

# Transdermal Patch of Rotigotine Attenuates Freezing of Gait in Patients with Parkinson's Disease: An Open-Label Comparative Study of Three Non-Ergot Dopamine Receptor Agonists

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## Abstract

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**Objective** Parkinson's disease (PD) is characterized by the progressive degeneration of the nigrostriatal dopaminergic neurons. Rotigotine is a non-ergot dopamine receptor agonist (DA). Its transdermal patch maintains the effective concentrations for 24 hours. Freezing of gait (FOG) is a common and devastating symptom in PD patients. Little is known about therapeutic effects of rotigotine on FOG in PD patients. Herein we compared how three non-ergot DAs of rotigotine, pramipexole LA and ropinirole CR influence FOG, besides classical motor deficits in PD patients.

**Methods** Rotigotine (maintenance doses of 9-27 mg/day) was administered in 51 patients, 36 patients received pramipexole LA (1.5-4.5 mg/day) and 35 patients received ropinirole CR (8-16 mg/day). The Unified PD Rating Scale (UPDRS) parts I-IV, FOG questionnaire (16 items) and wearing off time were examined from baseline to 7 months after DA administration. UPDRS parts I-IV were evaluated during on time and FOG was recorded during off time if patients experienced wearing off.

**Results** A total of 111 patients completed the study. UPDRS parts II-III scores and wearing off time were significantly reduced after each DA treatment compared to baseline. FOG was found in 54 patients (49%). Most patients developed FOG during off time only. FOG scores were significantly decreased at 2 months after rotigotine treatment whereas pramipexole LA and ropinirole treatment did not alter FOG scores.

**Conclusion** The present study indicates that transdermal patch of rotigotine attenuated the FOG off time. The similar binding affinities to dopamine receptors between rotigotine and dopamine, and 24 hours steady hemodynamics could contribute to the therapeutic mechanism of rotigotine on FOG in PD patients with wearing off.

**Key words:** rotigotine, non-ergot dopamine receptor agonist, continuous dopaminergic stimulation, freezing of gait, Parkinson's disease

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## Introduction

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Parkinson's disease (PD) is a chronic neurological disease which is characterized by the progressive degeneration of nigrostriatal dopaminergic neurons. PD patients experience rigidity, tremor, bradykinesia and gait disturbance. Freezing of gait (FOG) is characterized by an episodic inability to walk that the patient's feet get stuck or fixed although the

upper body continues to move. The forward movements of the feet are markedly decreased despite the intention to walk (1-4). This abnormal locomotion of initial gait often occurs in patients with advanced PD. As FOG is a main risk of falls, the medication is very important in PD patients.

Rotigotine, (6S)-6-[propyl (2-(2-thienyl) ethyl) amino]-5,6,7,8-tetrahydro-1-naphthalenol, is a non-ergot dopamine receptor agonist (DA) and this drug is used as the transdermal patch for 24 hours (h) with continuous dopaminergic

stimulation in patients with PD or restless legs syndrome (5, 6). However, little is known about the effect of rotigotine on FOG in PD patients. The present study aimed to examine how treatment with three non-ergot DAs (rotigotine, pramipexole LA and ropinirole CR) influence FOG and typical motor deficits in PD patients.

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## Materials and Methods

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### Enrolled PD patients

PD was diagnosed according to the United Kingdom Parkinson's Disease (UKPD) Society Brain Bank criteria (7). PD patients who fulfilled the following criteria were enrolled between 2011 and April 2015 in the present study: 1) age  $\geq 40$  years; 2) Hoehn & Yahr stage of 3 or 4; and 3) Unified PD Rating Scale (UPDRS) Part III sum score  $>10$ ; and 4) no prior history of non-ergot DAs administration. The dose of levodopa was maintained from 28 days before rotigotine treatment and during this study. When other anti-parkinsonian medications, including anticholinergics, amantadine, droxidopa, selegiline, entacapone and zonisamide were administered, those doses were also not changed for 28 days before and during the study. Active physiotherapy for gait was completed before the present study and not performed during this study. We excluded patients who had psychiatric symptoms, orthostatic hypotension, arrhythmia, liver dysfunction, drug allergy and prior histories of epilepsy and serious cardiac disease. Informed consent of the present study was obtained from all patients. The present study was carried out in accordance with the recommendation in the Guide for Clinical Studies of Toho University. The protocol was approved by the Committee on the Ethics of Human Research of Toho University Omori Medical Center.

