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ORIGINAL ARTICLE

Opicapone versus entacapone: Head-to-head retrospective data-based comparison of healthcare resource utilization in people with Parkinson's disease new to catechol-O-methyltransferase (COMT) inhibitor treatment

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Abstract

Background and purpose: Motor fluctuations are a significant driver of healthcare resource utilization (HCRU) in people with Parkinson's disease (pwPD). A common management strategy is to include catechol-O-methyltransferase (COMT) inhibition with either opicapone or entacapone in the levodopa regimen. However, to date, there has been a lack of head-to-head data comparing the two COMT inhibitors in real-world settings. The aim of this study was to evaluate changes in HCRU and effect on sleep medications when opicapone was initiated as first COMT inhibitor versus entacapone.

Methods: In this retrospective cohort study, we assessed HCRU outcomes in pwPD naïve to COMT inhibition via UK electronic healthcare records (Clinical Practice Research Datalink and Hospital Episodes Statistics databases, June 2016 to December 2019). HCRU outcomes were assessed before (baseline) and after COMT inhibitor prescription at 0–6 months, 7–12 months and 13–18 months. Opicapone-treated pwPD were algorithm-matched (1:4) to entacapone-treated pwPD.

Results: By 6 months, treatment with opicapone resulted in 18.5% fewer neurology outpatient visits compared to entacapone treatment; this effect was maintained until the last follow-up (18 months). In the opicapone group, the mean levodopa equivalent daily dose decreased over the first year and then stabilized, whereas the entacapone-treated group showed an initial decrease in the first 6 months followed by a dose increase between 7 and 18 months. Neither COMT inhibitor had a significant impact on sleep medication use.

Conclusions: This head-to-head study is the first to demonstrate, using 'real-world' data, that initiating COMT inhibition with opicapone is likely to decrease the need for post-treatment HCRU versus initiation of COMT inhibition with entacapone.

KEYWORDS
COMT inhibitor, entacapone, healthcare resource usage (HCRU), opicapone, Parkinson's disease

INTRODUCTION

The success of levodopa and other dopaminergic therapies has meant that people with Parkinson's disease (pwPD) generally enjoy good symptomatic control for longer periods. However, over half of pwPD using levodopa experience response fluctuations within 5 years of diagnosis, and up to 100% within 10 years [1, 2]. Often, the first motor complication to emerge is 'end-of-dose wearing-off' [3, 4], when patients experience a re-emergence of their parkinsonian symptoms before their next dose is due [5, 6]. In a substantial proportion of pwPD, motor fluctuations are also accompanied by non-motor fluctuations [7], as well as sleep disturbances that can be related to nocturnal motor function, neuropsychiatric problems, insomnia or urinary difficulties [8].

Catechol-O-methyltransferase (COMT) inhibitors were specifically designed to mitigate end-of-dose motor fluctuations. They act to reduce the peripheral metabolism of levodopa, thereby prolonging its plasma half-life and decreasing the peak–trough variations in levodopa plasma levels that are associated with response fluctuations [9, 10]. Currently available COMT inhibitors, tolcapone, entacapone and opicapone, are indicated for the management of end-of-dose motor fluctuations in pwPD who cannot be stabilized on levodopa/dopa-decarboxylase inhibitor therapy, although tolcapone is now only used under specialist supervision [11]. For the remaining two, aside from the pivotal study showing non-inferiority of opicapone efficacy to entacapone in reducing OFF-time [12] and the open-label phase from the same study indicating a benefit of switching from entacapone to opicapone [13], there have been no head-to-head studies comparing opicapone and entacapone in real-world settings.

In this retrospective observational study of routine care, we used linked electronic healthcare records from the United Kingdom to evaluate healthcare resource utilization (HCRU) and effect on sleep medications (as a measure of the impact of COMT inhibition on nocturnal motor function) when opicapone was initiated as first COMT inhibitor versus entacapone. All data were collected before the COVID-19 pandemic (June 2016 to December 2019).

METHODS

Database description

The Clinical Practice Research Datalink (CPRD) and the Hospital Episode Statistics (HES) databases are widely used electronic healthcare databases [14, 15]. The CPRD Gold and CPRD Aurum are large UK primary care databases of anonymized medical records collected from general practitioners in the community and include data from 18 million registered patients [15, 16]. HES is a database curated by NHS Digital, containing patient-level data on all admissions, accident and emergency (A&E) attendances, and outpatient appointments at National Health Service (NHS) hospitals in England [17]. Anonymized primary care patient data contained within the CPRD can be individually linked to HES datasets. This study analyses data from the CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The interpretation and conclusions are those of the authors.

