 62.6 ± 11.5 years. The median ropinirole dose in Group 2 was 14.25 mg/day (6-24 mg/day). No significant differences were found in the demographic characteristics between the two groups **(Table 1A)**.

Efficacy

Primary endpoints

The baseline median UPDRS II score of the patients in Group 1 was 9, which improved to 7 at the end of the study (p=0.003). The median UPDRS III score decreased from 23 at baseline to 18 at the end of the 6-month period (p=0.002). The median UPDRS II+III score was 32 at baseline, 30 at the end of the third month, and 25.5 at the end of the study (p=0.002 compared to baseline). An improvement was found in the median UPDRS total scores at the end of the study (p=0.002 compared to baseline). The UPDRS II, III, II+III scores and the total scores in Group 2 improved, but these changes were not significant **(Table 2A)**. There were no differences in the UPDRS scores between the two groups (data not shown).

Secondary Endpoints

The median CGI-S score of the patients in Group 1 was 4 at the beginning of the study and 3 at the end of the study; the difference was statistically significant (p=0.011). The median CGI-S score of the patients in Group 2 was 3.5 at baseline and 3 at the 6th month (p=0.157). The median BDI score of the patients in Group 1 was 11 at baseline and 9 at the end of 6 months (p=0.126), in Group 2 it was 12 at baseline and 1 at the end of the

Table 2A. *Total and subscale UPDRS scores of the dopamine agonist monotherapy groups*

Variables [median (25th-75th) percentiles]	Month 0	Month 1	Month 3	Month 6
UPDRS II				
Group 1	9 (5.5-10)[a]	7.5 (4.25-9.50)	7.5 (4.25-9)	7 (4.25-8)[a]
Group 2	8.5 (4.25-10)	7 (4.25-9.75)	6.5 (4.25-8)	5.5 (4.25-8)
UPDRS III				
Group 1	23 (12-33.75)[a]	21 (11.25-30)	20.5 (11.25-28.75)	18 (9.50-28)[a]
Group 2	24 (20.50-26.75)	21.5 (18.25-26)	20.5 (16.25-26)	19 (16-24)
UPDRS II+III				
Group 1	32 (17.50-43.50)[a, b]	29 (16-41.75)	30 (15.50-36.75)[b]	25.5 (13.75-35.25)[a]
Group 2	30.5 (29-35.75)	29 (26-31)	26.5 (23-30.75)	24.5 (22.25-31.50)
UPDRS total				
Group 1	33.5 (18.75-46.50)[a]	31 (18.25-44)	33.5 (17.50-37.75)	28 (14.75-36.25)[a]
Group 2	33 (29-38.25)	30.5 (27-33.75)	28.5 (24-33.50)	26.5 (23.25-32.75)

Multiple comparisons between the time points within groups were done with Wilcoxon signed-rank test. The results were considered statistically significant at $p<0.0042$ after Bonferroni correction. [a]The difference between months 0 and 6 was statistically significant ($P<0.0042$). [b]The difference between months 0 and 6 was statistically significant ($P<0.0042$).

Table 2B. *Total and subscale UPDRS scores of the levodopa add-on groups*

Variables [median (25th-75th) percentiles]	Month 0	Month 1	Month 3	Month 6
UPDRS II				
Group 3	17.75 (15.25-20.125)	15.75 (12.75-20)	13.5 (10.50-17.25)	13 (10.75-15.625)
Group 4	16.5 (14.25-21)	16 (12.75-19.25)	13 (11.50-14.50)	12.5 (9.75-14.50)
UPDRS III				
Group 3	42.65 (39.875-48.875)	42 (36.50-46.125)	37.5 (32-45.25)	35.5 (29.75-39.50)
Group 4	45.5 (37.25-49)	39.5 (35.50-48.50)	36 (27-39.50)	32 (25.75-40.25)
UPDRS II+III				
Group 3	62 (56.25-69.25)	58.75 (48.75-66)	51 (42.50-60.25)	48.5 (39.50-57.375)
Group 4	63 (51.50-72)	55.5 (48.25-66.25)	48.5 (38.50-55)	44.5 (35.50-56.25)
UPDRS total				
Group 3	67.25 (61-75.125)	64.75 (53.125-71.625)	55.25 (47-65)	52.25 (42.50-63.50)
Group 4	64 (52.25-76)	57 (51.25-68.75)	50.5 (38.75-57)	48 (35.50-57.25)