### DA administration

Rotigotine transdermal patch was administered initially at 4.5 mg/day for one week and increased to 9 mg/day for the following three weeks. The total dose of rotigotine contained per patch is described in Japan, whereas the nominal dose delivered in 24 h is expressed in the United States of America and Europe. The initial dose of 4.5 mg/day corresponds to the nominal dose of 2 mg/h (5). Afterwards, the daily doses of rotigotine were used at 9-27 mg (4-12 mg/24 h) for six months. Pramipexole LA was initiated at 0.375 mg/day and maintained at the dose of 1.5-4.5 mg/day. Ropinirole CR was used at the initial dose of 2 mg/day and maintained at 8-16 mg/day. The maintenance dose of each DA was administered at least 6 months. One of rotigotine, pramipexole LA and ropinirole CR was selected by attending physicians. DAs were not switched in all patients during the study. The study was designed as an open-label and non cross-over study.

### Neurological evaluation

Neurological examination and UPDRS parts I to IV were

performed every month at baseline and during DA treatment. These scores were evaluated on time in patients who experienced the wearing off phenomenon. Daily hours of off time were measured in those patients. The 16-item FOG questionnaire described by Giladi et al. (8) was also performed. FOG was divided into the following 2 types: FOG off time, defined as FOG during off time only, and FOG on time, defined as FOG that developed during on and off time. The FOG score was recorded during off time in patients with wearing off.

### Data analysis

UPDRS parts I to IV scores, FOG score, and hours of off time before and after DA treatment were statistically analyzed using repeated analysis of variance (ANOVA) followed by Dunnett type multiple comparison test. The significance level was set at 0.05. Statistical analyses were performed using PASW Statistics 18.0 software program (IBM, Chicago, USA).

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## Results

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### Demographic data of PD patients

A total of 121 patients (64 men and 57 women) participated in the present study. Ten patients [rotigotine (n=3), pramipexole LA (n=3) and ropinirole CR (n=4)] were excluded from this study because anti-PD medications and those doses were changed. The demographic data of patients who completed the study (n=111) are shown in Table. There were no significant changes of clinical profiles between patients treated with rotigotine (n=47), pramipexole LA (n=33) and ropinirole CR (n=31).

### Type and patient number of FOG

FOG was found in 54 patients (49%), including 24 patients (51%) in the rotigotine group, 16 patients (48%) in the pramipexole LA group and 14 patients (45%) in the ropinirole CR group. FOG off time was observed in 48 patients: 21 patients in the rotigotine group, 14 patients in the pramipexole LA group and 13 patients in the ropinirole CR group. FOG on time existed in 6 patients: 3 patients in the rotigotine group, 2 patients in the pramipexole LA group and 1 patient in the ropinirole CR group (Table).

### UPDRS scores before and after each DA administration

At one month after treatment with each DA, UPDRS parts I-IV scores did not differ significantly from the baseline data. UPDRS part II score (Fig. 1) and part III score (Fig. 2) were decreased significantly from 2 months after each DA administration compared to baseline. Alternations of UPDRS part II and III scores did not significantly differ between three groups of rotigotine, pramipexole LA and ropinirole CR. There were no statistical differences of UPDRS parts I and IV scores before and after treatment

