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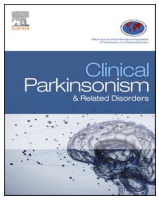

Dopamine agonist monotherapy utilization in patients with Parkinson's disease

Monica Frazer [a], Steve Arcona [b], Lisa Le [c,*], Rahul Sasane [b]

[a] QualityMetric, USA
[b] Cerevel Therapeutics, USA
[c] Optum HEOR, USA

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ABSTRACT

Objectives: To characterize patients with Parkinson's disease (PD) who initiated dopamine agonist (DA) monotherapy, describe medication utilization and provider types, and estimate medication adherence and discontinuation rates.

Methods: Retrospective study identified patients with PD in the Optum Research Database and included those with ≥1 claim for DA or levodopa between 09/01/2012 and 12/31/2018, ≥2 PD diagnoses, commercial or Medicare Advantage Part D (MAPD) insurance, ≥40 years old, and continuous medical and pharmacy coverage ≥12 months before and after index date. A subset of patients receiving DA monotherapy was selected for this analysis. Variables were analyzed descriptively. Adherence was measured with medication possession ratio (MPR) and proportion of days covered (PDC); defined as ≥0.80.

Results: Patients (N = 642) had mean (SD) age of 70.2 (9.9) years, 70.6 % had MAPD coverage, and 61.7 % were male. Neurologists prescribed 64.6 % of DA monotherapy, and 56.9 % of patients had ≥2 PD diagnoses before or on the index date. Index therapy was discontinued by 44.1 % of patients, and 55.9 % persisted for 12 months without change. Mean (SD) time to discontinuation was 102 (79) days. Mean (SD) MPR for patients (n = 562) with ≥2 fills was 0.84 (0.2); 70.3 % were MPR adherent. Mean (SD) PDC for all 642 patients was 0.66 (0.3); 50.5 % were PDC adherent.

Conclusion: Adherence and continuation of therapy were suboptimal, which could translate into poor patient outcomes. Future studies could provide insights on the impact of low adherence and persistence with DA monotherapy.

1. Introduction

Parkinson's disease (PD) is a long-term neurodegenerative disorder that is characterized by motor symptoms that worsen with time [1] and nonmotor symptoms with serious complications that impair patients' quality-of-life and overall daily functions, and have devastating effects on both patients and their caregivers [2]. The prevalence of PD has grown twofold during the past two decades, driven by population aging and increasing life expectancy [3], and prevalence increases with age [1]. The etiology of PD is largely unknown, however, genetic and environmental factors have been implicated [4]. With no available cure or disease modifying treatment, the main goal of PD treatment is to control patients' motor symptoms and manage function [5].

The number and types of treatment options for PD increased substantially in the past thirty years [6]. Levodopa, developed in the 1960s, and dopamine agonists (DAs), developed in the 1970s, have been mainstay initial therapies for mild to severe PD for decades [7]. These agents act as dopamine replacement or proxies in the treatment of PD [8]. The likely mechanism of action of levodopa entails entering dopaminergic neurons, where it is metabolized into dopamine, and replaces the endogenous neurotransmitter [9]. DAs act by mimicking the effects of dopamine without a conversion process [9]. They were introduced in practice with the goal of avoiding levodopa-related side effects supported by data from clinical studies demonstrating that DAs such as bromocriptine, pramipexole, and pergolide delayed dyskinesia and motor fluctuations compared with levodopa [10].

While treatment recommendations exist, there is no consensus on a treatment initiation or sequencing strategy for patients with PD. In

* Corresponding author at: Optum Life Sciences, 11000 Optum Circle, Eden Prairie, MN 55344, USA.
E-mail address: lisa.le@optum.com (L. Le).

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general, the selection and start of DA treatment align with patient preference and are aimed at optimal adherence in line with treatment recommendations [1]. A mixed pattern of initial treatment emerges from a few available studies.