Protocol approval, inclusion and ethics

The study protocol (Application Number 21_000335) [18] was approved by the MHRA. Each individual English practice participating in CPRD collection of their primary care data can choose to revoke their consent for data collection at any point. Patients who have registered an opt-out are not extracted for CPRD research nor for data linkage.

Study cohorts

The COMT inhibitor-treated study population included all permanently registered adult (≥18 years) patients in the CPRD with a diagnosis of Parkinson's disease (PD), seen by hospital-based neurologists and therefore with linked HES outpatient files, and a prescription for opicapone or entacapone as their first COMT inhibitor. Patients were excluded if they had: (i) no contact with a neurology department in the 12 months up to the index date; (ii) a history of dementia; (iii) any off-label use of COMT inhibitors (prescription before PD diagnosis); or (iv) a prescription for tolcapone. The observation period started at the most recent of three dates: (1) database registration date; (2) standard date plus 120 days; or (3) 1 July 2016 (time of UK opicapone launch); and ended on the earliest of three dates: (1) database deregistration (including death); (2) last data collection date; or (3) 31 December 2019 (prior to the start of the COVID-19 pandemic). Baseline data are based on 120 days of recording prior the index date (date of first opicapone or entacapone prescription).

Currently, most Integrated Care Systems in the United Kingdom mandate that opicapone should be used second line in patients either not tolerating or contraindicated for entacapone, meaning that the opicapone population was expected to be smaller than the entacapone group and limited to those prescribers who will prescribe opicapone first line. For the purposes of matched analysis, patients were therefore matched (1 opicapone: 4 entacapone) using a greedy nearest-neighbour approach [19] on sex, age in 10-year intervals, early onset of PD (diagnosis at <50 years of age), years from PD diagnosis to index in 5-year intervals, baseline HCRU, baseline levodopa equivalent daily dose (LEDD) and baseline use of sleep medications (yes/no). Exclusion criteria included a prescription for a different COMT inhibitor after index date and during observation, and lack of contact with a neurology department in the 12 months up to and including the index date.

Endpoints

Primary endpoints for this study were assessed at baseline, 0–6 months, 7–12 months and 13–18 months post-index date and included:

(i) The percentage of patients who had neurology outpatient contacts, defined as a record of any contact on the HES outpatient file with the specialty neurology ('tretspef' = 400), as well as the number of contacts normalized to 100 treatment-months.
(ii) LEDD, defined as any change in PD therapy that resulted in a change in LEDD. The LEDD was estimated using the CPRD dosage file and the conversion factors in Tomlinson et al. [20] for all PD medications except entacapone or opicapone.
(iii) Percentage of patients prescribed any sleep medication.

Healthcare resource use was assessed at 6-monthly intervals for the first 18 months and any use post-18 months was noted. Where sufficient patient numbers remained on drug, normalization of number of visits per 100 treatment-months allowed independent assessment of the outcome regardless of the duration of follow-up post-18 months. Other endpoints were also assessed: percentage of patients having a visit and number of visits normalized per 100 treatment-months for all outpatient and non-neurology visits, A&E attendances, and use of sleep medication.

Statistical analyses

Exploratory statistical comparisons between the opicapone and entacapone groups were conducted using chi-squared tests. Comparisons for continuous variables were conducted using *t*-tests for variables normally distributed, and Wilcoxon signed-rank tests for variables non-normally distributed. No multiplicity adjustment of *p* values was conducted for statistical testing due to the exploratory nature of this retrospective cohort study; a standard alpha level of 0.05 was used, however, *p* values should be interpreted with caution. Only observed and available data were used and are included in the appendices alongside the corresponding average, median, standard deviation (SD), interquartile range and 95% confidence interval (CI) and *p* values (where appropriate).

In addition, generalized linear regression analyses were performed for the primary endpoints (number of neurology outpatient visits, any change in LEDD in mg) and logistic regressions were performed for the secondary endpoint (sleep medication dose reduction: yes or no), adjusting for baseline sex, age in 10-year intervals, young onset of PD (diagnosis at <50 years of age), years from PD diagnosis to index in 5-year intervals, baseline HCRU, baseline medications, and concomitant medications. The full list of covariates is included in Table S1. Microsoft SQL and SAS version 9.4 (SAS Institute Inc.) were used for data cleaning and analysis.