Multiple comparisons between the time points within groups were done with Wilcoxon signed-rank test. The results were considered statistically significant at $p<0.0042$ after Bonferroni correction.

study (p=0.107). There were no significant differences in these variables between the groups **(Table 3A)**. According to the CGI-I scale scores, the number of patients with significant clinical improvements in the 6th month was 5 (41.7%) in Group 1 and 3 (25.0%) in Group 2. The number of patients with mild improvement or no change was 7 (58.3%) in Group 1 and 7 (58.3%) in Group 2. The clinical condition was not worsened in any of the patients in Group 1. In Group 2, however, the clinical condition of 2 (16.7%) patients worsened. Seven (58.3%) patients in Group 1 and 10 (83.3%) in Group 2 developed medication side effects.

Safety

The most common side effects in the patients in Group 1 and 2 were nausea and/or vomiting **(Table 4A)**.

FINDINGS FOR LAGS

Baseline and demographic data

The study included a total of 20 LAG patients: 11 (55%) males and 9 (45%) females. The patients were in the age range of 42-80 years, and the mean age was 67.9 ± 8.6 years. The patients were ran-

Table 3A. *Changes in some of the study variables over time in the dopamine agonist monotherapy groups*

Variables [median (25th-75th) percentiles]	Initial (month 0)	Final (month 6)	p-value[a]	Change	P-value[b]
CGIs score					0.443
Group 1	4 (3-4)	3 (3-3)	0.011c	-1 (-1 – 0)	
Group 2	3.5 (3-4)	3 (3-4)	0.157	-0.5 (-1 – 0)	
BDI score					0.755
Group 1	11 (8.25-18.75)	9 (4-16.50)	0.126	-1.5 (-7.75 – 0.75)	
Group 2	12 (9.25-20.75)	11 (8.50-15)	0.107	0 (-5.5 – 0.75)	

[a]Intra-group comparisons were done with Wilcoxon signed-rank test. The results were considered statistically significant at p<0.025 after Bonferroni correction. [b]Inter-group comparisons were done with the Mann-Whitney U test. The results were considered statistically significant at p<0.05. cP<0.025.
CGIs: Clinical Global Impression - Severity of Illness, BDI: BECK Depression Inventory, LD: levodopa

Table 3B. *Changes in some of the study variables over time in the levodopa add-on groups*

Variables [median (25th-75th) percentiles]	Initial (month 0)	Final (month 6)	p-value[a]	Change	P-value[b]
LD dose (mg/day)					0.684
Group 3	593.75 (468.75-656.25)	500 (359.375-625)	0.105	-62.5 (-140.625 – 0)	
Group 4	562.5 (421.875-656.25)	500 (375-750)	0.194	-31.25 (-125 – 0)	
CGIs score					0.684
Group 3	5.5 (5-6.25)	4 (4-5.25)	0.006[c]	-1 (-2 – -1)	
Group 4	5 (4.75-6)	4 (3.75-4.25)	0.016[c]	-1 (-2 – 0)	
BDI score					0.123
Group 3	24 (14-26.75)	16 (7.75-21)	0.012[c]	-3.5 (-10.25 – -0.75)	
Group 4	11 (5.25-23.50)	9 (4-12.75)	0.672	0 (-6.25 – 2.25)	

[a]Intra-group comparisons were done with Wilcoxon signed-rank test. The results were considered statistically significant at p<0.025 after Bonferroni correction. [b]Inter-group comparisons were done with the Mann-Whitney U test. The results were considered statistically significant at p<0.05. cP<0.025.
CGIs: Clinical Global Impression - Severity of Illness, BDI: BECK Depression Inventory, LD: levodopa

domized to Group 3 and 4, each consisting of 10 patients. The patients in Group 3 were in the age range of 63-80 years, and the mean age was 69.8 ± 5.9 years. The median pramipexole dose was 4.5 (3-4.5) mg/day. The median LD dose at the beginning of the study was 593.7 (375-875) mg/day. The patients in Group 4 were in the age range of 42-77 years and the mean age was 66.0 ± 10.6 years. The median ropinirole dose given to the patients was 24 (6-24) mg/day; the median LD dose at the beginning of the study was 562.5 (375-875) mg/day. No significant differences were found in the demographic characteristics between the two groups **(Table 1B)**.

