ORIGINAL RESEARCH

Comparative Effectiveness of Carbidopa–Levodopa Enteral Suspension and Deep Brain Stimulation on Parkinson's Disease-Related Pill Burden Reduction in Advanced Parkinson's Disease: A Retrospective Real-World Cohort Study

Michael J. Soileau · Fernando Pagan · Alfonso Fasano ·
Ramon Rodriguez-Cruz · Lin Wang · Prasanna L. Kandukuri ·
Connie H. Yan · Ali Alobaidi · Yanjun Bao · Pavnit Kukreja ·
Mok Oh · Mustafa S. Siddiqui

ABSTRACT

Introduction: In advanced Parkinson's disease (PD), a high pill burden is associated with poor compliance, reduced control of symptoms, and decreased quality of life. We assessed the impact of carbidopa–levodopa enteral suspension (CLES) and deep brain stimulation (DBS) on PD-related pill burden.

Methods: A retrospective cohort analysis was conducted in the IBM MarketScan and Medicare Supplemental databases. Patients with

M. J. Soileau (✉)
Texas Movement Disorder Specialists, 204 S. Interstate 35, Suite 103, Georgetown, TX 78628, USA
e-mail: msoileau@txmds.net

F. Pagan
Department of Neurology, Georgetown University Hospital, Washington DC, USA

A. Fasano
Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, ON, Canada

A. Fasano
Division of Neurology, University of Toronto, Toronto, ON, Canada

A. Fasano
Krembil Brain Institute, Toronto, ON, Canada

R. Rodriguez-Cruz
Synaptic Precision, Inc, Orlando, FL, USA

L. Wang
Johns Hopkins School of Public Health, Baltimore, MD, USA

L. Wang · P. L. Kandukuri · C. H. Yan · A. Alobaidi · Y. Bao · P. Kukreja · M. Oh
AbbVie Inc., North Chicago, USA

C. H. Yan · A. Alobaidi
Department of Pharmacy Systems, University of Illinois at Chicago, Chicago, IL, USA

M. Oh
College of Pharmacy, University of Arizona, Tucson, AZ, USA

M. S. Siddiqui
Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC, USA

advanced PD, taking only PD medications, and initiating CLES or DBS between 9 January 2015 and 31 July 2019 were identified. CLES patients were matched to DBS patients in a 1:3 ratio based on a propensity score to balance patient characteristics. Pill burden was measured as a 30-day average number of PD-related pills per day and was captured monthly. Pill-free status was evaluated as the percentage of patients receiving CLES or DBS monotherapy. Descriptive statistics were used to compare pill counts and assess the proportion of patients on monotherapy at 6 and 12 months after initiating CLES or DBS.

Results: The cohorts included 34 CLES patients matched to 97 DBS patients. A significant reduction in PD-related pill burden was observed at 6 months after initiation of CLES or DBS (ΔCLES: -5.62, $p < 0.0001$; ΔDBS: -1.48, $p = 0.0022$). PD-related pill burden reduction in CLES patients was significantly greater than in matched DBS patients at 6 months (Δ: -4.14, $p < 0.0001$), which was sustained at 12 months after initiation. At 12 months, nearly three times more CLES patients were pill free than DBS patients (29.41% and 10.31%, respectively, $p = 0.0123$).

Conclusions: Device-aided therapies such as CLES and DBS are effective in significantly reducing PD-related pill burden. Patients treated with CLES were more likely to achieve pill-free status than patients receiving DBS.

Key Summary Points

Why carry out this study?

As Parkinson's disease progresses, patients often require more intensive treatment regimens and an increasingly high pill burden.

As a high pill burden can be associated with poor adherence, which is an important medication-related problem in patients with Parkinson's disease, the purpose of this study was to compare the real-world impact of initiating carbidopa–levodopa enteral suspension (CLES) or deep brain stimulation (DBS) on the pill burden in patients with advanced Parkinson's disease in the USA.

What was learned from the study?

This retrospective cohort analysis of insurance claims from the IBM MarketScan and Medicare Supplemental databases showed that CLES and DBS were effective in significantly reducing Parkinson's disease-related pill burden.

CLES was observed to reduce pill burden to a greater extent than DBS, allowing approximately three times more patients to achieve an entirely pill-free status.

Limitations inherent in studies using insurance claims data should be taken into consideration in the interpretation of these results.

