Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

Levodopa treatment patterns in Parkinson's disease: A retrospective chart review

Prakash Navaratnam [a], Steve Arcona [b,*], Howard S. Friedman [a], Matthew Leoni [b], Rahul Sasane [b]

[a] DataMed Solutions, LLC, New York, NY, United States
[b] Cerevel Therapeutics, Cambridge, MA, United States

A R T I C L E   I N F O

A B S T R A C T

Background: Medication regimens for Parkinson's disease (PD) may change as the disease progresses, symptoms fluctuate, or medication-related adverse events occur. This study evaluated treatment trends by observation year for patients initially receiving monotherapy with levodopa and a peripheral dopa decarboxylase inhibitor (PDDI).

Methods: In this retrospective chart review, therapy changes were evaluated for patients across the US diagnosed with PD on or before 6/30/2014 who initially received levodopa-PDDI monotherapy. Index date was the first clinic visit. Post-index was any time between the first 31 days after index and study end (6/30/2019). Index Hoehn-Yahr (H-Y) score and medication changes were also analyzed by index low (<400 mg/day) or high (≥400 mg/day) levodopa doses in the levodopa-PDDI combinations.

Results: In the levodopa-PDDI cohort (n = 95), there were 0.39 dose escalations, 0.16 dose reductions, 0.12 discontinuations, 0.19 therapy switches, and 0.24 add-ons per patient per year during the study. Most dose escalations or add-ons occurred within the first 6 months post-index. Of those who ever stopped levodopa-PDDI (n = 34), 31 (91%) restarted within the study period. Most (83%) patients who restarted levodopa-PDDI did so in the same year as stopping treatment. Index low dose users were associated with lower H-Y scores, were more inclined to escalate their dose, and were less inclined to reduce their dose in the first 2 years of treatment than index high dose users.

Conclusions: Prescribers and patients tend to experiment with levodopa-PDDI treatment. Although many patients appeared to stop levodopa-PDDI after an initial course of treatment, most subsequently restarted treatment.

1. Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative movement disorder that results in a loss of dopaminergic neurons in the brain [1]. Dopamine levels become low, triggering motor symptoms including bradykinesia, limb rigidity, resting limb tremor, dystonia, and postural instability [2]. There are no approved treatments to prevent the progression of PD, and medications to control the various symptoms are tailored for each patient based on intra-patient factors (i.e., age, predominant symptoms, disease severity, previous treatment, etc.) and clinician experience and judgment [3]. An individual's medication regimen may change over time as the disease progresses, symptoms fluctuate, or medication-related adverse events occur.

Current treatment for the motor symptoms of PD aims to increase the low levels of dopamine in the brain [4]. Levodopa is a potent dopamine precursor that effectively improves the motor symptoms of PD [5]. However, adverse effects such as dyskinesia, nausea, and hallucinations have historically limited its use among older patients with substantial physical impairment [3]. The National Institute for Health and Care Excellence (NICE) recommends offering levodopa to patients in the early stages of PD whose motor symptoms impact their quality of life, regardless of age [6]. Patients may experience a wearing-off effect and fluctuating efficacy with levodopa, necessitating additional medications [2,4] or need to discontinue because of adverse events. Anecdotally, levodopa is being used earlier in treatment than in previous years, but possibly at a low dose when used in the beginning stages of the disease. However, the treatment patterns of levodopa in clinical, real-world settings have not been well characterized.

We previously conducted a retrospective medical chart review to longitudinally characterize the natural history and patterns of treatment associated with PD over time [7]. In the 203 patient charts analyzed, disease progression during the 5-year study period was observed. A high rate of therapy changes including dose escalations, add-on treatments, switches, and discontinuations were observed for common treatments used to treat the motor symptoms of PD, including levodopa with a peripheral dopa decarboxylase inhibitor (PDDI). Given the heterogeneity in treatment approaches, disease progression, PD symptomology, and adverse events, subtle shifts in treatment and outcomes may have been masked over the long time horizon. In this secondary, hypothesis-generating analysis, the objective was to evaluate if treatment patterns and outcomes for patients initially receiving levodopa-PDDI monotherapy varied by year of observation, stratified based on initial maintenance dose.

2. Methods

2.1. Study design

Details of this study and the primary results have been previously reported [7]. Briefly, medical charts of patients diagnosed with PD on or before June 30th, 2014 who were treated in 18 clinics across the US were retrospectively reviewed. The study protocol was reviewed by a central Institutional Review Board and a waiver of patient informed consent was obtained. Patient chart data collected for the analysis were completely de-identified of any protected patient health information.

