Clinical Outcomes in Patients with Parkinson’s Disease Treated with a Monoamine Oxidase Type-B inhibitor: A Cross-Sectional, Cohort Study

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STUDY OBJECTIVE To evaluate the long-term risk of developing cognitive symptoms (e.g., dementia, hallucinations), dyskinesia, falls, and freezing of gait (FoG) in patients with Parkinson’s disease (PD) who received monoamine oxidase type B inhibitors (MAOB-Is) compared with patients who had never received MAOB-Is.

DESIGN Retrospective, cross-sectional, cohort study.

SETTING Academic movement disorders clinic.

PATIENTS One hundred eighty-one patients with idiopathic PD who were receiving MAOB-I therapy on a long-term basis for a minimum of 1 year (MAOB-I current-user cohort) and 121 patients with idiopathic PD who had never received MAOB-I therapy (MAOB-I never-user cohort [control group]) between January 1, 1996, and November 30, 2011.

MEASUREMENTS AND MAIN RESULTS The five study outcome variables were dementia, dyskinesia, falls, FoG, and hallucinations. Baseline and outcome data were collected from medical records. Patients in the MAOB-I current-user group were included only if absence of the specified outcomes was documented at baseline. Adjusted multiple logistic regression analyses were performed to calculate the odds ratios (ORs) for MAOB-I use versus never use on clinical outcomes. MAOB-I treatment was associated with a 44.7% reduced risk of dyskinesia (adjusted OR 0.553, 95% confidence interval 0.314–0.976, p=0.041), with the greatest risk reduction observed after 2 years of treatment. No significant association was noted with MAOB-I use and development of dementia, falls, FoG, or hallucinations.

CONCLUSION Long-term use of MAOB-I therapy was associated with reduced risk of dyskinesia in patients with PD.

KEY WORDS dyskinesia, monoamine oxidase inhibitor, Parkinson’s disease, rasagline, selegiline.

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Idiopathic Parkinson’s disease (PD) is an α-synucleinopathy characterized by intracellular and extracellular accumulation of abnormal filament proteins along with degeneration of melanin-containing, dopaminergic neurons in the substantia nigra.1 Clinical worsening of
motor and nonmotor symptoms is correlated with progressive neuropathologic changes consisting of α-synuclein-positive Lewy bodies and Lewy neuritis, and widespread neuronal loss. The presence of cognitive symptoms (e.g., dementia, hallucinations), falls, freezing of gait (FoG), and dyskinesia are milestones in disease progression and are associated with increased disability and poor effect on quality of life. These symptoms present a therapeutic challenge because dopaminergic therapy provides only limited benefit and may worsen these symptoms.2

The principal efficacy rationale for monoamine oxidase type B (MAO-B) inhibition in PD is enhancement of striatal dopamine activity, which is anticipated to result in symptomatic motor benefits.3 However, a secondary rationale is based on evidence that selective MAO-B inhibitors (MAOB-Is) exhibit pharmacologic properties that may translate into slowing of disease progression.4 Therapies that can delay or reduce the risk of developing poor prognostic milestones such as dementia, dyskinesia, falls, FoG, and hallucinations are an unmet need. The MAOB-Is provide symptomatic motor benefits; however, there are limited data on the effect of MAOB-Is on development of cognitive symptoms (e.g., dementia, hallucinations), falls, FoG, and dyskinesia in patients with PD. With regard to dementia, long-term data suggest no significant difference in the development of dementia between patients treated with the MAOB-I selegiline or a dopamine agonist.5 Long-term data on the effect of rasagiline, another MAOB-I, on cognition are lacking. With regard to dyskinesias, the evidence base indicates that selegiline is non efficacious for the prevention or delay of dyskinesia, and evidence is insufficient for rasagiline in the prevention or delay of motor complications.6 To our knowledge, there are no empiric data assessing the effect of MAOB-Is on risk of falls. With regard to gait deterioration, post-hoc analysis of data from a long-term study suggest that rasagiline is associated with less deterioration of gait compared with placebo,7 and long-term data suggest that selegiline is associated with greater dyskinesia but less FoG.8 With regard to hallucinations, several lines of evidence demonstrate that selegiline is associated with an increased risk of hallucinations;9–11 however, the risk of hallucinations with long-term rasagiline treatment is unknown.

The objective of this study was to evaluate the long-term risk of developing cognitive symptoms (e.g., dementia, hallucinations), dyskinesia, falls, and FoG in patients with PD who received MAOB-Is compared with those who had never received MAOB-Is. The results can be used to inform the design of quasi-experimental (e.g., prospective cohort) and experimental (e.g., randomized, controlled) clinical studies.