INTRODUCTION

As Parkinson's disease (PD) progresses, motor symptoms are not always well controlled by oral PD medications [1–3]. Patients often experience debilitating fluctuations in symptom control, resulting in increased morbidity and limitations in activities of daily living (ADL). To manage motor complications, patients often need to take complex polypharmacy-based oral regimens but may still develop troublesome motor fluctuations and unpredictable transitions from mobility to immobility. Many oral treatments are available for PD, including levodopa (in combination with a decarboxylase inhibitor such as carbidopa, and sometimes a catechol-o-methyl transferase [COMT] inhibitor), dopamine agonists, monoamine oxidase inhibitors (MAOI), anticholinergic agents, and amantadine. The increased pill burden required to manage advanced PD is associated with decreased compliance [4], which may lead to inadequate control of PD symptoms [5, 6]. People with PD demonstrated high adherence to once-daily medication, but this dropped to below 75% adherence when > 5 doses per day were required [4]. In a recent study, based on the 8-Item Morisky Medication Adherence Scale [7], only 33.9% of people with PD who were taking ≥ 3 pills a day reported a high level of adherence (29.8% and 36.3% had a medium and low level of adherence, respectively) [8]. Nonadherence is an important medication-related problem in patients with PD and is associated with poor motor control, reduced quality of life (QoL), increased caregiver burden, and higher healthcare costs [9, 10].

In advanced PD, even optimized oral therapies can fail to control PD symptoms due to erratic gastric emptying and a narrowing therapeutic window [11]. For patients with PD suboptimally managed by oral regimens, device-aided therapies such as carbidopa–levodopa enteral suspension (CLES; also referred to as levodopa–carbidopa intestinal gel [LCIG]) or deep brain stimulation (DBS) may offer an effective alternative [12–15]. Both CLES [10] and DBS [16, 17] are effective in reducing "off"-time and improving QoL, even when used as monotherapy, and may have the potential to reduce pill burden. However, little is known about the impact of CLES compared with DBS on reducing pill burden or helping patients achieve pill-free status. Therefore, the purpose of this study was to compare the real-world impact of initiating CLES or DBS on the pill burden in patients with advanced PD in the USA.

METHODS

Data Source

This study was a retrospective cohort analysis of the IBM MarketScan (IBM Watson Health) 2015–2019 Commercial and Medicare supplemental databases, representing over 100 million individuals with an employer-sponsored health plan and approximately 9 million retired adults with primary or supplemental Medicare coverage in the USA. The databases contained all paid annual claims of commercial or Medicare-supplement insured individuals, with member identification codes that allowed individuals to be followed long-term. Both databases included inpatient and outpatient medical claims for identification of diagnoses (International Classification of Disease [ICD]), procedures undertaken (Common Procedural Terminology [CPT]; Healthcare Common Procedure Coding System [HCPCS]), and outpatient pharmacy claims for identification of dispensed medications (National Drug Codes [NDCs]). The data collected from the IBM MarketScan research databases were deidentified to comply with the Health Insurance Portability and Accountability Act (HIPAA). Therefore, Ethics Committee Review approval for the conduct of this study was not necessary. The data are licensed by IBM Watson Health through a multiple-year contract to AbbVie, and AbbVie has the full

permission based on the license to access and analyze the data and share/publish the findings.

Participants

Eligible patients were adults ($\geq$ 18 years of age) with $\geq$ 2 diagnoses for PD as assessed by ICD codes (ICD-9: 332.0x; ICD-10: G20) during the therapeutic identification period (between 9 January 2015 and 31 July 2019) and were taking only oral PD medications before the initiation of CLES or DBS. Patients had to be newly initiated on CLES (CLES cohort; HCPCS: J7340; NDC: 0074-3012-07) or DBS (DBS cohort; CPT-4: 61863, 61864, 61867 or 61868) during the therapeutic identification period. The NDC code for CLES became effective in January 2015, and the HCPCS J7340 code was assigned to CLES in January 2016. The date of initiation of CLES or DBS was defined as the index date. Patients had to have continuous enrollment in a medical and pharmacy insurance plan 6 months before (baseline) up until 12 months after (follow-up period) the index date. Patients were excluded from the study if they had received dual CLES and DBS at baseline or during the follow-up period, or had < 2 oral PD medications filled in the 3 months prior to the index date. Furthermore, patients in the CLES cohort were excluded if they had < 2 fills of CLES in the 3 months after the index date.