The index date was the first clinic visit and the post-index period was any time between the first 31 days after the index date and the end of the study (June 30th, 2019). The diagnosis of PD was based on International Classification of Disease, Ninth or Tenth Revision, Clinical Modification codes. Patients included in the analysis were required to have initiated an anti-PD medication within 30 days after diagnosis, had at least 2 PD clinic visits between the index date and the end of the study, and had an order for an anti-PD medication within 6-months of the end of the study. Patients with dementia at index or who had a deep brain stimulation surgical procedure during the study period were excluded.

Data on demographics, clinic site characteristics, patient PD characteristics and comorbidities, and anti-PD medication use (i.e., levodopa-PDDI, dopamine agonist [DA], and monoamine oxidase B inhibitors [MAOBI]) were collected from the patient charts. Patients' disease stage (Stages 1–5) were based on Hoehn-Yahr (H-Y) scores [8]. In this secondary analysis, the unit of observation was 1 year, and yearly trends were tracked for each patient for a total of 5 years.

2.2. Outcomes

The primary analysis evaluated the frequency of PD medication changes longitudinally over the 5-year post-index period. The main outcomes of this secondary analysis were levodopa-PDDI medication changes over time by year of post-index event observation. Full definitions of the medication changes have been previously described [7], but in brief, included dose escalations or dose reductions (an increase or decrease of at least 25% in the maintenance daily dose from the index date), switching (discontinuation of index drug and reporting of initiation with another anti-PD medication within 30 days), and add-on (addition of one or more anti-PD medications to the index anti-PD medication). For this secondary analysis, treatment interruptions (stop and restart) of the index levodopa-PDDI were also assessed. Discontinuation was defined as a stop in treatment with no restart for the remainder of that observation year. Patients may have had multiple therapy changes and each change was counted separately. The number of therapy change events was analyzed at 6-month intervals through the 5-year treatment period and by the year of event observation (e.g., year 1, year 2).

Index H-Y score and medication changes over time were further analyzed by index low (<400 mg/day) or high (≥400 mg/day) levodopa doses in the levodopa-PDDI combinations. A list of previously defined [7] potential reasons for levodopa-PDDI treatment changes (e.g., discontinuations, switching, add-ons, etc) were tracked in a binary fashion (yes/no) during the post-index period. Baseline variables potentially associated with ever discontinuing levodopa-PDDI were also assessed.

2.3. Statistical analysis

As the study was primarily hypothesis-generating and the number of cases was low, analyses were primarily limited to descriptive statistics. The number of therapy changes was normalized to per patient per year because of the variable observation time windows for each patient. In an exploratory analysis, the potential association between baseline variables and ever discontinuing levodopa-PDDI was assessed by a logistic regression model controlling for high index levodopa-PDDI dose, H-Y severity scoring, age of PD onset, duration of PD, male sex, and the presence of depression. The analyses were conducted using SAS version 9.4 statistical software (Cary, NC).

3. Results

A total of 203 patients were included in the primary analysis population. Demographics and baseline characteristics for the levodopa-PDDI monotherapy study population and the subpopulations with low and high index levodopa doses are shown in Supplemental Table S1.

Of the primary analysis population, 95 patients were on levodopa-PDDI monotherapy at index. Among these patients, there were 0.39 dose escalations, 0.16 dose reductions, 0.24 add-ons, 0.12 discontinuations, and 0.19 therapy switches per patient per year during the study period. Most events of levodopa-PDDI dose escalations or add-on treatments occurred within the first 6 months post-index (Fig. 1). Peaks in discontinuation and switching events occurred at 55–60 months post-index (Fig. 1).

Cumulative treatment interruption patterns show that 31 (91%) of the 34 patients who ever stopped levodopa-PDDI restarted levodopa-PDDI within the study period (Table 1). Most (83%) of the patients who restarted levodopa-PDDI did so in the same year as stopping treatment (Table 2). Reasons for levodopa-PDDI treatment interruptions were underreported and no clear trends were evident.