Efficacy

Primary endpoints
Although improvements were found in the median UPDRS II, III, II+III scores and in the total UPDRS scores compared to the baseline in Group 3 and Group 4, these improvements were not statistically significant **(Table 2B)**. There were no differences in the UPDRS scores between the groups (data not shown).

Secondary endpoints
The median LD dose decreased by 93.7 mg/day in Group 3, and by 62.5 mg/day in Group 4. Four patients in Group 3 had Levodopa-related motor complications at the beginning of the study, and an increase in dyskinesia was observed in one of these patients during the sixth-month follow-up. In group 4, only two patients had motor complications and no change was observed during their follow-up. The median CGI-S score of the patients in Group 3 was 5.5 at the beginning of the study and 4 at the end of the 6th month; the difference was statistically significant (p=0.006). The median CGI-S score of the patients in Group 4 was 5 at baseline

Table 4A. *Drug side effects in the dopamine agonist monotherapy groups*

Variables	Group 1 (n=12)	Group 2 (n=12)	P-value[a]
Nausea / vomiting	4 (33.3%)	6 (50.0%)	0.680
Increased daytime sleep	3 (25.0%)	4 (33.3%)	1.000
Decreased night sleep	-	1 (8.3%)	1.000
Pretibial edema	2 (16.7%)	2 (16 7%)	1.000
Severe throat pain[b]	-	1 (8.3%)	1.000
Orthostatic hypotension	-	2 (16.7%)	0.478
Increased sexual activity[b]	2 (16.7%)	1 (8.3%)	1.000
Increased ınterest in gambling[b]	-	1 (8.3%)	1.000

[a]Fisher's Exact Chi-Square test, P<0.05 was considered statistically significant. [b]Side effect that caused lowering to the previous dose.

and 4 at the end of the 6th month; the improvement was statistically significant (p=0.016). The median BDI score of the patients in Group 3 was 24 at baseline and 16 (6-26) at the end of the 6th month; the improvement was statistically significant (p=0.012). In Group 4, the improvement in the median BDI score was not significant (p=0.672). There were no significant differences in these variables between the groups (p=0.123, **Table 3B**). According to the CGI-I scale, the number of patients with significant clinical improvements at the end of the study compared to the baseline was 4 (40%) in Group 3 and in Group 4. The number of patients with mild improvement or no change was 6 (60%) in Group 3 and in Group 4. None of the patients in Group 3 or Group 4 had a worsened clinical condition. Eight (80%) of the patients in Group 3 and 6 (60%) in Group 4 developed medication side effects.

Safety

There were no significant differences in the medication side effects between the two groups. Pretibial oedema was the most common side effect in Group 3 and 4 **(Table 4B)**.

Discussion

In this study, at the end of the 6-month period, we found significant improvements in the scores of UPDRS II, III, II+III, and in the total UPDRS scores in Group 1. Although there was clinical improvement in the patients in Group 2, the results were not significant. In Group 1, we observed significant improvements in the CGI-S scores at the end of the sixth month (p=0.011).

