JMD
https://doi.org/10.14802/jmd.18005 / J Mov Disord 2018;11(2):65-71
pISSN 2005-940X / eISSN 2093-4939

ORIGINAL ARTICLE

# Amantadine and the Risk of Dyskinesia in Patients with Early Parkinson's Disease: An Open-Label, Pragmatic Trial

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## ABSTRACT

**Objective** We examined whether amantadine can prevent the development of dyskinesia.

**Methods** Patients with drug-naïve Parkinson's disease (PD), younger than 70 years of age and in the early stage of PD (Hoehn and Yahr scale < 3), were recruited from April 2011 to December 2014. The exclusion criteria included the previous use of anti-parkinsonian medication, the presence of dyskinesia, significant psychological disorders, and previous history of a hypersensitivity reaction. Patients were consecutively assigned to one of 3 treatment groups in an open label fashion: Group A-1, amantadine first and then levodopa when needed; Group A-2, amantadine first, dopamine agonist when needed, and then levodopa; and Group B, dopamine agonist first and then levodopa when needed. The primary endpoint was the development of dyskinesia, which was analyzed by the Kaplan-Meier survival rate.

**Results** A total of 80 patients were enrolled: Group A-1 ($n$ = 27), Group A-2 ($n$ = 27), and Group B ($n$ = 26). Twenty-four patients were excluded from the analysis due to the following: withdrawal of amantadine or dopamine agonist ($n$ = 9), alternative diagnosis ($n$ = 2), withdrawal of consent ($n$ = 1), and breach in the protocol ($n$ = 12). After exclusion, 5 of the 56 (8.93%) patients developed dyskinesia. Patients in Group A-1 and A-2 tended to develop dyskinesia less often than those in Group B (cumulative survival rates of 0.933, 0.929, and 0.700 for A-1, A-2, and B, respectively; $p$ = 0.453).

**Conclusion** Amantadine as an initial treatment may decrease the incidence of dyskinesia in patients with drug-naïve PD.

**Key Words** Amantadine; dyskinesias; Parkinson's disease; levodopa.

Levodopa-induced dyskinesia (LID) is a serious motor complication in patients with Parkinson's disease (PD) who receive medical treatment. It develops in up to 50% of PD patients within 5 years after the initiation of levodopa treatment.[1] Risk

**Received:** January 22, 2018 **Revised:** March 9, 2018 **Accepted:** March 12, 2018
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factors for LID include female gender, low body mass index, younger age of onset, disease severity, and a high dose of levodopa.[2-4] Due to the potential risk of LID, levodopa has been less preferred as an initial treatment for PD, especially in young patients, even though it is the most potent treatment. Monotherapy with dopamine agonist can delay the onset of LID; however, it is not feasible in many cases.[5-7] More than half of the patients who start on dopamine agonists as an initial treatment need to switch to levodopa monotherapy due to adverse events or to a combination of dopamine agonist and levodopa within 4−5 years to obtain a satisfactory clinical benefit.[8]

Among the marketed drugs targeting non-dopaminergic pathways, amantadine is the only drug that has sufficient data to support its antidyskinetic effect. The previous studies on the antidyskinetic effect of amantadine targeted patients who were already dyskinetic and were observed only for a short time.[9-13] However, the preventive effect for LID of amantadine in *de novo* PD has not been examined, although there is an ongoing prospective randomized controlled trial called PREMANDYSK (Amantadine and L-DOPA-induced Dyskinesia in Early Parkinson's diseases. https://clinicaltrials.gov/ct2/show/NCT01538329?cond=PREMANDYSK&rank=1. Accessed on January 19, 2018). To examine whether amantadine can reduce the incidence of LID in patients with early PD, we used amantadine as an initial treatment in drug-naïve PD patients and compared it with a dopamine agonist in the following trial: A long-term observation study of the incidence of dyskinesia in patients with early PD who received Amantadine or a dopamine agonist (ADAD). Our prospective findings suggest the possible preventive effect of amantadine for dyskinesia.

## MATERIALS & METHODS

### Subjects

Patients with PD who were newly diagnosed and were drug-naïve were recruited at the movement disorder clinic at Seoul National University Hospital. PD was diagnosed by movement disorder specialists based on the UK Parkinson's Disease Society Brain Bank Criteria from April 2011 to December 2014. Patients younger than age 70 years and in the early stage of PD (Hoehn and Yahr stage < 3) at enrollment were included in the study. The exclusion criteria were as follows: previous use of antiparkinsonian medication, diagnosis of Parkinson plus syndrome, other significant psychological problems including major depression or dementia, previous history of hypersensitivity reaction to medication similar to the study drug, and possibility of pregnancy or breast-feeding. The participants were evaluated in the clinic by movement disorder specialists for 60 months on average at an interval of every 6 months. The analysis was conducted in July 2017.