Levodopa-PDDI treatment patterns were further analyzed by index high or low levodopa maintenance dose. Lower H-Y scores were associated with the index low dose users in the first 2 years of treatment. Index low dose users were more inclined to escalate their dose and less inclined to reduce their dose in the first 2 years of treatment than those starting at a high dose (Fig. 2). Other treatment changes by dose were variable. There was a general trend towards increasing therapy changes from index to year 5 of treatment in index low dose users, whereas all therapy changes except discontinuations tended to decrease from index by year 5 of treatment in index high dose users (Fig. 2). Discontinuations in the index high dose group were lower at year 1 and year 5 compared with the index low dose group. Cumulative treatment interruption patterns were comparable between index high and low dose groups, with most patients in both groups ultimately restarting levodopa-PDDI (Table 1). DA seemed more likely to be added-on in index high dose users than index low dose users (Table 1).

A multiple variable logistic regression model of "ever discontinuing levodopa-PDDI" did not identify any statistically significant baseline variables.

4. Discussion

Among patients prescribed levodopa-PDDI at PD diagnosis, treatment patterns are variable, disrupted, and not well-sustained over time. The data indicate that prescribers and patients experiment with levodopa-PDDI treatment by changing doses, adding-on treatments, and
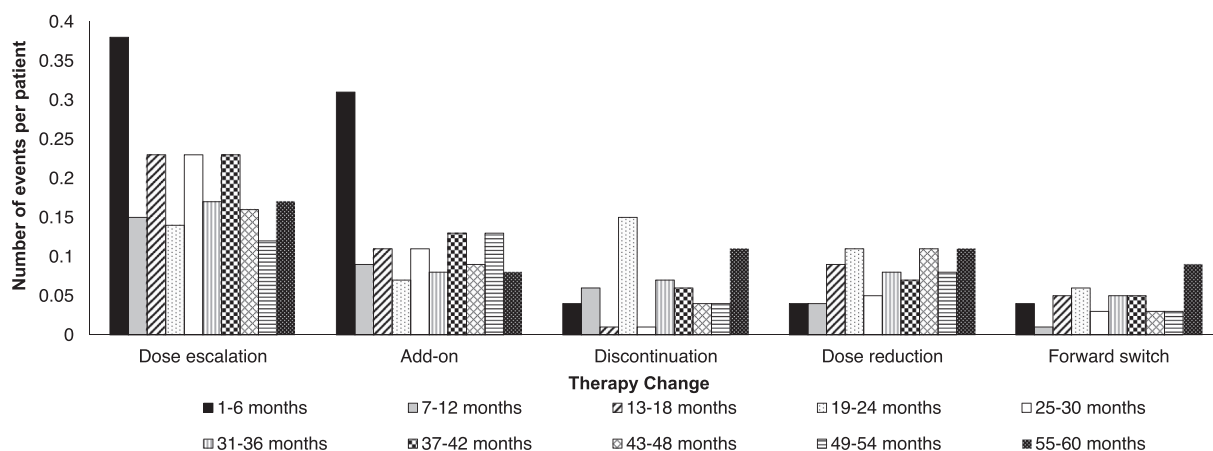
Fig. 1. Time to therapy change among patients receiving levodopa-PDDI at index and who had a therapy change.

Table 1
Cumulative treatment interruption patterns with levodopa-PDDI.

Interruption Pattern	All Index Doses			Low Index Dose (<400 mg/day)			High Index Dose (≥400 mg/day)		
	N	Total Levodopa-PDDI Population, %	Stopped Levodopa-PDDI Population, %	N	Total Levodopa-PDDI Population, %	Stopped Levodopa-PDDI Population, %	N	Total Levodopa-PDDI Population, %	Stopped Levodopa-PDDI Population, %
Levodopa-PDDI monotherapy at index	95			32			63		
Ever stopped levodopa-PDDI	34	36%	100%	11	34%	100%	23	37%	100%
Ever stopped levodopa-PDDI and restarted levodopa-PDDI	31	33%	91%	9	28%	82%	22	35%	96%
Ever stopped levodopa-PDDI and added DA	17	18%	50%	3	9%	27%	14	22%	61%
Ever stopped levodopa-PDDI and added MAOBI	11	12%	32%	4	13%	36%	7	11%	30%

DA, dopamine agonist; MAOBI, monoamine oxidase B inhibitor; PDDI, peripheral dopa decarboxylase inhibitor.

Table 2
Restart and add-on treatment patterns by year of levodopa-PDDI stop.