Methods

Patient Cohorts

This was a retrospective, cross-sectional, cohort study conducted at the Loma Linda University Movement Disorders Clinic (Loma Linda, CA), an academic movement disorders clinic. We identified patients who had idiopathic PD between January 1, 1996, and November 30, 2011, by performing a search of the medical records database using International Classification of Diseases, Ninth Revision, code 332 (parkinsonism). Medical records were then manually screened by independent research personnel, and patients with the following were excluded: atypical parkinsonism, secondary parkinsonism, or vascular parkinsonism. Medical records were then further reviewed, and patients were categorized into two cohorts: patients currently receiving MAOB-I therapy on a long-term basis for a minimum of 1 year (MAOB-I current-user cohort) and those who had never received MAOB-I therapy (MAOB-I never-user cohort [control group]). Patients in the MAOB-I current user cohort consisted of those currently treated with an MAOB-I; patients were excluded if the duration of MAOB-I use was less than a year, they were previously treated with an MAOB-I for any duration but discontinued the drug, or any of the study outcomes were present prior to MAOB-I treatment. Patients not currently receiving MAOB-I therapy were included in the never-user cohort but were excluded if they were not currently taking medications for PD and had a history of prior treatment exposure to MAOB-Is. Any patients with exposure to selegiline transdermal patch were excluded.

Outcome Variables and Data Acquisition and Analyses

A standardized template was used by research personnel to extract baseline demographics (age, sex, time since PD diagnosis), details of PD treatment interventions (antiparkinsonian medications and doses, surgeries), and details of
study outcome variables from the electronic medical record. Prior to data extraction, a study investigator (JJC) performed an independent clinical audit of the cohort medical records to verify inclusion and exclusion criteria adherence. The five study outcome variables were dementia, dyskinesia, fall, FoG, and hallucinations. Patients with medical records that had incomplete or missing demographic and treatment information were excluded. Documentation of the presence or occurrence of dementia, dyskinesia, falls, FoG, and hallucinations in patients with PD is a standard of practice performed by the movement disorders neurologists at the Loma Linda University Movement Disorders Clinic. Antiparkinsonian medication doses were converted to levodopa equivalent doses (LEDs; Table 1).\textsuperscript{12}

| Treatment                          | Dose Conversion Factor |
|------------------------------------|------------------------|
| Levodopa/carbidopa                 | ×1                     |
| Levodopa/carbidopa CR              | ×0.75                  |
| Entacapone                         | ×0.33                  |
| Tolcapone                          | ×0.5                   |
| Pramipexole (as salt)              | ×100                   |
| Ropinirole                         | ×20                    |
| Rotigotine                         | ×30                    |
| Selegiline, oral                   | ×10                    |
| Selegiline, ODT                    | ×80                    |
| Rasagiline                         | ×100                   |
| Amantadine                         | ×1                     |
| Apomorphine                        | ×10                    |
| Deep brain stimulation             | LED × 1.3              |

CR = controlled release; ODT = orally disintegrating tablet; LED = levodopa equivalent dose.

After data extraction and prior to data analyses, a second group of research personnel independently performed a medical record audit to verify accuracy of data extraction, and discrepancies were reconciled in consultation with two study investigators (KD and JJC). Statistical analysis was performed by using IBM SPSS Statistics, version 22 (1989, 2013; IBM Corp., Armonk, NY). Descriptive statistics are expressed as mean ± standard deviation for quantitative variables and number with percentage for qualitative variables. Continuous data were analyzed by the Student t test. The χ² test or Fisher exact test, when numbers were small, were used for comparison of categorical data. Pearson correlation coefficients were calculated to determine the correlation between continuous variables. Univariate logistic regression analyses were applied to calculate the crude odds ratios (ORs) of MAOB-I used versus never used on each outcome variable and to identify covariates. For each outcome identified with a statistically significant OR result, multiple logistic regression analysis was applied to calculate an adjusted OR. A two-tailed p value less than 0.05 was considered to be statistically significant. The goodness-of-fit of the final model was evaluated by using Hosmer–Lemeshow statistics. The investigations are part of normal clinical practice at the site, and the study was approved by the Loma Linda University Institutional Review Board.

Results

Demographic and Clinical Characteristics

Of 423 patients with PD screened, complete data were available for 302 patients: 181 patients in the MAOB-I user cohort and 121 in the never-user cohort. In the MAOB-I user cohort, approximately 94% (170 patients) were taking rasagiline, with a mean daily dose of 0.96 mg (range 0.25–1 mg), and 6% (11 patients) were taking selegiline (including the orally disintegrating formulation). Between the two cohorts, baseline demographic and clinical characteristics were similar except for a higher mean LED as well as a greater proportion of patients receiving