All patients in this study signed a written informed consent form according to the Declaration of Helsinki. The objectives and procedures of the study were approved by the Institutional Review Board (Seoul National University Hospital: reference number 1109-057-332). This trial is registered on ClinicalTrials.gov, identifier number NCT01338662.

### Study design

ADAD was a single-center, prospective, open-label, parallel-group, and pragmatic trial. Patients were consecutively assigned to one of three treatment groups in an open-label manner. Patients in Group A-1 started the treatment with amantadine first, and then levodopa was added when needed. Amantadine was prescribed from 150 mg to 300 mg divided into 3 times a day. Patients in Group A-2 were prescribed amantadine first, dopamine agonist when needed, and then levodopa. Patients in Group B started with a dopamine agonist as an initial treatment, and then levodopa was added when needed. Amantadine was not prescribed in Group B unless dyskinesia developed. All patients were required to maintain amantadine and the dopamine agonist through the end of the study (Figure 1). When parkinsonian symptoms were not controlled well enough by the standard dose of amantadine or by the maximum tolerated dose of the dopamine agonists, investigators were allowed to add other drugs as needed. Selegiline, rasagiline, and entacapone were allowed to be added for optimal treatment at any time. On the other hand, any drug or treatment that could suppress LID, including deep brain stimulation and antipsychotics, was not allowed.

### Outcome measures

The primary endpoint of the ADAD was the devel-


**Figure 1.** Study protocol.

opment of LID, including both peak-dose dyskinesia and diphasic dyskinesia. The secondary outcomes were as follows: 1) adverse events and adherence to each drug, 2) initial non-motor symptoms (NMS) as a predictor for the later development of dyskinesia, and 3) clinical characteristics and final doses of medication related to dyskinesia.

The data on dyskinesia were collected in the clinic by interviews and neurologic examinations conducted by the movement disorder specialists. Neurologists interviewed the patients and evaluated the adverse events as well as the presence of dyskinesia. Baseline characteristics, including the age of onset, age at enrollment, sex, disease duration, Hoehn and Yahr stage, Unified Parkinson's Disease Rating Scale (UPDRS), Mini Mental Status Examination, Frontal Assessment Battery, and initial NMS including REM sleep behavior disorder (RBD), constipation, urinary frequency or incontinence, and orthostatic dizziness, were evaluated at the first visit. The final doses of medication were calculated at the point of the development of dyskinesia for the patients with dyskinesia and at the last visit during 60 months for those without dyskinesia.

### Statistics

Kaplan-Meier survival analysis was used to analyze the development of LID. All analyses followed the per-protocol analysis, and the log-rank test was used to examine the difference between the development rates of dyskinesia in each treatment group. We also applied the Cox proportional hazards model with Firth's correction to evaluate the difference in the development of LID between the treatment groups. Kruskal-Wallis analysis and the Mann-Whitney U test were used to analyze the difference in the baseline characteristics of each group for numerical data. The chi-squared test and independent *t*-test were used for the univariate analysis with $p < 0.05$ as the threshold for statistical significance. SPSS software version 21 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

## RESULTS

### Levodopa-induced dyskinesia in each group

A total of 80 patients (34 men and 46 women) were enrolled: Group A-1 ($n = 27$), Group A-2 ($n = 27$), and Group B ($n = 26$). During the trial, patients presenting any of the following were excluded from the analysis: 1) withdrawal of amantadine and dopamine agonist ($n = 9$), 2) alternative diagnosis on the follow-up ($n = 2$; multiple system atrophy and corticobasal degeneration), 3) withdrawal of consent ($n = 1$), and 4) breach in the protocol ($n = 12$) (Figure 2). A breach in the protocol included the following: dopamine agonist given in Group A-1 ($n = 5$), levodopa given before dopamine agonist in Group A-2 ($n = 1$), and use of antiparkinsonian medication before the study, which was recognized after the enrollment ($n = 6$). After the exclusion, 56 patients were eligible for Kaplan-Meier survival analysis for the development of dyskinesia. The baseline characteristics of the patients were compa-