The antiparkinsonian efficacy of these drugs was shown in previous monotherapy studies[13–16]. In a placebo-controlled study conducted by *Shannon* et al.[13], the mean UPDRS III score in the pramipexole group was 18.8 at the beginning, however, it was reported to decrease to 14.1 at the end of the follow-up period (p<0.0001). Parkinson's Disease Study Group[14] compared 213 patients with early PD receiving four separate fixed-dose pramipexole treatments with 51 patients with early PD receiving placebo. A significant improvement was observed in total UPDRS scores in pramipexole groups compared to the placebo group (p<0.005). *Korczyn* et al.[15] found a decrease in UPDRS III scores of the *ropinirole* group by 35% and in the bromocriptine group by 27%. The difference between the groups was found to be statistically significant. In a study by *Singer* et al.[16] sumanirole and ropinirole were compared in patients with early PD. Change in the UPDRS II + III score in the ropinirole group (-5.20) was found to be significant compared to the placebo group (p<0.001). We, too, have observed in our study that their efficacy was similar in DAMG patients. The fact that the improvement in the activity variables over time was not statistically significant in the ropinirole group might be attributed to the low number of patients included in the study. In addition, it is difficult to predict how long the two drugs will delay the need for LD since the study period covers 6 months.

In the second stage of our study, we found that changes in the median UPDRS II, III, II+III scores and in the total UPDRS scores were clinically significant but pramipexole and ropinirole were not superior to each other in LAG patients. In Groups 3 and 4, we have found significant improvements in the CGI-S scores at the end of the sixth month compared to baseline (p=0.006 and p=0.016, respectively). The improvement in these scores reflects the clinical improvement and supports the efficacy of both drugs in the treatment of advanced PD, as demonstrated by *Mizuno* et al.[11, 17] The fact that the effects of two drugs on the CGI-S scores are not superior to each other suggests that their clinical effects are comparable. In the study by *Lieberman*

Table 4B. *Drug side effects in the levodopa add-on groups*

Variables	Group 3 (n=10)	Group 4 (n=10)	P-value[a]
Nausea / vomiting	3 (30%)	1 (10%)	0.582
Increased daytime sleep	1 (10%)	2 (20%)	1.000
Pretibial edema	4 (40%)	3 (30%)	1.000
Orthostatic hypotension	2 (20%)	1 (10%)	1.000
Dyskinesia[b]	1 (10%)	1 (10%)	1.000
Visual hallucination[b]	1 (10%)	2 (20%)	1.000
Nightmares	1 (10%)	-	1.000
Chest pain[b]	-	1 (10%)	1.000
Dizziness	1 (10%)	-	1.000

[a]Fisher's Exact Chi-Square test, P<0.05 was considered statistically significant. [b]Side effect that caused lowering to the previous dose.

et al.[18] the daily LD dose was decreased by 27% in the pramipexole group at the end of week 32. In the study by *Im* et al.[19] the LD dose was decreased from 711.1 ± 239.2 mg/day to 548.0 ± 216.3 mg/day in the ropinirole group at the end of 16 weeks. In our study, the LD dose was decreased from 593.7 mg/day to 500 mg/day in Group 3 and from 562.5 mg/day to 500 mg/day in Group 4. The decreases in the LD doses were quite similar in both groups (p=0.684).

The efficacy of pramipexole and ropinirole as antiparkinsonian drugs and their effects on motor complications when used with LD treatment for PD have been demonstrated in several previous studies[11, 18–21]. In a placebo-controlled study by Lieberman et al.[18] investigating the efficacy of pramipexole in advanced PD, UPDRS II score was found to be improved significantly (averages of *on* and *off periods and averages of only on* period). In a similar study by *Wermuth* et al.[20], the change in total UPDRS score in the pramipexole group (16.9±14.9) was found to be significantly higher than in the placebo group (p=0.0184). In a study investigating the efficacy of ropinirole in advanced PD, Im et al.[19] compared the ropinirole and bromocriptine in patients with advanced PD and they found no difference between the groups in terms of UPDRS III scores (ropinirole: 5.9 ± 5.9, bromocriptine: 4.6 ± 9.1). *Barone* et al.[21] compared ropinirole, sumanirole and placebo in patients with advanced PD. The decrease in UPDRS II + III, UPDRS II (average of *on* and *off* periods) and UPDRS III (*on* period) scores were found to be statistically significant in the ropinirole (-13.4, -3.45, and -9.58, respectively) and sumanirole groups compared to placebo group (p<0.0001). No difference was observed between ropinirole and sumanirole groups. Although the improvement in the UPDRS parameters was not statistically significant in our study, the significant improvements in the CGI-S values of both groups suggest that pramipexole and ropinirole were effective and their efficacies were similar.