RESULTS

Patient disposition and baseline characteristics

Of the 209,670 patients permanently registered in the CPRD with a PD diagnosis and end-of-dose motor fluctuations, 7341 adult patients had ≥1 prescription of entacapone or opicapone during the observation period (Figure S1). After applying the exclusion criteria, the final dataset included 173 patients who initiated COMT inhibition with opicapone (first-line opicapone) and 2429 who initiated COMT inhibition with entacapone (first-line entacapone). Following propensity matching, 173 first-line opicapone patients were compared to 433 first-line entacapone patients. Only post-matching results are reported in this study; however, the same trend was observed when all data were analysed prior to any matching strategy being applied.

Baseline characteristics for the matched populations prior to initiation of COMT inhibitor therapy are provided in Table 1 and Table S2. Patients in the opicapone group had significantly higher HCRU at baseline compared with the entacapone group when measured in terms of percentage of patients who had any outpatient visit for the following departments: neurology (94.2% vs. 72.3%; $p < 0.001$), any (94.8% vs. 78.8%; $p < 0.001$), non-neurology (69.4% vs. 55.0%; $p = 0.002$) and any A&E attendances (33.5% vs. 25.2%; $p = 0.007$). Patients in the opicapone group also had a statistically significant higher mean (95% CI) total levodopa dose (763.3 [698.5, 828.0] mg vs. 746.9 [709.1, 784.8] mg; $p < 0.001$) and a higher LEDD compared with the entacapone group (964.2 [892.1, 1036.4] mg vs.

TABLE 1 Baseline characteristics (120 days prior to index date) in the matched opicapone and entacapone populations.

	Opicapone group (*N* = 173)	Entacapone group (*N* = 433)	Standardized difference	*p* value
Age, mean ± SD (95% CI) years	68.5 ± 10.0 (67.0, 70.0)	69.8 ± 9.9 (68.9, 70.7)	0.01	0.069
Sex: male, *n* (%)	112 (64.7)	287 (66.3)	−0.03	0.776
Time since PD diagnosis, mean ± SD (95% CI) years	8.34 ± 5.62 (7.50, 9.18)	7.97 ± 5.80 (7.42, 8.52)	−0.03	0.208
Sleep medications, *n* (%)	37 (21.4)	99 (22.9)	−0.04	0.694

Note: *p* values are derived from *t*-tests or Wilcoxon rank-sum tests (depending on normality distribution assumptions being met or not) for continuous variables and from chi-squared tests for categorical variables. Standardized difference was calculated as described in Austin, 2009 [35].
Abbreviations: CI, confidence interval; PD, Parkinson's disease.

946.7 [897.7, 995.8] mg; $p < 0.001$). The LEDDs for dopamine agonists were similar in the two groups (Table S2).

The mean (95% CI) duration of follow-up was 1.2 (1.0, 1.3) years for the opicapone and 1.9 (1.7, 2.0) years for the entacapone group.

Post-baseline hospital visits

After initiating COMT inhibition treatment, first-line opicapone patients had fewer neurology outpatient visits than first-line entacapone patients. This was evidenced by (i) the significantly lower percentage of opicapone patients who had ≥1 neurology outpatient visit in each 6-month period and (ii) the greater and more consistent reduction in the normalized number of visits (visits per 100 treatment-months) compared with the entacapone group (Figure 1, Table S3). The normalized mean (95% CI) number of neurology outpatient visits decreased in the first 6 months of treatment with opicapone (from 24.9 [21.4, 28.3] to 16.6 [12.6, 20.6] visits per 100 treatment-months), whilst it increased with entacapone (from 16.7 [15.0, 18.5] to 20.3 [17.8, 22.8] visits per 100 treatment-months). In a longitudinal analysis of patients who had data for >18 months, the normalized mean (95% CI) number of neurology outpatient visits remained lower than baseline for patients in both the opicapone group (9.7 [6.0, 13.4] visits per 100 treatment-months) and the entacapone group (13.3 [10.5, 16.1] visits per 100 treatment-months; $p < 0.001$ [Table S3]). Regression analyses of post-index date neurology outpatient visits showed that, while controlling for other covariates (Table S1), first-line opicapone patients had 18.5% [0.1%, 33.6%] fewer neurology outpatient visits within 6 months of initiation compared to first-line entacapone patients ($p = 0.049$). The beneficial