Levodopa is typically prescribed to patients with PD when symptom control appears unattainable with other antiparkinsonian pharmaceuticals such as MAO-B inhibitors and DAs [8]. Treatment with levodopa, however, is associated with side effects including nausea, dizziness, anxiety, orthostatic hypotension, dyskinesia, and somnolence. Use of the drug may also cause confusion, hallucination, agitation, and psychosis, especially in older patients with PD [11,12].

DAs were initially developed as add-on therapies to levodopa. Because of the potential serious side effects of levodopa, however, DA monotherapy has been used as a means of delaying levodopa-related adverse events [13]. In 2021, American Academy of Neurology (AAN) guidelines reviewed the available evidence on new medications and reformulations of older agents, and provided guidance on treatment initiation with dopaminergic drugs for PD [1].

Amidst inadequate evidence about the safety and efficacy of DAs, recommendations indicate that treatment decisions should consider patient choice and emphasize compliance with treatment guidelines [1]. Appropriate considerations could include cost of therapy, frequency of dosing and administration mode [1]. Guidelines also recommend starting at the lowest possible dose and increasing gradually until the required treatment results or side effect is seen [1]. Among the side effects linked to DAs are decreased psychosocial functioning, hallucination, impaired interpersonal relationships, and diminished quality of life for patients and their caregivers. Physical symptoms include impulse control disorder, excessive daytime sleeping, sudden onset sleep, and nausea in patients with early PD [1]. Mitigation measures may include medication adjustments and, where appropriate, additional behavioral and pharmacological interventions [1].

Like other therapeutic areas, adherence and persistence to treatment are critical for the successful management of PD [14]. A few available real-world studies, however, have reported suboptimal adherence to treatment by patients with PD; adherence defined as a medication possession ratio (MPR) >0.80. Davis et al reported only 39 % of patients were adherent to treatment (mean MPR of 0.58) in a study that examined insurance claims across 30 US health plans. The most prevalent therapy was levodopa, which was received by 60 % of patients, followed by carbidopa, dopamine agonists, anticholinergics, catechol-O-methyltransferase (COMT) inhibitors, seligiline, and amantadine [15].

A slightly higher adherence rate, 54 %, was reported by Richy et al in an analysis that evaluated MPR using a large patient-centric claims database. The most commonly prescribed regimen was levodopa, which was received by 38.7 % of patients, and 30.8 % had MPR ≥0.80. Approximately-one-third (34.0 %) of the patients received levodopa and DA, and 39.7 % had MPR ≥0.80. Only 5.7 % received DA, and 5.0 % had MPR ≥0.80. Amantadine, DA and levodopa combination was received by 12.7 % of the patients, amantadine alone by 0.8 %, amantadine plus levodopa by 5.7 % and amantadine and DA by 1.2 % [16].

A study by Tarrants et al using a large longitudinal prescription database also reported that 54 % had compliance rates >0.80 [17]. The medications assessed were rasagiline, levodopa/carbidopa, levodopa/carbidopa/entacapone, the COMT inhibitors (entacapone and tolcapone), pramipexole, ropinirole, and selegiline. The weighted MPR for rasagiline was consistently higher for patients at >70 %, >80 %, and >90 % compliance rates, and levodopa/carbidopa was consistently performed below the average.

Only a handful of studies have analyzed patients with commercial or Medicare coverage who were diagnosed with PD and who initiated treatment on DA monotherapy [15,16]. Similarly, only a few studies have examined patient adherence to DA monotherapy [15–17].

More and updated data on the characteristics of patients, the treatments they initiated, the types of providers, and patients' compliance with treatment, among other factors are needed to guide the management of PD patients. The objectives of this study were to characterize an updated population of patients who initiated DA monotherapy for PD, examine their medication utilization, assess the types of providers, and estimate their adherence to treatment and risk of medication discontinuation.