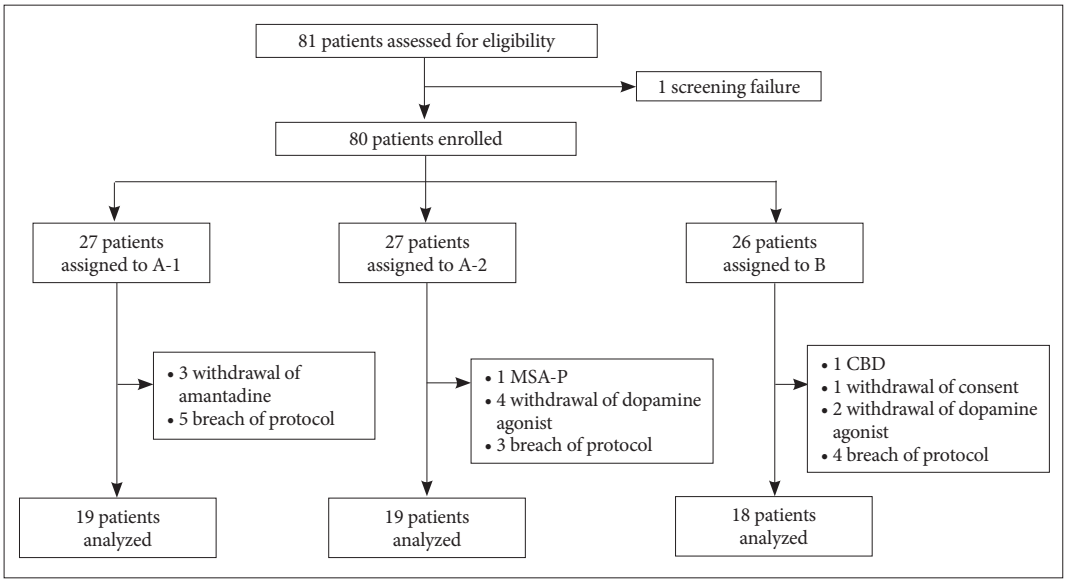


**Figure 2.** Trial flowchart. MSA-P: multiple system atrophy-parkinsonian type, CBD: corticobasal degeneration.

**Table 1.** Baseline characteristics of the patients in each group

| | All patients (*n* = 56) | A-1 (*n* = 19) | A-2 (*n* = 19) | B (*n* = 18) | *p* value |
|---|---|---|---|---|---|
| Men | 26 (46.4) | 11 (57.9) | 6 (31.6) | 9 (50.0) | 0.249 |
| Age (yr) | 55.27 ± 8.69 | 54.95 ± 6.52 | 55.68 ± 9.22 | 55.17 ± 10.44 | 0.978 |
| Age of onset (yr) | 53.57 ± 9.41 | 53.32 ± 6.94 | 54.00 ± 9.76 | 53.39 ± 11.58 | 0.985 |
| PD duration (yr) | 1.71 ± 1.96 | 1.63 ± 1.83 | 1.68 ± 1.77 | 1.83 ± 2.36 | 0.955 |
| H&Y | 1.63 ± 0.54 | 1.47 ± 0.51 | 1.63 ± 0.50 | 1.81 ± 0.57 | 0.175 |
| UPDRS I | 1.48 ± 1.72 | 1.69 ± 1.67 | 1.33 ± 2.06 | 1.41 ± 1.42 | 0.521 |
| UPDRS II | 5.17 ± 4.00 | 5.44 ± 4.59 | 5.17 ± 4.60 | 4.88 ± 2.64 | 0.920 |
| UPDRS III | 19.29 ± 8.01 | 19.62 ± 9.12 | 17.85 ± 6.37 | 20.70 ± 8.70 | 0.727 |
| Tremor-dominant subtype* | 27 (54.0) | 9 (52.9) | 11 (55.0) | 7 (50.0) | 0.982 |
| MMSE | 27.10 ± 4.60 | 27.36 ± 1.91 | 25.93 ± 7.66 | 28.00 ± 1.56 | 0.744 |
| FAB | 15.71 ± 2.64 | 16.14 ± 1.23 | 15.00 ± 4.11 | 16.00 ± 1.62 | 0.959 |

Data are expressed as *n* (%) or mean ± standard deviation.*calculations of the percentage of patients with the tremor-dominant subtype and the chi-squared test were performed after excluding 6 patients with incomplete evaluations. PD: Parkinson's disease, H&Y: Hoehn and Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini-Mental Status Examination, FAB: Frontal Assessment Battery.

rable across the 3 treatment groups (Table 1). Median follow-up duration was 30.0 months.