Time of Restart or Add-on	Restart of Add-on Treatment Occurrences, n = 24*		
	Levodopa-PDDI Restart	DA Add-on	MAOBI Add-on
Same year as levodopa-PDDI stop, n (%)	20 (83%)	10 (42%)	3 (13%)
Year after levodopa-PDDI stop, n (%)	7 (29%)	3 (13%)	1 (4%)
2 years after levodopa-PDDI stop, n (%)	9 (38%)	5 (21%)	5 (21%)

DA, dopamine agonist; MAOBI, monoamine oxidase B inhibitor; PDDI, peripheral dopa decarboxylase inhibitor.
*Percentages total more than 100% because patients cycled between stopping and restarting levodopa-PDDI treatment.

switching to other PD medications. Most of the patients who stopped levodopa-PDDI ultimately restarted it after gaps in use. The reasons for restarting levodopa-PDDI after stopping were not clearly captured, but one likely explanation is that motor symptoms worsened to the point that restarting treatment was necessary. These data imply that caution will be needed to account for potential restarts in future analyses of apparent levodopa discontinuations.

Analyses were conducted to determine if levodopa-PDDI index high versus low dose had an impact on treatment patterns. Those starting on a low dose were associated with lower H-Y scores in the early years of treatment, which is as expected and is in agreement with a previous

analysis of PD medication patterns [9]. This result also corresponds with treatment algorithms that suggest levodopa treatment should be reserved for patients with substantial disability from motor symptoms [3]. Not surprisingly, patients starting on a low dose were also more inclined in the early years to have dose escalations and were less inclined to have dose reductions than those starting on a high dose. Discontinuations were actually lower at year 1 in patients who started on a high dose compared with patients who started on a low dose, which is counterintuitive if most discontinuations were because of adverse events (assuming a higher dose induces more adverse events). A retrospective cohort study of Medicare beneficiaries with advanced PD found that levodopa discontinuations, defined as a ≥90 day treatment gap during the 12-month study period, were dose dependent, with higher initial doses having more discontinuations [10]. Reasons for discontinuation could not be clearly elucidated because of lack of data and is an area for further research.

Few other real-world studies have evaluated therapy changes for initial levodopa monotherapy, and none were chart reviews. One prospective observational study of PD treatments found that in patients receiving levodopa monotherapy, 38.1% remained on their therapy over the 3-year study [11]. Discontinuations and restarts were not characterized. In a retrospective claims database of PD patients in the US, 30.4% of patients who initiated levodopa treatment had a switch or add-on; the median time to switch or add-on was 7.3 years [12]. In contrast, the current study found that add-on and dose escalations tended to occur within the first 6 months of levodopa-PDDI treatment. This is likely because neuropsychiatric medications need to be tailored to the
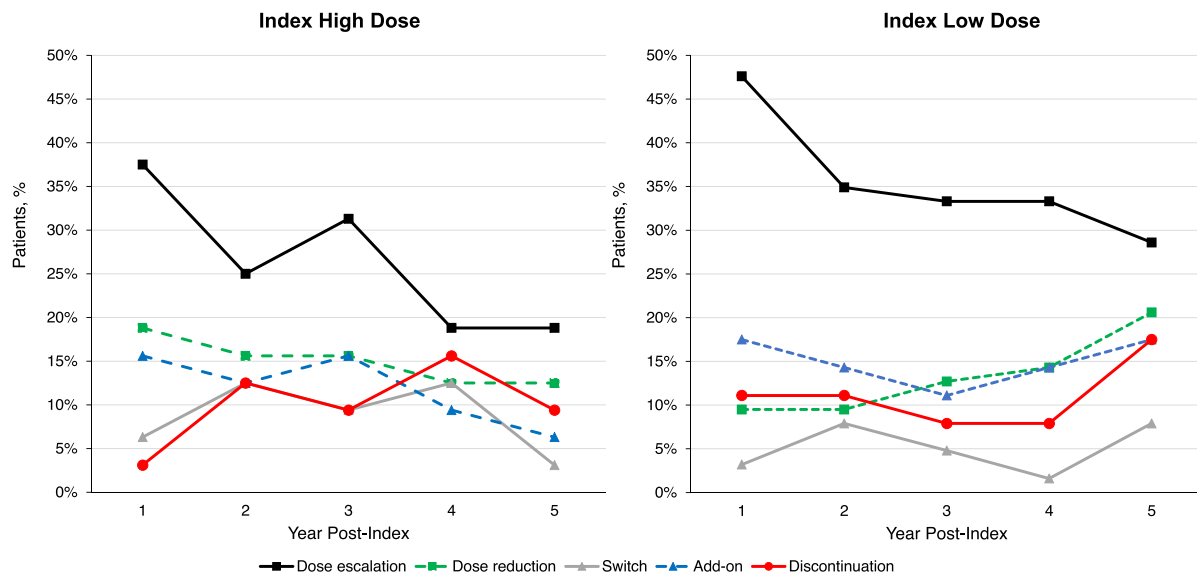
Index High Dose

Index Low Dose

Fig. 2. Levodopa-PDDI therapy changes over time by index high or low dose.

individual as symptoms appear, disappear, and fluctuate in intensity. Doses are often adjusted in the early stages of treatment as prescribers seek to find the optimal efficacious and tolerable dose for each individual.