2. Methods

2.1. Study design and data source

This retrospective study analyzed administrative claims data in the Optum Research Database (ORD) to identify patients diagnosed with PD who were treated with DA monotherapy between 01 September 2011 and 31 December 2019. The ORD, used with permission here, is a repository of deidentified administrative claims data for >73 million enrollees with commercial or Medicare Advantage Part D (MAPD) information. The index date was defined as the date of the first claim for DA during the identification period. Institutional Review Board approval or waiver was not required as researchers only accessed deidentified information for the study patients. Patient privacy was strictly preserved, and compliance with relevant Health Insurance Portability and Accountability Act (HIPAA) data handling rules was observed throughout.

3. Study population

3.1. Inclusion/exclusion criteria

Patients ≥1 claim for DA (apomorphine, bromocriptine, pramipexole, ropinirole, rotigotine) or levodopa (alone or in combination with carbidopa or entacapone) between 01 September 2012 and 31 December 2018 (identification period) were included. Patients were also required to have ≥2 medical claims with a diagnosis code for PD (ICD-9 332.0 or ICD-10 G20), ≥1 of which occurred during the pre-index period or on the index date and ≥1 during the post-index period. Patients were required to be commercial and MAPD enrollees, ≥40 years old in the year of the index date and have continuous enrollment with medical and pharmacy benefits ≥12 months before the index date and through ≥12 months beginning on and following the index date. Patients with evidence of DA treatment and who had missing information on age, sex, or region were excluded from the study. A subset of patients whose index medication was DA and had no other PD treatments during the post-index period comprised the population for this study.

4. Variable definitions

4.1. Pre-index measures

The Elixhauser score, an algorithm applicable to administrative claims data and based on a range of comorbidities separate from other factors in a patient's health status, was calculated from diagnosis codes (any position) on medical claims during the pre-index period [18]. Patient demographics including age (defined as of the index year), age groups (40–49, 50–59, 60–69, 70–79, 80+ years), sex (male or female), insurance type (MAPD or commercial) and geographic setting (urban or rural). Comorbid mental health and cognitive disorders of interest were also measured.

4.2. Outcome measures

All outcomes were examined in the post-index period, beginning on and continuing for 12 months following the index date. Index PD medication and DA prescriber specialty were derived from the index PD pharmacy claim. Discontinuation was defined as a treatment gap of ≥60 days. Adherence with the index therapy was measured using MPR: the sum of the number of days supply of the index therapy for all but the last

fill in the post-index period, divided by the number of days between the first and the last refill among patients with ≥2 pharmacy fills. Adherence was categorized as adherent (MPR ≥ 0.80) or non-adherent (MPR < 0.80). Adherence with the index therapy was also assessed using proportion of days covered (PDC) and categorized as adherent (PDC ≥ 0.80) and non-adherent (PDC < 0.80). PDC was calculated by dividing the number of days on which index therapies were available (based on filled prescriptions) by the number of days between the earliest index therapy claim in the post-index period through the end of the observation period [19]. Diagnoses and symptoms of dyskinesia were flagged and the time to dyskinesia diagnosis or symptom was measured as number of days until the first dyskinesia indicator.

4.3. Statistical analysis

All study variables, including pre-index and outcome measures, were analyzed descriptively, Counts and percentages were calculated for dichotomous and polychotomous variables, and means, standard deviations (SD), and medians for continuous variables. All statistical analyses were performed with SAS v 9.4 (SAS Institute, Cary, NC).

5. Results

5.1. Patient disposition

A total of 338,299 patients were identified with ≥1 claim for DA (apomorphine, bromocriptine, pramipexole, ropinirole, rotigotine) or levodopa (alone or in combination with carbidopa or entacapone). Most DA monotherapy was in the form of oral tablets, 88.9 %, including 8.2 % extended-release tables- and 11.1 % was administered with a transdermal patch (data not shown). Upon applying all exclusion criteria, a total of 642 patients who initiated treatment on DA monotherapy were included in the study (Supplemental Fig. 1).