Outcome Measures

Baseline patient and clinical characteristics and medication use were evaluated at baseline. Oral PD medications were identified using NDCs, including carbidopa–levodopa formulations, COMT inhibitors, dopamine agonists, MAOI, anticholinergic agents, and amantadine. Prescription claims with < 5 or > 180 days' supply and/or quantity > 1350 pills were excluded. Pill burden was measured as a 30-day average of the total number of individual PD-related pills per day and was captured on a monthly basis, from baseline until the end of the 12-month follow-up period. This included carryover of multi-month prescriptions within each monthly period. The monthly pill burden was calculated by dividing the number of pills by the number of treated days (days' supply of medication filled). Pill-free status was defined as the percentage of patients who were taking no oral PD medication after the index date. Pill-free status was evaluated monthly and is reported at months 3, 6, 9, and 12.

Statistical Analyses

Baseline patient demographics and clinical characteristics are presented as mean and standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. CLES patients were matched to DBS patients in a 1:3 ratio based on a propensity score to account for different patient characteristics and potential confounding factors in treatment initiation (including age, gender, Charlson Comorbidity Index, Elixhauser Comorbidity Index, medication costs, and claims-based indicators for PD severity [dementia, dyskinesia, hallucination, and repeated falls]), which was calculated using logistic regression [1, 18, 19]. The balance of these covariates between the matched CLES and DBS patient cohorts was checked. Unpaired T-test, Wilcoxon rank-sum, chi-squared, and Fisher exact tests were used, where relevant, to compare monthly pill counts and the proportion of patients achieving pill-free status at 3, 6, 9, and 12 months after the index date in the CLES and DBS matched cohorts.

Generalized linear mixed models were used to estimate the difference between the pill burden reduction in patients receiving CLES or DBS during the 1–6 and 7–12 month periods after the index date, accounting for repeated measurements [20]. Covariates that were not balanced by propensity score matching (e.g., age, Elixhauser Comorbidity Index, and medical costs) were adjusted for in the generalized linear mixed models, to ensure robustness of the model estimates. All analyses were performed using Instant Health Data (IHD) software (Panalgo, Boston, MA, USA), R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 121 PD patients initiated on CLES, 34 patients met inclusion criteria and were matched to 97 PD patients initiated on DBS. After matching, the two groups were similar in all covariates except for age, with patients receiving DBS observed to be younger than patients receiving CLES (mean age 60.28 years and 67.50 years, respectively; Table 1).

Pill Burden

Four to six months before treatment initiation, the PD-related pill burden (number of pills per day) was significantly higher in the CLES cohort than in the DBS cohort (Fig. 1). For example, at 6 months before initiation of device-aided therapy, patients in the CLES matched cohort had greater PD-related pill burden than the DBS-matched cohort (9.63 PD-related pills per day and 7.01 PD-related pills per day, respectively; $p = 0.0444$; Fig. 1). At 1 month before initiating treatment, patients in both cohorts had a similar mean number of PD-related pills per day (CLES: 10.79; DBS: 9.71; $p = 0.3835$; Fig. 1). From 3 months post-treatment initiation and beyond, the PD-related pill burden in the CLES cohort was significantly lower than in the DBS cohort. For example, at 12 months after initiating device-aided therapy, the CLES group was taking 3.18 pills per day while the DBS group was taking 6.0 pills per day ($p = 0.0004$; Fig. 1). During the 0–6 month period after initiating CLES/DBS, the mean (SD) pills per day in the DBS and CLES group were 7.74 (5.31) and 5.79 (4.18), respectively ($p = 0.0332$), and during the 7–12 month period after initiating CLES/DBS, these values were 6.46 (4.51) and 4.30 (3.79), respectively ($p = 0.0084$).

Based on regression estimates, a significant reduction in PD-related pill burden was

Table 1 Baseline clinical and patient characteristics

Characteristic	Overall sample ($n = 131$)	DBS matched ($n = 97$)	CLES matched ($n = 34$)
Mean (SD) age on index, years	62.15 (9.78)	60.28 (8.74)*	67.50 (10.71)*
Geographic region, n (%)			
Midwest	26 (21.14)	22 (24.18)	4 (12.50)
Northeast	31 (25.20)	24 (26.37)	7 (21.88)
South	44 (35.77)	29 (31.87)	15 (46.88)
West	22 (17.89)	16 (17.58)	6 (18.75)
Male, n (%)	66 (50.38)	45 (46.39)	21 (61.76)
Elixhauser Comorbidity Index, mean (SD) score	2.75 (1.63)	2.64 (1.50)	3.06 (1.95)
Charlson Comorbidity Index, mean (SD) score	0.79 (1.20)	0.71 (1.08)	1.03 (1.49)
Having dementia, n (%)	23 (17.56)	15 (15.46)	8 (23.53)
Having dyskinesia, n (%)	9 (6.87)	7 (7.22)	2 (5.88)
Having hallucination, n (%)	121 (92.37)	88 (90.72)	33 (97.06)
Having repeated falls, n (%)	5 (3.82)	4 (4.12)	1 (2.94)