| Characteristic                  | MAOB-I Current-User Cohort (n=181) | MAOB-I Never-User Cohort (n=121) |
|--------------------------------|-------------------------------------|----------------------------------|
| Age (yrs)                      | 70.1 ± 10.4                         | 72.5 ± 10.6                      |
| Male sex                       | 102 (56.4)                          | 66 (54.5)                        |
| Duration of Parkinson's disease (yrs) | 6.9 ± 4.9                           | 8.2 ± 6.3                        |
| LED (mg)\textsuperscript{a}    | 644.6 ± 448.7                       | 790.6 ± 683.5                   |
| Levodopa/carbidopa use\textsuperscript{b} | 134 (74.0)                          | 115 (95.0)                      |
| Amantadine use                 | 36 (19.9)                           | 25 (20.7)                       |
| Dopamine agonist use           | 63 (34.8)                           | 35 (28.9)                       |
| Deep brain stimulation use\textsuperscript{b} | 21 (11.6)                           | 28 (23.1)                       |
| Duration of MAOB-I use (yrs)   | 2.5 ± 1.3                           | –                                |

MAOB-I = monoamine oxidase type B inhibitor; LED = levodopa equivalent dose.

Data are mean ± SD values or no. (%) of patients.

\textsuperscript{a}p<0.05 for the comparison between cohorts.

\textsuperscript{b}p≤0.01 for the comparison between cohorts.
levodopa/carbidopa and deep brain stimulation (DBS) in the never-user cohort (Table 2).

Prevalence of Outcome Variables

Of the 302 patients, 78 (25.8%) developed dementia, 85 (28.1%) experienced hallucinations, 91 (30.1%) had FoG, 93 (30.8%) had dyskinesias, and 152 (50.3%) had falls. The prevalence of these outcomes is consistent for this population of patients with a mean PD disease duration of 7–8 years.

MAOB-I Use and Outcome Variables

Univariate logistic regression analysis revealed that MAOB-I use was associated with a statistically significant reduced crude odds ratio of 0.504 (95% confidence interval [CI] 0.306–0.828, p=0.007) for dyskinesia, compared with never users (Table 3). Other outcome variables (dementia, falls, FoG, hallucinations) did not have statistically significant associations. Using dyskinesia as the dependent variable, the covariates associated with dyskinesias were MAOB-I use, amantadine use, DBS use, dopamine agonist use, levodopa/carbidopa use, PD duration, and LED (Table 4). These covariates were tested in a stepwise, multivariate logistic regression model to produce a final adjusted model (adjusted for age, PD duration, LED, sex, amantadine use, and DBS use, multivariate logistic regression analysis revealed that patients receiving an MAOB-I for at least 2 years but less than 3 years were 87.3% less likely to develop dyskinesia compared to MAOB-I never users (OR 0.127, 95% CI 0.037–0.441, p=0.001).

Discussion

In this cross-sectional study of predominantly patients with moderate-to-advanced PD, the cohort of MAOB-I long-term users had a 44.7% reduced likelihood of developing dyskinesias compared to MAOB-I never users, with the greatest reduction appearing after 2 years of treatment. Associations for MAOB-I use and occurrence of dementia, falls, FoG, and hallucination were not significant. Consistent with the literature, we found that dyskinesia risk was inversely correlated with dopamine agonist use (i.e., dopamine agonist use was associated with reduced risk of dyskinesia).13 Our finding of a positive correlation with longer disease duration, amantadine use, DBS use, levodopa/carbidopa use, and higher LED is also consistent with the literature and current treatments for dyskinesia. Longer disease duration and high dose levodopa use are known risk factors for development of dyskinesia, and amantadine and DBS are common therapies for management of dyskinesia.13,14 In the current study, we did not determine the onset of dyskinesia in relation to amantadine initiation or DBS; however, based on the study center’s local standard of practice, these therapies are typically initiated in response to onset of dyskinesia. Future studies should delineate timing of these therapies in relation to dyskinesia onset.

| Table 3. Outcome Variables Associated with MAOB-I Therapy |
|----------------------------------------------------------|
| **Outcome** | **Slope** | **Crude Odds Ratio (95% CI)** | **p Value** |
|----------------------------------------------------------|
| Dementia | –0.413 | 0.662 (0.393–1.114) | 0.120 |
| Dyskinesias | –0.686 | 0.504 (0.306–0.828) | 0.007 |
| Falls | –0.300 | 0.741 (0.466–1.177) | 0.204 |
| FoG | –0.300 | 0.741 (0.450–1.220) | 0.239 |
| Hallucinations | –0.271 | 0.763 (0.459–1.268) | 0.296 |

MAOB-I = monoamine oxidase type B inhibitor; CI = confidence interval; FoG = freezing of gait.