**Table. Clinical Background of PD Patients.**

	Rotigotine (n=47)	Pramipexole LA (n=33)	Ropinirole CR (n=31)
Men/women	26/21 patients	17/16 patients	16/15 patients
Age	74.0 (9.3) years	74.5 (10.3) years	75.3 (9.9) years
Men	73.7 (9.7) years	74.0 (9.9) years	74.7 (10.3) years
Women	74.5 (8.9) years	75.0 (10.9) years	75.5 (9.6) years
Disease duration	7.5 (5.5) years	7.4 (5.6) years	7.7 (5.5) years
Yahr stage III/IV	31/16 patients	20/13 patients	21/10 patients
UPDRS part I*	2.0 (1.5)	2.1 (1.6)	2.0 (1.7)
UPDRS part II*	15.9 (9.8)	16.4 (9.9)	15.8 (9.2)
UPDRS part III*	31.9 (12.4)	32.1 (11.7)	31.0 (12.1)
UPDRS part IV*	2.9 (1.4)	2.7 (1.5)	3.0 (1.5)
Wearing off	24 patients (51%)	17 patients (52%)	15 patients (48%)
FOG off time	21 patients (45%)	14 patients (42%)	13 patients (42%)
FOG on time	3 patients (6%)	2 patients (6%)	1 patients (3%)
FOG questionnaire**	30.1 (12.5)	29.5 (13.0)	30.4 (12.8)
Levodopa doses	545 (232) mg/day	550 (242) mg/day	552 (240) mg/day
DA doses <sup>†</sup>	18.5 (4.1) mg/day	2.2 (1.2) mg/day	11.3 (5.2) mg/day
Amantadine user	11 patients (23%)	7 patients (21%)	6 patients (19%)
Selegiline user	15 patients (32%)	7 patients (21%)	7 patients (22%)
Entacapone user	14 patients (30%)	10 patients (30%)	12 patients (38%)
Droxidopa user	15 patients (32%)	15 patients (45%)	15 patients (48%)
Zonisamide user	18 patients (38%)	12 patients (36%)	11 patients (35%)

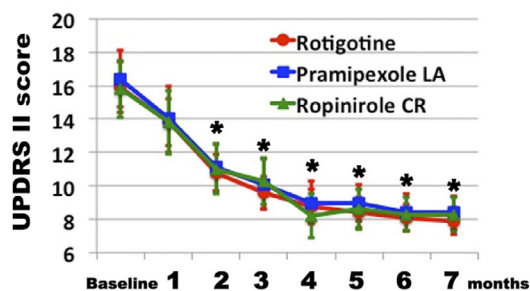
Data are expressed as the mean (SD).

\* UPDRS parts I-IV was recorded on time.

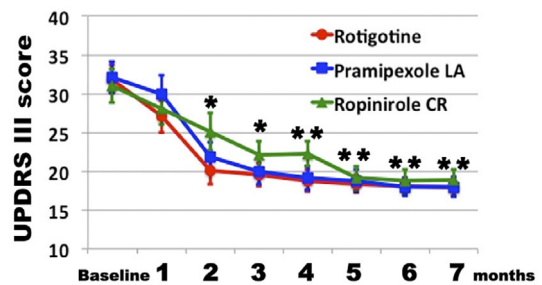
\*\* The FOG questionnaire was recorded during off time in patients with wearing off.

<sup>†</sup> Maintenance doses of DA.

DA: Dopamine receptor agonist, FOG: Freezing of gait, PD: Parkinson's disease, UPDRS: Unified Parkinson's disease rating scale



**Figure 1.** Changes of UPDRS part II scores. UPDRS part II scores were significantly decreased from 2 months post-administration of each DA compared to baseline. \* $p < 0.05$  versus baseline by repeated measures ANOVA followed by Dunnett type multiple comparison test. Data are expressed as the mean (SEM).



**Figure 2.** Changes of UPDRS part III scores. UPDRS part III scores were significantly decreased from 2 months post-administration of each DA compared to baseline. \* $p < 0.05$  and \*\* $p < 0.01$  versus baseline by repeated measures ANOVA followed by Dunnett type multiple comparison test. Data are expressed as the mean (SEM).

with each DA.

#### FOG scores before and after each DA administration

The mean FOG score (SEM) at baseline was 30.1 (1.8) in the rotigotine group, 29.5 (2.0) in the pramipexole LA group and 30.4 (2.2) in the ropinirole CR group.