Baseline period defined as the 6-month period prior to index date

CLES carbidopa–levodopa enteral suspension, *DBS* deep brain stimulation, *PD* Parkinson's disease, *SD* standard deviation
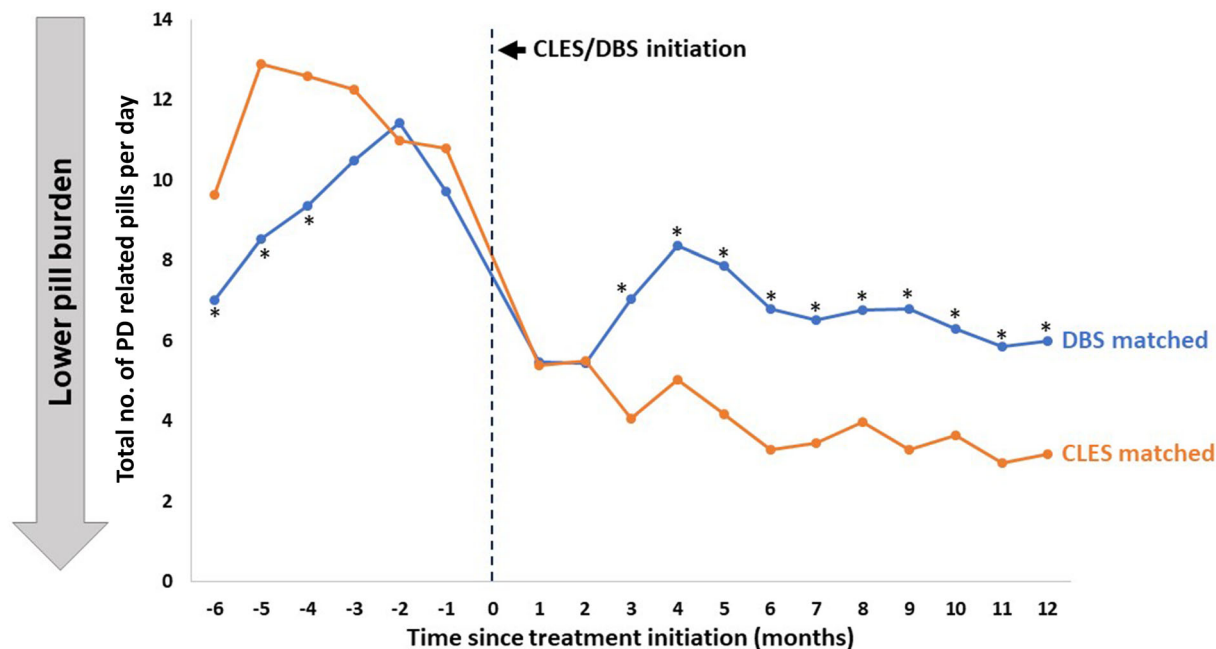
*$p < 0.05$ after matching cohorts

Fig. 1 Monthly average PD-related pills per day in CLES and DBS cohorts. Cohort of DBS and CLES patients matched using propensity-score based approach. *$p < 0.05$ in pill burden between CLES and/or DBS groups.

CLES carbidopa–levodopa enteral suspension, *DBS* deep brain stimulation, *PD* Parkinson's disease

observed at 1–6 months of CLES and DBS compared with baseline (CLES: −5.62, $p < 0.0001$; DBS: −1.48, $p = 0.0022$; Δ: −4.14, $p < 0.0001$). Between 7 and 12 months post-initiation, there was a sustained reduction in the PD-related pill burden for both CLES and DBS patients compared with baseline (CLES: −7.11; $p < 0.0001$; DBS: −2.76; $p < 0.0001$; Δ: −4.35, $p = 0.0003$).