A total of 5 (8.93%) patients developed dyskinesia during the observation. The results showed that amantadine may reduce the incidence of LID, but it was not statistically significant. Patients in Group A-1 and A-2 who were administered amantadine for the initial treatment tended to develop dyskinesia less than those in Group B (cumulative survival rate of 0.933, 0.929, and 0.700 for A-1, A-2, and B, respectively). The *p* value in the log-rank test was 0.453 between all 3 groups and 0.207 between Group A-2 and B (Figure 3). When the Cox proportional hazard model with Firth's correction was applied, the same trend was observed (hazard ratio of Group A-2 and B vs. A-1; 0.54 and 1.58, 95% confidence interval 0.04−7.26 and 0.18−14.09, $p = 0.645$ and 0.682). All dyskinesia in this study developed after the addition of levodopa. There was no significant difference in the final dose of medication, which included amantadine, dopamine agonist, and levodopa, between the 3 treatment groups (Supplementary Table 1 in the online-only Data Supplement).

## Characteristics of patients with LID

The patients with LID were prescribed a significantly higher total levodopa equivalent daily dose at the last follow-up ($p = 0.039$). When amantadine and dopamine agonist doses were subtracted, the rest of the levodopa equivalent dose was also higher in patients with LID ($p = 0.020$). Other characteris-

tics, including sex, age of onset, disease duration at enrollment, UPDRS, and clinical subtype of PD were not different between the patients with LID and those without LID (Supplementary Table 2 in the online-only Data Supplement). NMS at baseline, including RBD, constipation, urinary frequency or incontinence, and orthostatic dizziness, were not different between the patients with and without LID (chi-squared test, $p = 0.554$, 1.000, 1.000, and 1.000, respectively).

### Adverse events and adherence to the medication

The adverse events of each drug are shown in Supplementary Table 3 (in the online-only Data Supplement). The most common adverse events were livedo reticularis for amantadine and dizziness for the dopamine agonist. Some of the adverse events were severe enough to stop the medication: 2 patients with livedo reticularis on amantadine, 3 patients with dizziness on the dopamine agonists, and 1 patient each with hypersomnia, edema, and impulse control disorder on the dopamine agonists.

## DISCUSSION

This study showed that amantadine as an initial treatment in patients with *de novo* PD tends to reduce the incidence of LID. In addition, the use of amantadine followed by dopamine agonist tends to lower the incidence of LID compared to dopamine agonist alone.

The antidyskinetic effect of amantadine is considered to be related to the antagonistic activity at the N-methyl-D-aspartate (NMDA) receptor. The glutamatergic signaling from the cortex to the striatum goes through adaptive changes after chronic treatment with levodopa, resulting in an aberrant functioning of the NMDA receptors at the striatal medium spiny neuron dendritic spines.[14] The abnormal glutamatergic transmission in motor areas following levodopa administration in dyskinetic patients was also shown in one *in vivo* study.[15] In addition, trafficking and localization of NMDA receptor regulatory subunits are altered at the postsynaptic membrane in experimental models of LID.[16] Amantadine binds to the NMDA receptors and shows an inhibitory action, mainly through stabilization of closed states of the channel.[17]