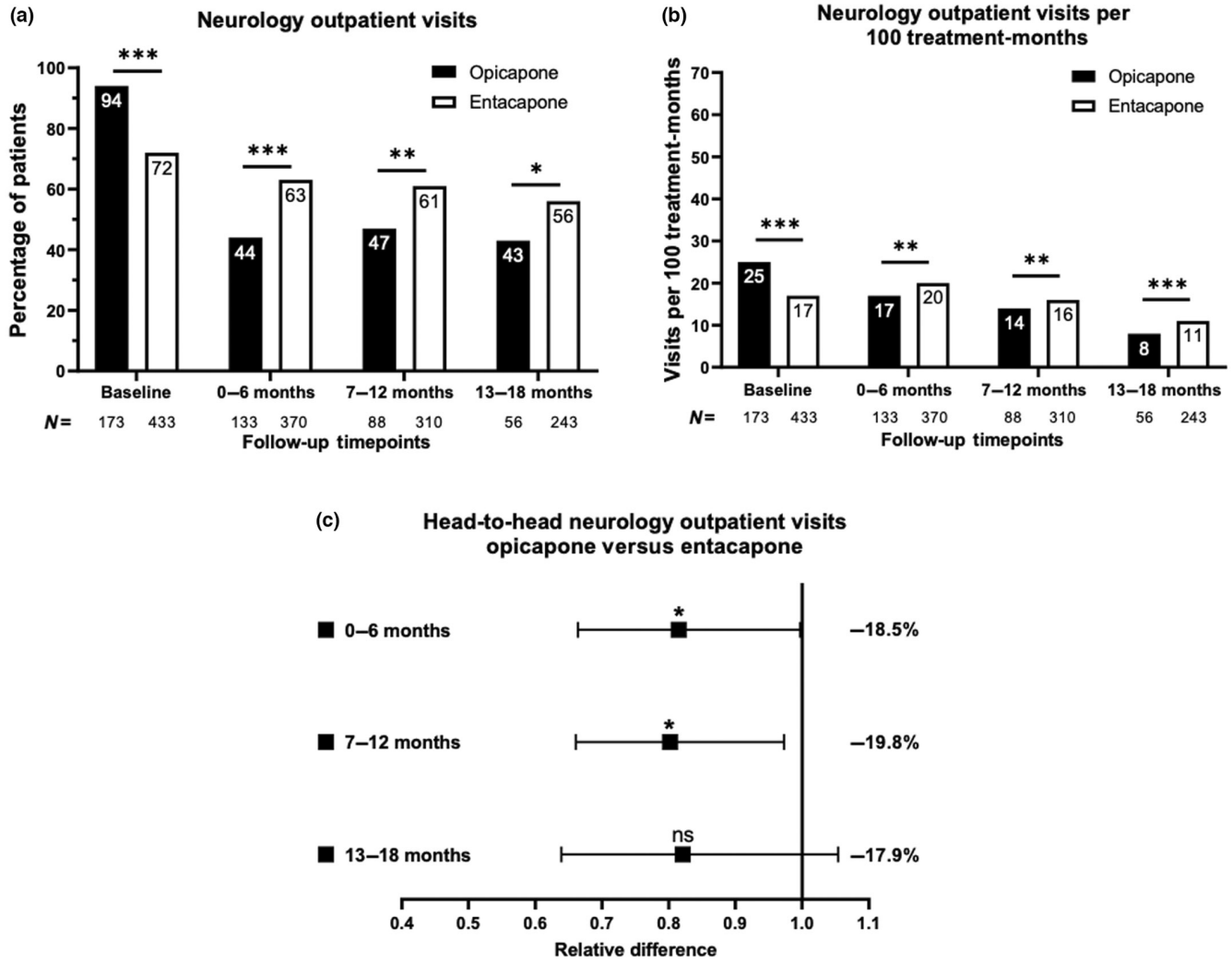

FIGURE 1 Neurology outpatient visits over 18 months of follow-up. (a) Percentage of patients who had ≥1 visit. (b) Number of visits per patient normalized to 100 treatment-months. (c) Regression analyses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. p values in a and b are derived from Wilcoxon rank-sum tests; p values in c are derived from generalized linear models. For the generalized linear regression analyses, mean (95% confidence interval) relative difference is shown. Entacapone outcomes are normalized to 1, points to the left of this line favour treatment with opicapone. Covariates included: sex, age in 10-year intervals, young onset of Parkinson's disease (PD; first diagnosis at <50 years of age), years from PD diagnosis to index in 5-year intervals, baseline healthcare resource utilization and baseline medications including sleep medication.

effect of opicapone versus entacapone on post-treatment resource utilization was consistent within 12 and 18 months of initiation (Figure 1c). Table S4 provides the list of covariates fitted in regression analyses that showed a statistically significant effect across all time points evaluated.