As early as 3 months after treatment initiation, patients were observed to achieve pill-free status (i.e., have zero PD-related pills per day) in 26.47% of the CLES cohort and 8.25% of the DBS cohort ($p = 0.0143$; Fig. 2). A similar trend was also observed at 6 months post-treatment initiation, with 23.53% versus 4.12% of patients pill free in the CLES and DBS cohort, respectively ($p = 0.0022$). Sustained pill-free status was demonstrated for up to 12 months after treatment initiation, with a greater percentage of patients achieving pill-free status among those initiated on CLES than on DBS ($p = 0.0123$; Fig. 2).

DISCUSSION

In this retrospective cohort study of national insurance claims, both CLES and DBS were effective in significantly reducing pill burden. This effect could be observed as early as 3 months after CLES or DBS initiation and was sustained at 12 months after treatment initiation. Patients initiating CLES were observed to have a significantly greater reduction in pill burden than patients initiating DBS, which was sustained throughout the year. Approximately 2–6 times more patients on CLES achieved pill-free status than patients on DBS at different times in the 12 months after treatment initiation.

In this study, patients received approximately 10 pills per day, on average, prior to initiation of device-aided therapies. Consistent with this observation, patients with PD are commonly reported to take up to 12 PD-related pills per day, and the number of PD-related pills per day increases as disease progresses [21, 22].
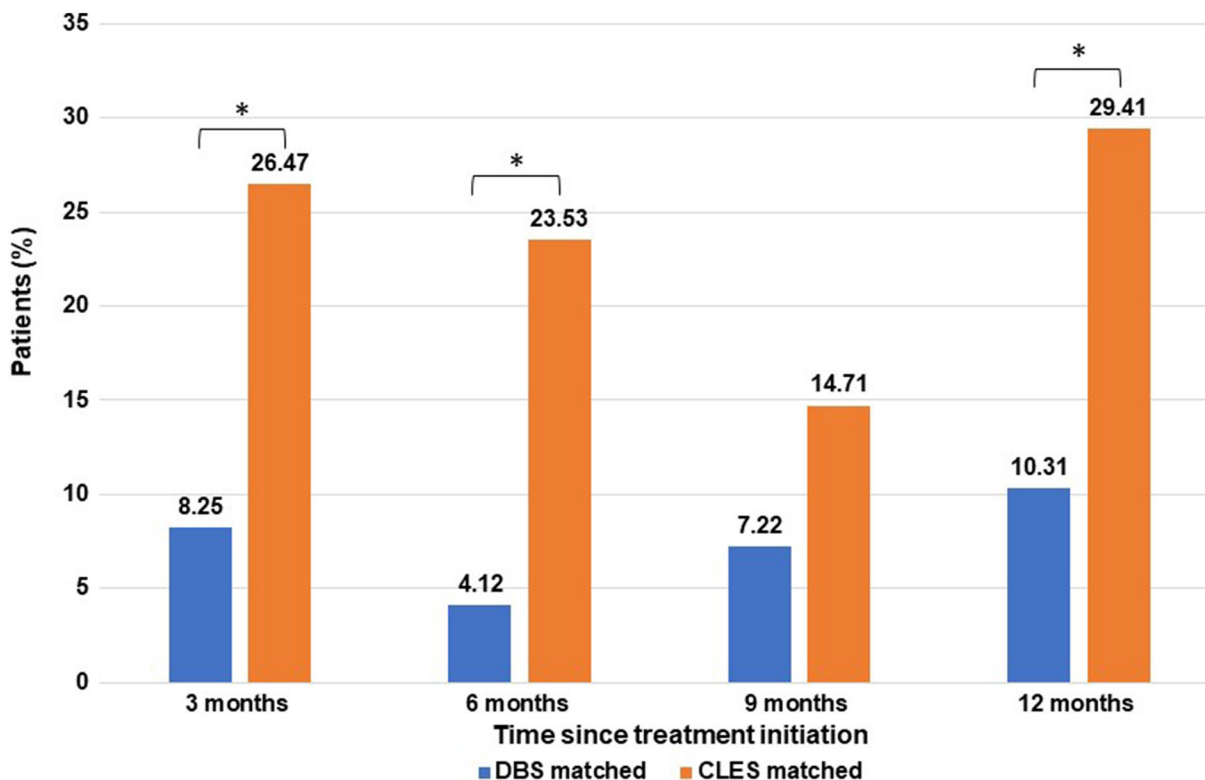
Fig. 2 Percentage of patients achieving pill-free status after initiating CLES or DBS. Cohort of DBS and CLES patients matched using propensity-score based approach.