No baseline variables were predictive of ever discontinuing levodopa-PDDI, but the study was not powered for this outcome. Furthermore, there were limitations of the study, including the small sample size and incomplete or inconsistent chart documentation for some the clinical characteristics, that hindered the regression modeling. Additional research, possibly from electronic medical records or charts linked to claims databases, are needed to better elucidate levodopa discontinuation patterns.

5. Conclusions

The treatment patterns of levodopa-PDDI for PD are variable. Although it appeared that many patients stopped levodopa-PDDI after an initial course of treatment, most subsequently restarted treatment.

Data availability

All data supporting the conclusions of the study are reported within the manuscript.

CRediT authorship contribution statement

Prakash Navaratnam: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. **Steve Arcona:** Conceptualization, Methodology, Funding acquisition, Visualization, Writing – review & editing. **Howard S. Friedman:** Methodology, Data curation, Formal analysis, Software, Visualization, Writing – review & editing. **Matthew Leoni:** Conceptualization, Methodology, Visualization, Writing – review & editing. **Rahul Sasane:** Conceptualization, Methodology, Visualization, Writing – review & editing.

Declaration of Competing Interest

P. Navaratnam and H. Friedman are employees of DataMed Solutions, LLC, which provides contracted services to Cerevel Therapeutics. S. Arcona, M. Leoni, and R. Sasane are employees of Cerevel Therapeutics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2022.100135.

References

[1] D. Weintraub, C.L. Comella, S. Horn, Parkinson's disease–Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment, Am. J. Manag. Care 14 (2008) S40–S48.
[2] S. Sveinbjornsdottir, The clinical symptoms of Parkinson's disease, J. Neurochem. 139 (Suppl 1) (2016) 318–324.
[3] B.S. Connolly, A.E. Lang, Pharmacological treatment of Parkinson disease: a review, JAMA 311 (16) (2014) 1670.
[4] P. Troncoso-Escudero, D. Sepulveda, R. Pérez-Arancibia, et al., On the right track to treat movement disorders: promising therapeutic approaches for Parkinson's and Huntington's Disease, Front. Aging Neurosci. 12 (2020), 571185.
[5] S.H. Fox, R. Katzenschlager, S.Y. Lim, et al., International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease, Mov. Disord. 33 (2018) 1248–1266.
[6] Parkinson's disease in adults.: National Institute for Health and Care Excellence (NICE); 2017 [cited 2021 September 30]. Available from: https://www.guidelinecentral.com/summaries/parkinsons-disease-in-adults/#section-442.
[7] P. Navaratnam, S. Arcona, H.S. Friedman, M. Leoni, S. Shaik, R. Sasane, Natural history and patterns of treatment change in Parkinson's Disease: a retrospective chart review, Clin. Parkinsonism Relat. Disord. 6 (2022), 100125.
[8] Parkinson's Disease Diagnosis-Rating Scales.: Health Union, LLC; 2017 [cited 2021 September 30]. Available from: https://parkinsonsdisease.net/diagnosis/rating-scales-staging/.
[9] S. Neo, S.Y.A. Wong, H.L. Ng, et al., Evolution of initial pharmacologic treatment of newly diagnosed Parkinson's disease patients over a decade in Singapore, Parkinsons Dis. 2020 (2020) 6293124.

[10] N. Dahodwala, J. Jahnke, A.R. Pettit, et al., Low sustainment of high-dose oral medication regimens for advanced Parkinson's disease in Medicare beneficiaries, J. Parkinsons Dis. 11 (2021) 675–684.

[11] T. Muller, E. Tolosa, L. Badea, et al., An observational study of rotigotine transdermal patch and other currently prescribed therapies in patients with Parkinson's disease, J. Neural Transm. (Vienna) 125 (2018) 953–963.

[12] R. Houghton, F. Boess, L. Verselis, et al., Treatment patterns in patients with incident Parkinson's disease in the United States, J. Parkinsons. Dis. 9 (2019) 749–759.