Depression is one of the most common psychiatric complication in PD and may affect the patients quality of lifes[22]. There are few studies investigating the treatment of depressive symptoms in PD with pramipexole. Despite methodological limitations, these studies have shown that pramipexole was effective[23]. *Barone* et al.[24] have found that the average improvement in the BDI score was 5.9 points in the pramipexole group and 4.0 points in the placebo group (p=0.01). This study has shown that pramipexole directly improves depressive symptoms in PD through direct antidepressant effects. It is also known that pramipexole is effective in the treatment of primary depression. *Rektorova* et al.[25] included a total of 44 patients with PD [16 with motor complications (MC+) and 28 without (MC-)] in their six-month prospective study to evaluate the effect of ropinirole on non-motor symptoms. They demonstrated that ropinirole was effective for depression in MC+ patients.

In our study, we found that pramipexole and ropinirole were not superior to each other (p=0.755), although there was an improvement in the median BDI scores in DAMG patients at the end of the sixth month compared to the baseline. In the LAG, the median BDI score in Group 3 showed a significant improvement at the end of the study compared to the baseline (p=0.012). However, we have not observed the superiority of pramipexole over ropinirole. The possible mechanism of the antidepressant effect of pramipexole may involve its high affinity to D3 receptors, which are predominantly located in the mesolimbic regions[23]. In addition, pramipexole exhibits relatively higher activity at D3 receptors compared to other DAs[2, 10, 26].

None of the DAMG or LAG patients had to prematurely leave the present study due to life-threat-

ening side effects. Nausea and vomiting were controlled with domperidone. Increased sexual activity was found in two patients in Group 1, increased sexual activity and interest in gambling were found in a patient in Group 2; the severity of these side effects decreased with reduced doses of DA. It has been suggested that such drug-induced pathological behaviour might be related to the medications' selective affinity for D3 receptors[27]. Pretibial oedema was the most common side effect in patients in Group 3 and 4. Oedema tends to develop in the later stages of PD[28]. Cases with visual hallucinations showed improvement with the administration of quetiapine. Pleural, pericardial, and peritoneal fibrosis and fibrotic heart-valve disease seen in the ergot-derived DAs were not observed[29]. Thus, both pramipexole and ropinirole might be considered as safe and tolerable DAs in the monotherapy and in the levodopa add-on therapy of PD. It is of great importance to select the appropriate DA at the required dose and with essential prudence[30].

LIMITATIONS

There were some limitations that should be mentioned. First, the study was not performed with a double-blind design. Second, since the study was conducted in a single center, the number of patients included was relatively low. Moreover, since the socioeconomic and sociocultural levels of the patients living in the province where the center was located and participating in the study were low, the number of cases leaving the study was more than expected. Third, the absence of the placebo group was another limitation of the study. Fourth, the total number of patients with Levodopa-related motor complications was low, therefore the effects of study drugs on levodopa-related dyskinesia could not be evaluated. Other limitations were the relatively short follow-up period of patients and the lack of screening for impulse control disorders. Finally, the fact that non-motor symptoms were not evaluated may cause limitations to determine the clinical changes that occur during the follow-up of patients.

Conclusion

Our study supports the efficacy and safety of pramipexole monotherapy in PD. Although the findings on the efficacy of ropinirole in the monotherapy for PD were not statistically significant, the findings of similar efficacy and safety suggest that pramipexole and ropinirole are not superior to each other. In LAG, findings support the efficacy and safety of both drugs and suggest that they are not superior to each other when they are administered together with LD. The significance of this study is the inclusion and evaluation of both DAMG and LAG patients and the evaluation of depressive state in patients, as non-motor symptoms becoming more important in disease prognosis.

DISCLAIMERS
None to declare.

SOURCE(S) OF SUPPORT
None to declare.

CONFLICT OF INTERESTS
All the authors declare no conflict of interests.

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