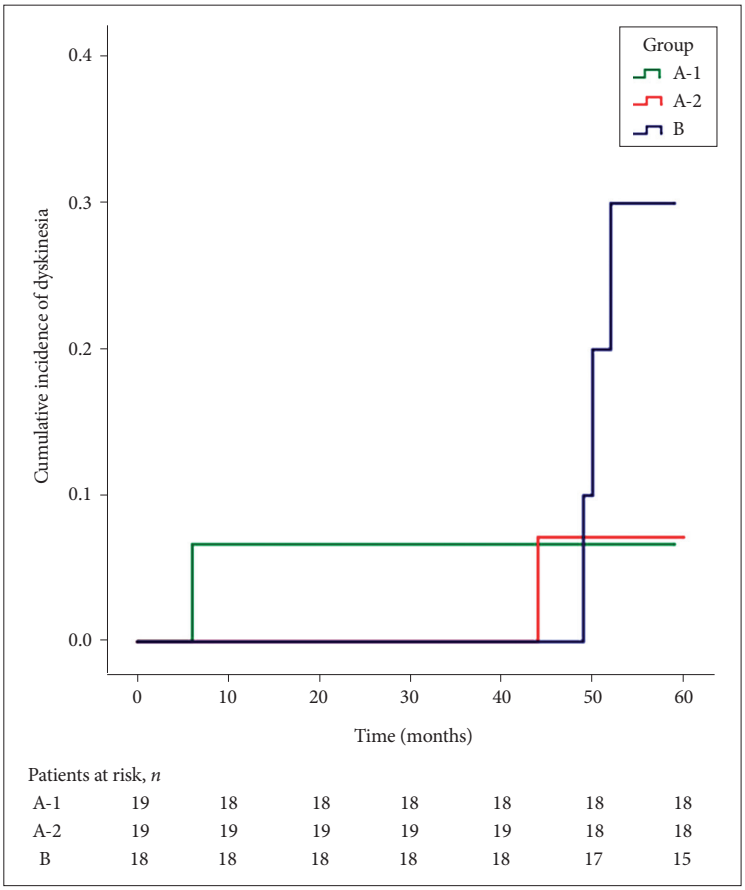


**Figure 3.** Reverse Kaplan-Meier curve for the development of dyskinesia. Per-protocol analysis was started with a total of 56 patients. Cumulative survival rates of dyskinesia were 0.933, 0.929, and 0.700 in Group A-1, A-2, and B, respectively. The *p* value in the log-rank test was 0.453 between all 3 groups, 0.207 between Groups A-2 and B, and 0.494 between Groups A-1 and B.

Use of amantadine at an early stage of PD can avoid a direct effect on postsynaptic dopaminergic receptors so that pulsatile stimulation could be reduced when compared to using levodopa as an initial treatment. Development of LID is closely associated with both dopaminergic denervation and chronic pulsatile stimulation of dopamine receptors with levodopa.[14,18] The antiparkinsonian efficacy of amantadine was estimated as "likely efficacious" for symptomatic monotherapy and adjunct therapy by expert opinion, although its effect on postsynaptic dopamine receptors is not clear.[19] In addition, there were no serious adverse events. Livedo reticularis, the most common adverse event in the current study, is not life threatening and is reversible when stopped.[20] Amantadine can be safely used as an initial treatment for PD.

In the current study, only 5 of 56 patients (8.93%)

developed dyskinesia during a median follow-up period of 30.0 months, which is much lower compared to the previous study.[1] Because all the patients in the current study were educated about dyskinesia at the study enrollment, they were more aware of the risk of LID and tended to avoid increasing medication. They preferred to stay with parkinsonism in a tolerable range than taking more medication, which may explain the low incidence of dyskinesia in this study. In addition, there may have been undetected dyskinesia during the interviews and neurologic examinations because LID is a fluctuating symptom.[8] When compared with the patients without dyskinesia, the dyskinetic patients were taking more levodopa at the last follow-up, which is consistent with previous studies.[4]

In previous studies, the antidyskinetic effect of amantadine was examined by targeting patients who were already dyskinetic and evaluated for a short duration or in a wash-out manner. The antidyskinetic effect of amantadine was assessed for the first time during an acute intravenous levodopa infusion in a small placebo-controlled study.[12] Amantadine reduced peak-dose dyskinesia depending on its plasma level, and the effect was sustained for 1 year in the same patients.[12,13] In another placebo-controlled randomized trial with advanced PD patients, there was a reduction by 45% in the total dyskinesia scores after 15 days of amantadine treatment and rebound dyskinesia in 11 patients after withdrawal of amantadine.[21] Wolf et al.[22] reported that the withdrawal of amantadine in patients who had been taking amantadine more than 1 year worsened their dyskinesia when observed after 3 weeks. In a more recent randomized placebo-controlled study, wash-out of amantadine significantly worsened the dyskinesia without a significant effect on motor parkinsonism during the 3-month observation.[9] ADS-5102, an extended-release amantadine, also showed an antidyskinetic effect in patients with LID.[11] It is noteworthy that our findings targeted drug-naïve patients with PD, with a prospective design as well as a longer observation period.

The current study included a relatively small number of patients, and the age of onset of the participants was younger compared to the epidemiological studies, such that our results may not represent all patients with PD.[23,24] Discontinuation of amantadine for a week every year was planned but was not done due to a lack of resources.

To summarize, amantadine as an initial treatment may prevent the development of LID in the later course of PD. Amantadine can be considered the initial treatment in patients with *de novo* PD, even before starting dopamine agonists.

## Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.18005.

## Conflicts of Interest

B Jeon received a research grant from Kunil Pharmaceuticals, Peptron, Novartis Korea, Ipsen Korea, Samil Pharmaceuticals, Abbvie Korea, and Lundbeck Korea. He is a medical advisor to Bukwang Pharmaceuticals.

## Acknowledgments

The authors would like to thank Joongyub Lee (Biomedical Research Institution, Seoul National University Hospital), who provided the team with expert opinion on the statistical methods used in the project. This study was supported in part by the Seoul National University Hospital Grant (0620120560). We would also like to acknowledge the generous support of the Sinyang Cultural Foundation and Mr. Byung-Suk Park.

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