At one month after each DA administration, FOG scores were not significantly different between from the baseline data. The mean FOG score (SEM) at 2 months after rotigotine treatment was significantly decreased to 21.0 (1.2) significantly compared to baseline ( $p < 0.05$ ). The mean FOG score (SEM) was 8.2 (0.8) at the final examination at 7 months post-administration ( $p < 0.01$ ). The FOG scores did not differ statistically in patients treated with pramipexole

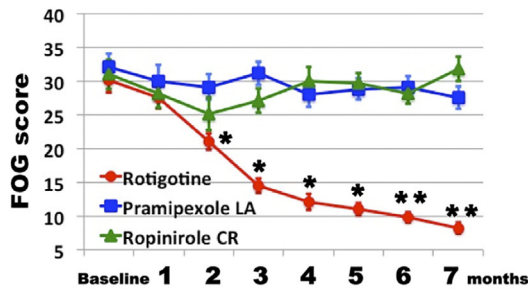
LA or ropinirole CR compared to baseline (Fig. 3).

#### Off time before and after each DA administration

Wearing off occurred in 24 patients (51%) treated with rotigotine, 17 patients (52%) with pramipexole LA and 15 patients (48%) with ropinirole CR at baseline (Table).

The mean off time (SD) at baseline was 3.9 (2.0) h in the rotigotine group, 3.8 (2.2) h in the pramipexole LA group and 4.0 (2.1) h in the ropinirole CR group.

After each DA administration, the off time was shorter compared to baseline. On the final examination at 7 months post-administration, the mean off time (SD) was 2.1 (1.2) h in the rotigotine group, 2.2 (1.2) h in the pramipexole LA group and 2.3 (1.3) h in the ropinirole CR group. The daily hours of off time were significantly decreased at 7 months



**Figure 3.** Changes of FOG scores. FOG scores were significantly decreased from 2 months after rotigotine administration compared to baseline. The FOG scores were not altered statistically after pramipexole LA or ropinirole CR treatment. \* $p < 0.05$  and \*\* $p < 0.01$  versus baseline by repeated measures ANOVA followed by Dunnett type multiple comparison test. Data are expressed as the mean (SEM).

post-treatment with each DA compared to baseline ( $p < 0.05$ ).

## Discussion

The present study revealed that the transdermal rotigotine patch ameliorated UPDRS parts II-III scores and shortened the wearing off time in PD patients. These benefits were similar in degree to pramipexole LA or ropinirole CR treatment. FOG was observed in half of patients in the present study. Most of our patients developed FOG during off time only. Rotigotine treatment significantly decreased the FOG scores whereas pramipexole LA or ropinirole CR treatment did not respond to have any effect on FOG. Such amelioration of FOG did not depend on reduction of off time after three DAs administration.

FOG is an episodic hesitation phenomenon that occurs at gait initiation. The prevalence of FOG varies in PD patients. In a longitudinal analysis of 800 patients with early-staged PD, 57 patients (7.1%) experienced FOG on entry of the deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP) study, and 193 patients (26%) developed FOG at the end of the study (9). A previous cross-sectional analysis showed the FOG prevalence of 32% in 990 patients with PD (10). FOG occurred more frequently in advanced PD and its prevalence increased to 53% (11). There are currently various approaches for FOG, including pharmacological and surgical medications, physiotherapy, and occupational therapy. Physiotherapy is recommended in patients with a mild degree of FOG (12). Our patients underwent gait rehabilitation before the present study, and none had physiotherapy for gait at baseline and after DAs administration. Definite beneficial pharmacological treatment has not been available for FOG in PD patients. With respect to DA treatment, previous studies described that ropinirole medication might deteriorate FOG in dopamine-responsive FOG patients with PD (12, 13). Therapeutic effects of rotigotine on FOG remain unknown. The present study first suggested that the rotigotine patch attenuated FOG in patients with

wearing off. Pramipexole LA or ropinirole CR treatment did not improve or worsen FOG. Previous pharmacological and pharmacokinetic profiles revealed that rotigotine, pramipexole LA and ropinirole CR are long-acting non-ergot DAs with continuous dopaminergic stimulation. The equivalent dose of three DAs is 9 mg of rotigotine, 1 mg of pramipexole LA and 4 mg of ropinirole CR. In the present study, the mean maintenance dose of rotigotine, pramipexole LA and ropinirole CR were 18.5 mg, 2.2 mg and 11.3 mg, respectively. These doses almost correspond to the equivalent dose among three DAs.