Similar findings were observed when all outpatient visits (any department) were analysed (Figure 2, Table S5). Whereas the mean (95% CI) normalized number of visits decreased over the first 6 months from 65.8 (56.7, 74.8) to 49.6 (38.7, 60.6) per 100 treatment-months with opicapone, it increased from 41.4 (37.1, 45.7) to 59.3 (52.5, 66.1) visits per 100 treatment-months for first-line entacapone patients ($p = 0.014$). In patients with data for >18 months, the mean (95% CI) normalized number of outpatient visits remained lower for first-line opicapone versus first-line entacapone patients (24.4 [15.7, 33.1] vs. 45.1 [30.9, 59.3] visits per 100 treatment-months, respectively; $p < 0.001$ [Table S5]). Analysis of non-neurology outpatient department normalized visits showed no significant differences between groups until 13–18 months, when patients in the opicapone group had significantly fewer visits than those in the entacapone group (26.5 [15.6, 37.3] vs. 37.1 [29.9, 44.3] visits per 100 treatment-months, respectively; $p = 0.039$ [Table S6]).

While the percentage of opicapone-treated patients who had any A&E attendances reduced from 33.5% at baseline to 13.6% over 18 months, the percentage of entacapone-treated patients showed a smaller reduction over the same time period (25.2% at baseline to 21.3% over 18 months; Figure 3, Table S7). The normalized number of A&E attendances tended to decrease or remain stable over time for patients in the opicapone-treated group but doubled during the first 6 months for entacapone-treated patients (Figure 3, Table S7). For patients with ≥18 months of data, the mean (95% CI) normalized number of A&E attendances was 1.35 (0.2, 2.5) in the opicapone and 8.5 (6.3, 10.8) visits per 100 treatment-months for the entacapone group ($p < 0.001$; Table S7).