| Table 4. Covariates Associated with Dyskinesia Outcome |
|-------------------------------------------------------|
| **Covariate** | **Slope** | **Crude Odds Ratio (95% CI)** | **p Value** |
|-------------------------------------------------------|
| MAOB-I use | –0.686 | 0.504 (0.306–0.828) | 0.007 |
| Amantadine use | 0.710 | 2.034 (1.132–3.656) | 0.018 |
| Deep brain stimulation use | 0.970 | 2.638 (1.405–4.953) | 0.003 |
| Dopamine agonist use | –0.695 | 0.499 (0.284–0.876) | 0.013 |
| Levodopa/carbidopa use | 1.234 | 3.434 (1.485–7.940) | 0.004 |
| Parkinson’s disease duration (per month) | 0.013 | 1.013 (1.009–1.018) | <0.001 |
| LED | 0.001 | 1.001 (1.001–1.002) | 0.001 |

MAOB-I = monoamine oxidase type B inhibitor; CI = confidence interval; LED = levodopa equivalent dose.
Baseline demographic and clinical characteristics were similar (including duration of disease) between the two cohorts except for a higher mean LED and a greater percentage of patients receiving levodopa/carbidopa and DBS in the never-user cohort. This suggests that the never-user cohort may have had more advanced disease at baseline; however, the statistical methods used serve to minimize the potential biasing influence of this variable on the outcomes. Limitations of this study include data imprecision due to the retrospective methodology and unidentified potential confounders.

The inverse correlation between MAOB-I use and dyskinesia risk may be due to a levodopa-sparing effect or a pharmacologic “dyskinesia sparing” property of the drug that directly alters dyskinesia-generating pathways. Medium spiny neurons (MSNs) are the major type of neurons found in the striatum. In PD, alterations that occur in striatal cells of the dopamine-dener-vated striatum are dystrophic changes in the dendrites of MSNs, with a loss of dendritic length and dendritic spine number. Morphologic changes in MSNs are associated with development of dyskinesias. The MAOB-I, rasagiline, has been shown to possess dendritic remodeling properties by increasing the length and the number of dendritic branch points. It is plausible that rasagiline provides dendritic remodeling and protection against development of dyskinesias; however, this activity may exhibit a ceiling effect that becomes overwhelmed with advancing PD pathology. This cellular mechanism may explain the disappearance of a MAOB-I “dyskinesia-sparing” effect after 3 years of treatment in our study. Consistent with this explanation, our statistical results show that PD duration is a significant predictor of the occurrence of dyskinesia (Table 4), with each additional month of PD duration associated with an increase in the risk of dyskinesia. In our study, the magnitude of this effect seems to be smaller in the first 2 years of the start of MAOB-I treatment (perhaps due to a putative remodeling effect of rasagiline). As the disease progresses, however, patients become more “dyskinesia prone” due to cumulative effects of the underlying PD pathology (at the cellular and molecular levels) and disease progression (which overwhelms any putative protective effect due to MAOB-Is).

Recently, results of the PD-MED study were published\(^2\). This was a large, prospective, quasi-experimental study of 1620 patients with early PD who were randomly assigned in an open-label manner to initial treatment with either a dopamine agonist, an MAOB-I, or levodopa therapy. After a median follow-up of 3 years, patients in the levodopa group were more likely to develop dyskinesias than those in the MAOB-I and dopamine agonist groups (hazard ratio 1.52, 95% CI 1.16–2.00, \(p=0.003\)). Patients in the MAOB-I initial therapy group were allowed to add or switch to a different drug for additional symptom control. The study results demonstrated that initial therapy with an MAOB-I was associated with a reduced risk of dyskinesia compared to patients initiated on levodopa (a subset who had previous exposure or who were eventually exposed to MAOB-I therapy) and is consistent with the findings from our retrospective, quasi-experimental study. A notable difference is that our study included a control group of MAOB-I never users (patients who were treated with dopamine agonists and/or levodopa but not allowed to have any exposure to MAOB-Is).

**Conclusion**

In this study, long-term use of MAOB-I therapy was associated with reduced risk of dyskinesia in patients with PD. To better assess and quantify the effect of MAOB-Is on dyskinesia development, prospective studies should incorporate a comparative treatment group that is free of any MAOB-I exposure. This can be accomplished with quasi-experimental (e.g., prospective cohort) or experimental studies designed with a minimum of 2 years of follow-up.

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Table 5. Adjusted Odds Ratios for Development of Dyskinesia by Duration of MAOB-I Therapy

| Duration of MAOB-I Therapy | Adjusted Odds Ratio (95% CI) | \( p \) Value |
|---------------------------|-----------------------------|--------------|
| ≥ 1 yr but < 2 yrs        | 0.668 (0.298–1.498)         | 0.328        |
| ≥ 2 yrs but < 3 yrs       | 0.127 (0.037–0.441)         | 0.001        |
| ≥ 3 yrs but < 4 yrs       | 0.315 (0.199–1.334)         | 0.172        |
| ≥ 4 yrs                   | 0.807 (0.341–1.909)         | 0.625        |

MAOB-I = monoamine oxidase type B inhibitor; CI = confidence interval.
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