5.2. Pre-index demographics

The mean (SD) age of the patients treated with DA monotherapy was 70.2 (9.9) years. Most patients (85.4 %) were age 60 or older. Males (61.7 %) outnumbered females. A higher percentage of study patients had MAPD coverage (70.6 %) relative to those with commercial insurance. Study patients were located predominantly in urban settings (93.9 %). Of the targeted conditions measured, about one-quarter of patients had diagnoses for depressive (29.0 %), anxiety (23.2 %) disorders while about one-tenth of patients had diagnoses for insomnia (10.3 %) and cognitive decline (11.1 %), and approximately-one-third of the patients were diagnosed with some form of dementia (Table 1).

5.3. Pre-index PD treatments

Most patients (89.9 %) had no PD treatment in the year before initiating DA monotherapy treatment. PD medications received by the other 10.1 % of patients consisted of MAO-B inhibitors (4.8 %) amantadine (2.7 %), levodopa (1.9 %) and anticholinergics (1.7 %) (Table 2).

5.4. Prescriber specialty and PD diagnosis status

Neurologists prescribed almost two-thirds (64.6 %) of the DA monotherapy on the index date. Other prescribing specialties included primary care (11.5 %) internal medicine (13.1 %), allied health professionals (7.8 %) and psychiatry (3.0 %). More than one-half (56.9 %) of patients had ≥2 PD diagnoses before or on the index date, while 43.2 % had their second or both diagnoses after the index date (Table 3).

5.5. Post-index PD treatment change

A total of 283 (44.1 %) of the patients discontinued their index therapy, while 359 (55.9 %) persisted for 12 months after initiation without any change. The mean (SD) time to discontinuation was 102.1 (78.8) days (Table 4).

Table 1
Demographics and Clinical Characteristics.

Demographic characteristics	Dopamine agonist monotherapy (N = 642)
Age (continuous)	
Mean (SD)	70.2 (9.9)
Median	70.0
Age (categorical), n (%)	
40–49	13 (2)
50–59	81 (12.6)
60–69	204 (31.8)
70–79	218 (34.0)
80+	126 (19.6)
Sex, n (%)	
Female	246 (38.3)
Male	396 (61.7)
Insurance type, n (%)	
Commercial	189 (29.4)
MAPD	453 (70.6)
Geographic setting, n (%)	
Urban	603 (93.9)
Rural	38 (5.9)
Multiple/Missing, n (%)	1 (0.2)
Elixhauser score	
Mean (SD)	9.6 (8.6)
Median	7.0
Comorbid conditions (≥1 medical claim with corresponding disorder), n (%)	
Depressive disorder	186 (29.0)
Anxiety disorder	149 (23.2)
Insomnia	66 (10.3)
Cognitive decline	71 (11.1)
Dementia	97 (15.1)
Alzheimer's disease	29 (4.5)
Vascular dementia	18 (2.8)
Frontotemporal dementia	2 (0.3)
Dementia with Lewy bodies	19 (3.0)
Other dementias	85 (13.2)

MAPD = Medicare Advantage Part D; Two-sample *t*-test was used for continuous measures; Pearson chi-square test was used for binary measures; CCI = Charlson comorbidity index; SD = standard deviation.
[1]Quan H et al. *Am J Epidemiology*. 2011; 173(6): 676–82.

Table 2
Other Pre-index Parkinson's Disease Treatments.

Pre-index PD medication class	Dopamine agonist monotherapy (N = 642)
Other PD medication, n (%)	65 (10.1)
MAO-B inhibitor	31 (4.8)
Amantadine	17 (2.7)
Anticholinergic	11 (1.7)
COMT inhibitor	0.0
Levodopa	12 (1.9)
No other pre-index PD medication	577 (89.9)

PD = Parkinson's disease; MAO-B = Monoamine oxidase B; COMT = Catechol-O-methyl transferase.
Pearson chi-square test was used for binary measures.

Table 3
Prescriber Specialty and Parkinson's Disease Diagnosis Status.