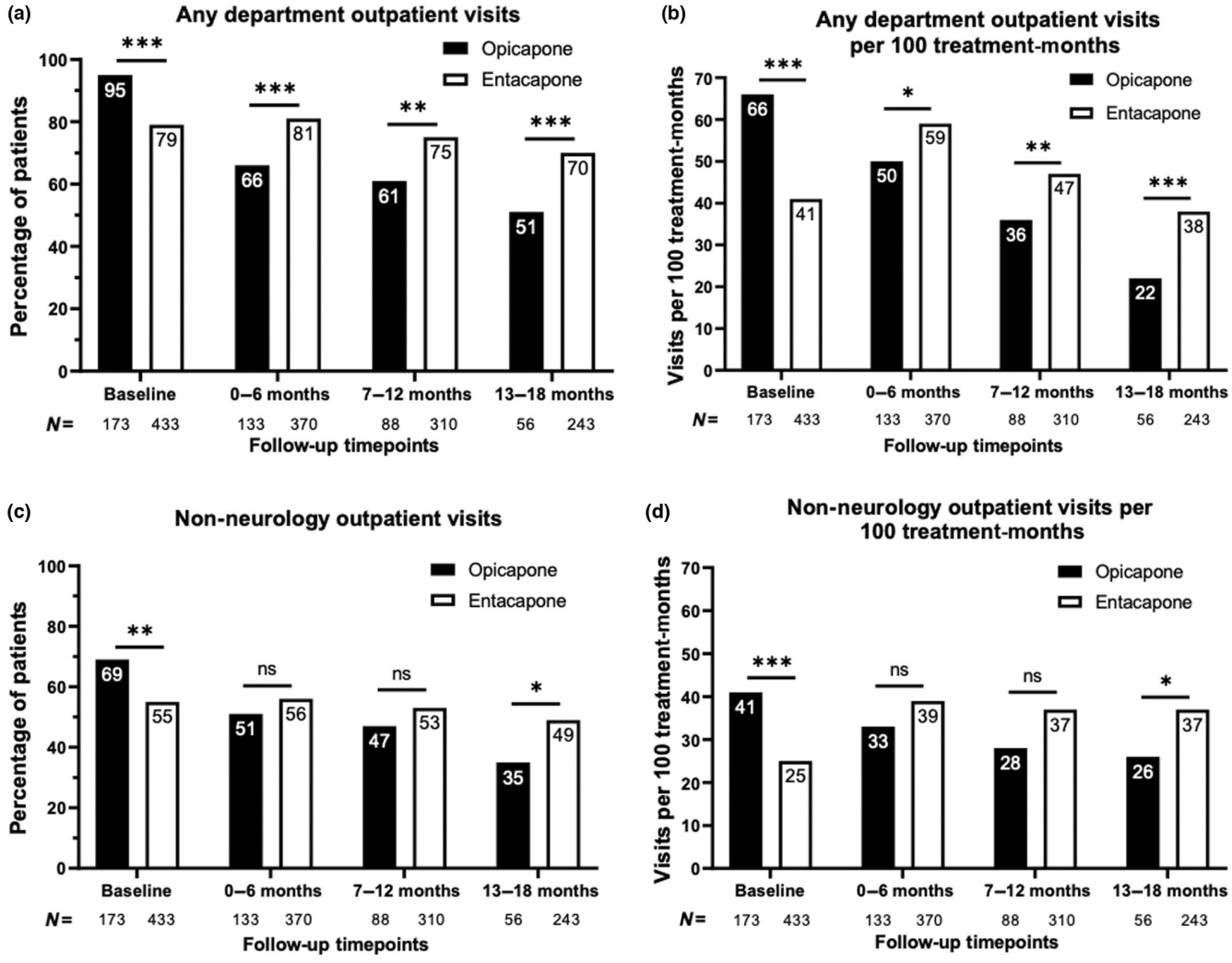

FIGURE 2 Overall outpatient visits over 18 months of follow-up. (a) Percentage of patients who had ≥1 outpatient (any department) visit, (b) number of outpatient (any department) visits per patient normalized to 100 treatment-months, (c) Percentage patients who had ≥1 outpatient (non-neurology department) visit and (d) number of outpatient (non-neurology department) visits per patient normalized to 100 treatment-months. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ derived from Wilcoxon rank-sum tests.

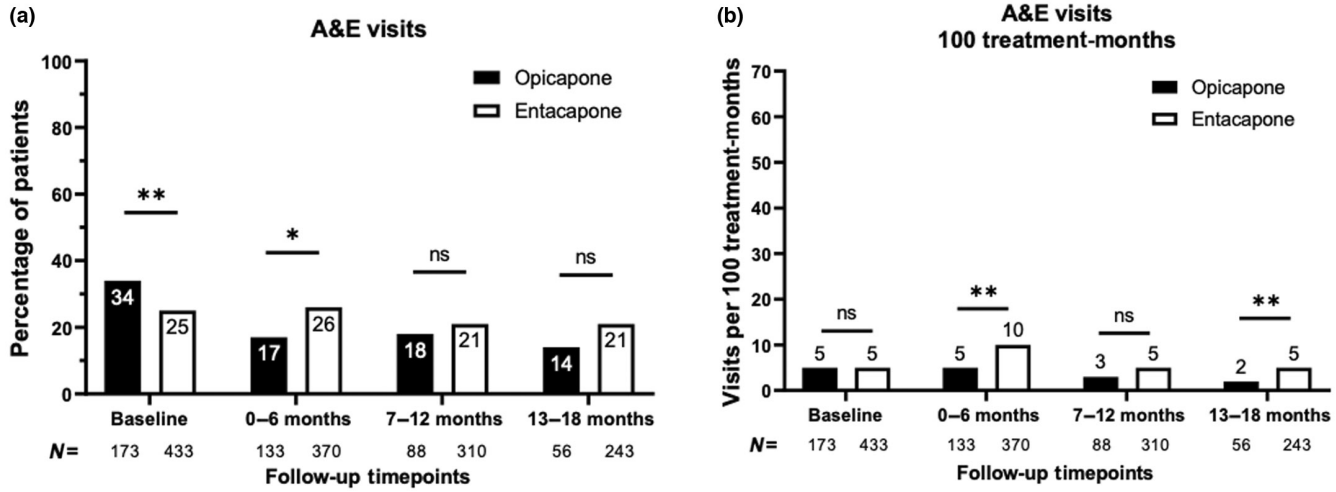

FIGURE 3 Any accident and emergency (A&E) attendances over 18 months of follow-up. (a) Percentage of patients who had ≥1 visit and (b) number of visits per patient normalized to 100 treatment-months. ns, non-significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ derived from Wilcoxon rank-sum tests.