*$p < 0.05$. *CLES* carbidopa–levodopa enteral suspension, *DBS* deep brain stimulation

Evidence indicates decreased adherence for each additional daily dose of chronic medication [23]. Nonadherence to PD-related pills causes or exacerbates morbidity [8] and incurs greater healthcare resource utilization and medical costs (e.g., hospitalizations, office visits) [24]. Pill burden reduction offers an opportunity to simplify treatment regimens and potentially improve treatment adherence. Reducing pill burden also provides a higher level of independence to patients by breaking the cycle of continuously taking pills multiple times a day, along with possible reduced drug–drug or drug–food interactions [5]. A reduction in pill burden may also facilitate improved QoL. For example, older patients may have trouble swallowing oral medication, and patients with motor symptoms may have difficulty in opening or closing medication bottles. Dementia and cognitive impairment are also common in patients with advanced PD and may

impact a patient's ability to comprehend treatment instructions, especially in terms of the timing and number of pills to take. Although not the subject of the current analysis, reduced pill burden also has the potential to offer benefits beyond those for patients with advanced PD. For example, it could reduce the burden on caregivers, as demonstrated in the PREDICT study, where caregivers experienced a lower burden of care for patients taking CLES than for patients on multiple oral PD-related pills. [10].

Recent studies demonstrated that patients receiving CLES monotherapy (i.e., with pill-free status) had significant improvements in motor and nonmotor symptoms, health-related QoL, and the ability to perform ADL [5, 25, 26]. Furthermore, patients on CLES monotherapy achieved reduced "off"-time and increased "on"-time without troublesome dyskinesia [22, 25]. While it was not possible to evaluate whether patients were receiving CLES for 16 h/day or

24 h/day from the MarketScan database, there is a possibility that patients receiving CLES for 24 h/day may have a greater reduction in pill burden [27]. Based upon previous studies and the findings of the current analysis, pill burden reduction may be considered an important treatment goal to optimize patient outcomes in advanced PD. Furthermore, oral PD-related pills are associated with adverse effects that can be debilitating or reduce a patient's QoL [28]. Achieving pill-free status or a reduction in polypharmacy can reduce a patient's experience of adverse medication effects. It should be noted that patients treated with DBS may still require oral levodopa medications for dopaminergic stimulation, and current post-DBS management aims to initially adjust medication dosage as opposed to achieving pill-free status, particularly to address the control of nonmotor symptoms [29, 30]. Furthermore, the specific DBS target (subthalamic nucleus [STN] or globus pallidus interna [GPi]) may impact treatment efficacy and the subsequent need for oral medication [29]. The MarketScan database lacked details on the DBS target and hours of CLES delivery per day, which may be areas for future research. It is important to note that the choice of treatment needs to be a shared decision between the multidisciplinary team, the patient, and their carer(s) [31]. Information on pill burden may help inform such treatment decisions and discussions.

There are limitations to the current study. As with any prescription-claims database study, dispensed prescriptions may not necessarily be the same as actual oral drug utilization. The nature of claims databases limits the ability to understand the clinical decisions driving the observed treatment patterns and restricts the ability to understand the impact of pill burden on clinical or safety outcomes. Residual confounders cannot be ruled out, and statistical inferences may be biased from unmeasured confounders and small sample size in the CLES group, which may limit the generalizability of the study findings. Propensity score matching and additional statistical adjustment utilized in the study may mitigate the aforementioned biases to some extent. Finally, there remains a possibility that matching of DBS to CLES patients may have resulted in the selection of characteristics in each group that may not reflect the population receiving CLES or DBS in the real world. Despite these limitations, the robustness of the analytic approach, in conjunction with the real-world source of data, provides a novel insight into this first-of-its-kind assessment of the comparative effectiveness of CLES and DBS in patients with advanced PD.

CONCLUSIONS

Device-aided therapies such as CLES and DBS are effective in significantly reducing PD-related pill burden in real-world patients with advanced disease, with sustained effects for 12 months after treatment initiation. Compared with DBS, patients initiated on CLES had a significantly greater reduction in pill burden, with more patients achieving pill-free status. Future research should evaluate the impact of reduced pill burden and frequency of daily dosing on patient outcomes and preference, to facilitate better treatment adherence.

ACKNOWLEDGEMENTS

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