The rotigotine patch has been shown to significantly reduce the off time in patients with advanced PD who do not sufficiently respond to levodopa (14-16). A multinational, double-blind, placebo-controlled trial of rotigotine exhibited significant improvement in early morning motor dysfunction and sleep disturbances (17). Of interest, previous studies provided therapeutic abilities of rotigotine for PD-related dysphagia (18) and sleep fragmentation (19). The steady and persistent dopaminergic stimulation by the rotigotine patch might result in a better control of motor and non-motor deficits during the day and night in PD patients. Regarding medications for FOG in PD patients, FOG occasionally responds to levodopa, but levodopa is not always effective. Therapeutic strategy has been difficult in dopamine-nonresponsive FOG patients (9-12). In a previous case report of a 79-year-old man with pure akinesia, the relative low dose of rotigotine (4 mg/h corresponding to 9 mg/day in Japan) improved several gait parameters (20). A recent study has also suggested that the rotigotine patch ameliorated various gait parameters in *de novo* untreated PD patients (21). However, the therapeutic mechanism of rotigotine on FOG remains unclear in the present study. Rotigotine is a non-ergot DA (5, 6) which binds to 5-hydroxytryptamine (5-HT) 1A receptors (22). 5-HT<sub>1A</sub> receptors are primarily located in the frontal cortex and the dorsal raphe nucleus and can regulate dopamine release from the striatum. Antidepressant medication, specifically selective serotonin reuptake inhibitors (SSRIs), was reported to improve depression in PD patients (23). However, there has been no effective evidence of SSRIs against FOG in PD patients. Therefore, serotonergic effects via 5-HT<sub>1A</sub> receptors of rotigotine might not influence attenuation of FOG. With respect to dopamine receptors, rotigotine has the binding affinity to D<sub>2</sub>/D<sub>3</sub>/D<sub>4</sub> receptors of D<sub>2</sub> family and D<sub>1</sub>/D<sub>5</sub> receptors of D<sub>1</sub> family. The binding affinities of rotigotine, pramipexole and ropinirole to D<sub>2</sub>/D<sub>3</sub>/D<sub>4</sub> receptors are similar degree. Otherwise, rotigotine has higher binding affinity to D<sub>1</sub>/D<sub>5</sub> receptors compared to pramipexole and ropinirole. Rotigotine, dopamine and apomorphine show almost the equal binding affinities to D<sub>1</sub>/D<sub>5</sub> receptors (6). Rotigotine may promote the transmission of dopamine nervous system through the direct action on both D<sub>2</sub>/D<sub>3</sub>/D<sub>4</sub> and D<sub>1</sub>/D<sub>5</sub> receptors in the basal ganglia. The pharmacokinetics of the rotigotine transdermal patch provides constant drug delivery over 24 h with the similar plasma concentration to continu-

ous intravenous infusion. Therefore, the distinct binding affinity to D<sub>1</sub>-D<sub>3</sub> receptors and 24-h steady hemodynamics could contribute to the improvement of FOG off time.

There are several limitations in the present study. First, this was an open-label study with a relative small number of patients. FOG can be influenced by the emotion or mental state of patients. Further large-scale randomized clinical trials of rotigotine or the switching study of three DAs are needed to design in PD patients with FOG.

In conclusion, the present study highlighted the therapeutic effect of rotigotine on FOG in PD patients with wearing off. The binding affinities of rotigotine and dopamine to D<sub>1</sub>-D<sub>3</sub> receptors are similar (6). The distinct pharmacological profile and 24-h steady hemodynamics of rotigotine might play a role in the therapeutic mechanism of FOG in PD patients with wearing off.

**The authors state that they have no Conflict of Interest (COI).**

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