Post-baseline medication use

The LEDDs (all antiparkinsonian medications) were reduced in both the opicapone- and entacapone-treated groups (Figure 4, Table S8). Whereas the mean (95% CI) LEDD tended to decrease over the first year and then stabilize in the opicapone group (from 964.2 [892.1, 1036.4] mg at baseline to 711.9 [629.2, 794.6] mg at month 12 and 709.8 [608.6, 811.0] mg at month 18), patients in the entacapone group had an initial decrease in the first 6 months (from 946.7 [897.7, 995.9] mg to 809.9 [768.0, 851.9] mg) followed by dose increases between 6 and 18 months (reaching 847.4 [793.5, 901.3] mg at month 18; Table S8). Dose reductions from baseline were significantly larger for the opicapone versus the entacapone group at 7–12 months ($p=0.002$) and 13–18 months ($p=0.015$) post-index date. Regression analyses of LEDD showed that, while controlling for other covariates, first-line opicapone patients had a 10.6% (2.7%, 17.8%) lower LEDD at 6 months compared to first-line entacapone patients ($p=0.009$). The beneficial effect of opicapone versus entacapone on post-treatment LEDD level consistently increased over time and the difference remained significant ($p<0.0001$) with an estimated reduction of 25.6% (17.5%, 33.0%) at 12 months and of 30.5% (20.3%, 39.3%) at 18 months (Figure 4d). There was no consistent statistically significant effect of any covariates in this regression analysis.

Analysis of levodopa therapy and dopamine agonists showed similar trends to the overall LEDD effect, although no significant differences were reported for the dopamine agonists analysis (Figure 4, Table S8). First-line opicapone patients reduced their mean (95% CI) levodopa daily doses from 763.3 (698.5, 828.0) mg at baseline to 568.2 (499.4, 636.9) mg at months 7–12 and 582.6 (494.4, 670.8) mg at months 13–18; reductions were significantly larger with opicapone versus entacapone at 7–12 months ($p=0.006$) and 13–18 months post-baseline ($p<0.001$; Figure 4, Table S8).

No significant impact nor differences between COMT inhibitor treatment groups were observed regarding concomitant sleep medication doses (Figure 5, Table S9).

DISCUSSION

To date, any clinical and health economic comparisons of the benefits of COMT inhibition with opicapone versus entacapone have previously been hindered by the limited availability of directly comparative data. Using a retrospective observational cohort study design in algorithm-matched patients, this study indicates that initiating COMT inhibition with opicapone as first-line COMT inhibitor therapy is likely to decrease HCRU, as well as lowering the LEDD, versus initiation of COMT inhibition with entacapone. Initiation of opicapone was associated with a lower number of outpatient neurology and general visits, A&E attendances as well as progressive reduction of LEDD versus initiation of entacapone. No significant impact was seen on the use of sleep medications.

Even after propensity matching, patients in the opicapone group had a higher number of hospital outpatient visits as well as higher LEDD at baseline than those who initiated COMT inhibition with entacapone, suggesting that patients initiated on opicapone had a greater 'severity' of disease. This suggests a tendency of clinicians to reserve opicapone prescriptions for the more 'difficult' patients, who they do not believe will derive enough benefit from entacapone. Such observations align with National Institute of Health and Care Excellence (NICE) [21] and local hospital [22] recommendations to start with entacapone because of the availability of generic forms and their lower medication price. In this respect, it is noteworthy that prescription data (collected during the same collection period) found that branded levodopa/carbidopa/entacapone (Stalevo) accounted for 56.5% of all entacapone use in England, thereby counteracting much of the cost savings of a generic product.