	Dopamine agonist monotherapy (N = 642)
Prescriber specialty, n (%)	
Primary care	158 (24.6)
Neurologist	415 (64.6)
Geriatrician	3 (0.5)
Psychiatry	19 (3.0)
Cardiology	5 (0.8)
Endocrinology	1 (0.2)
Pulmonary	3 (0.5)
Allied Health Professional*	50 (7.8)
Diagnosis status, n (%)	
Existing diagnosis (both diagnoses before or on the index date)	365 (56.9)
Newly diagnosed (the second diagnosis or both diagnoses occur during/after the index date)	277 (43.2)

Pearson chi-square test was used for binary measures.
*Includes physician assistants and nurse practitioners.

Table 4
Parkinson's Disease Treatment Change during the Post-index Period.

First treatment change	Dopamine agonist monotherapy (N = 642)
Discontinued index PD treatment, n (%)	283 (44.1)
No change (persistent with index medication to end of study period), n (%)	359(55.9)
Time to first treatment change/discontinuation of index therapy (days)	
Mean (SD)	102 (78.8)
Median	89.0
Discontinued all PD treatment (did not use or switch any medication after discontinuing), n (%)	200 (31.2)

5.6. Post-index treatment adherence

Mean (SD) MPR for the 562 patients who had ≥2 pharmacy fills for DA was 0.84 (0.2). A total of 395 (70.3 %) of patients were MPR adherent to treatment as defined by MPR ≥0.80. The mean (SD) PDC for the overall 642 patients was 0.66 (0.3). A total of 324 (50.5 %) of patients were PDC adherent to treatment as defined by PDC ≥0.80 (Table 5).

5.7. Post-index dyskinesia

A total of 66 (10.3 %) patients treated with DA monotherapy had ≥1 diagnosis for dyskinesia in the 12 months following the index date. The mean (SD) time to diagnosis was 91.5 (101.8) days. Only 7 (1.1 %) of patients had ≥1 dyskinesia symptom diagnosis. The mean (SD) time to the first symptom diagnosis was 111.0 (136.8) days (Supplemental Table 1).

Table 5
Treatment Adherence during the Post-index Period.

Adherence measure	Dopamine agonist monotherapy (N = 642)
MPR with index therapy (n)	562
Mean (SD)	0.84 (0.21)
Median	0.93
MPR adherent (MPR ≥0.80), n (%)	395 (70.28)
MPR non-adherent (MPR < 0.80), n (%)	167 (29.72)
PDC with index therapy (n)	642
Mean (SD)	0.66 (0.34)
Median	0.81
PDC adherent (PDC ≥0.80), n (%)	324 (50.47)
PDC non-adherent (PDC <0.80), n (%)	318 (49.53)

6. Discussion

This study evaluated a contemporary sample of insured patients between 01 September 2011 and 31 December 2019 diagnosed with PD who initiated treatment with DA monotherapy. The average age of study patients was about 70 years, with about two-thirds of the study population aged 60–79 years and about a fifth were 80 years and older. These results are similar to the findings of a study by Van Den Eeden et al based on medical records data that reported mean age at diagnosis of 70.5 years [20], and a study by Pagano et al that relied on patients' recall of disease onset — 61.6 years [21]. The mean age of patients in our study was higher than those reported for a Medicaid population: mean adjusted age of 54 years — a likely reflection of the broader array of age groups with Medicaid coverage [22] compared to MAPD (see Supplemental Table 1).

Slightly <40 % of the patients in this study were female, which is notably less than the 49.9 % in the Johnsrud et al study [22], and substantially less than the 58 % reported for a US-wide Medicaid population on patients with PD [23]. This could be only the second study reporting that more males relative to females initiated on DA monotherapy, however, despite considerable efforts to unravel the clinical pathology underlying this sex disparity it is still not well understood [22,24].

Over one-quarter of the patients were diagnosed with depression (29.0 %) and just less than one-quarter were diagnosed with anxiety (23.2 %) during the pre-index period. While such comorbidities were expected, a study by Seritan et al reported that the onset of comorbid depression and anxiety preceded a PD diagnosis in >50 % of patients [25]. Our results show substantially lower incidence of these conditions than the Johnsrud et al study, in which about half of the patients had depression and 40 % had signs of anxiety [22].

In this study, neurologists prescribed about two-thirds of the DA monotherapy, followed by primary care clinicians (24.6 %). While the proportions of prescriptions by provider specialty is not well represented in the literature, the Tarrants et al study reported that neurologists wrote prescriptions for 41.3 % of patients, primary care physicians for 45.8 % and unknown prescribers for 13.0 %. In addition, Tarrants et al reported that specialty did not affect adherence overall as mean MPRs for internists, neurologists, and unknown specialties were 72.8 %, 74.5 %, and 72.6 %, respectively [17]. This study did not evaluate adherence by physician specialty.

Less than one-half (44.1 %) of patients discontinued their index therapy with a mean time to discontinuation of about 102 days. Mean post-index treatment adherence values for both MPR (0.84) and PDC (0.66), and adherence percentages for MPR (70 %) and PDC (51 %) appear suboptimal. While these rates seem slightly better than the 33 %-54 % range reported in prior studies [15,17,22], they reflect a substantial degree of non-compliance possibly due to factors including efficacy, safety, and tolerability [26]. The DOMINION study, 2010, reported that impulse control disorders (ICDs) were significantly associated with the use of DA agents, and DA treatment increased the odds of having an ICD by 2- to 3.5-fold in patients with PD [27]. During that period, other DA safety concerns were identified including heart failure risk [28]. These may be plausible reasons for the decrease in prescribing DAs as first-line therapy in favor of levodopa, and an overall decrease of about 5 % in all DA prescriptions in the US between 2008 and 2011 [29].

These results, especially those related to low treatment adherence, have important implications for treatment development, optimization of medication use by the healthcare system and providers, and the welfare of patients and their caregivers.

6.1. Limitations

The results of this study must be approached with due caution because of some notable limitations. Analyses were based on administrative claims data, imposing intrinsic restrictions on how results gleaned from repurposing information from financial transactions for research- purposes may be interpreted. The presence of a diagnosis code on a medical claim does not universally indicate the presence of a disease. A code could have been incorrect or included as rule-out criteria rather than actual disease, introducing the possibility of misclassification and underreporting. To mitigate this limitation, ≥2 diagnoses (≥1 during the pre-index period or on the index date and ≥1 in the post-index period) were required for inclusion in the study. Clinical and disease-specific information that could influence outcomes, including family history, smoking status, body mass index, diet and exercise regimens and socioeconomic status, is not generally available in claims data. As a result, reasons for observed dyskinesias were not determined and there was no evidence to suggest that they were or were not due to DA therapy. In addition, the lack of clinical information on disease severity and progression, Hoehn & Yahr stage [30], and drug safety and tolerability precluded investigation into the reasons for discontinuation. Pharmacy claims do not necessarily mean than that all medications filled were consumed as intended, and do not include drug samples from providers or over the counter purchases. The ORD includes a combination of commercial and MAPD insurance enrollees and may not be generalizable to different patient populations such as Medicaid beneficiaries or uninsured individuals.

7. Conclusions

While adherence rates in this study appear slightly better than those reported in earlier studies, they remain suboptimal, indicating that large segments of patients with PD who were treated with DA monotherapy do not have effective symptom management. This study did not assess the reasons nor the effects of poor treatment adherence. However, prior studies suggest a link between low adherence rates and poor patient outcomes. Additional studies are needed to better understand the impact of suboptimal adherence to DA monotherapy treatment.

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Author disclosures

Le and Frazer (at time of study) are employees of Optum Life Sciences, which was contracted by Cerevel for the conduct of this study. Arcona and Sasane are employees of Cerevel Therapeutics. The authors report no further relevant conflicts of interest/financial disclosures.

Author contribution

All authors participated in the conceptualization and design of the study, conducted or consulted on the data analysis, and drafted and reviewed the various versions as they evolved into this manuscript. The authors were responsible for all drafting, rewriting, review and approval of the content of this manuscript. Le has complete access to all study data and takes responsibility for data integrity and accuracy of the analyses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The study was sponsored by Cerevel Therapeutics, USA.

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Appendix A. Supplementary data

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