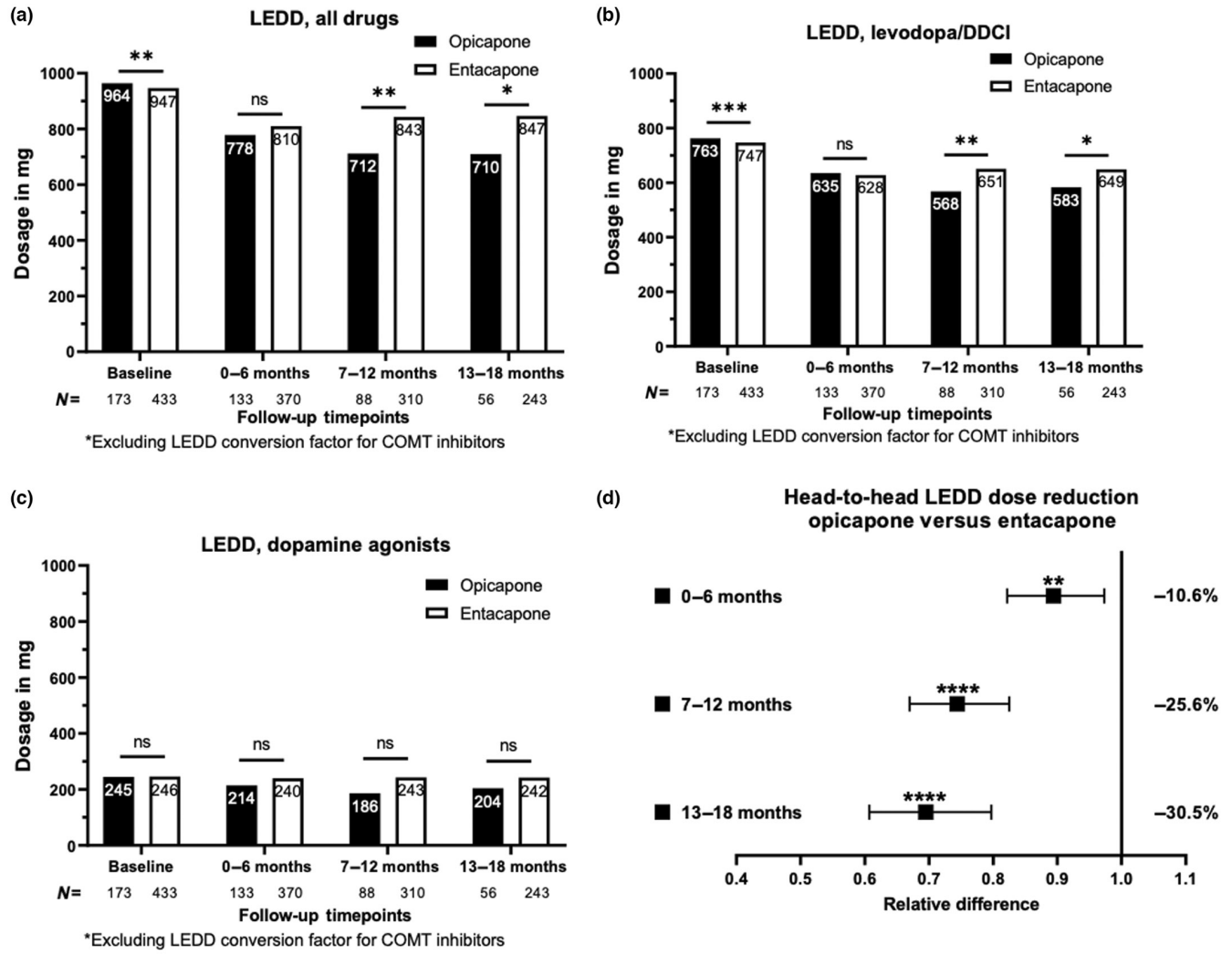

FIGURE 4 Mean levodopa equivalent daily doses (LEDD). (a) All antiparkinsonian medications. (b) Levodopa combinations. (c) Dopamine agonists. (d) Regression analyses. ns, non-significant, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. *p* values in a, b and c are derived from Wilcoxon rank-sum tests; *p* values in d are derived from generalized linear models. For the generalized linear regression analyses, mean (95% confidence interval) relative difference is shown. Entacapone outcomes are normalized to 1, points to the left of this line favour treatment with opicapone. Covariates included: sex, age in 10-year intervals, young onset of PD (first diagnosis at <50 years of age), years from PD diagnosis to index in 5-year intervals, baseline healthcare resource utilization and baseline medications including sleep medication, painkillers, and antidepressants.

After controlling for various baseline factors, head-to-head regression analysis demonstrated that patients in the opicapone-treated group had 18.5% fewer neurology outpatient visits within 6 months of initiation compared to entacapone-treated patients. Indeed, while there was a marked reduction in HCRU for patients in the opicapone group during the first 6 months, the number of visits per patient in the entacapone group increased compared to baseline in all HCRU parameters. Of note, the overall reduction in outpatient visits (any department) appears to have been primarily driven by the reduction in neurology visits, although the number of non-neurology outpatient visits was also significantly lower for the opicapone group at 13–18 months. Although the once-daily dosing of opicapone as compared with multiple-daily dosing of entacapone could also have driven the lower number of outpatient visits versus entacapone (which should be taken with each levodopa dose), the differences in HCRU in the early months post-COMT inhibitor initiation are also consistent with the idea that pwPD receiving entacapone often require frequent follow-up for tolerability post-initiation. For example, a Cochrane systematic review found that treatment with entacapone significantly increased the likelihood that participants would withdraw due to adverse events compared to placebo (Peto odds ratio 1.52, $p = 0.02$) [23]. While similar systematic data are not yet available for opicapone, rates of clinical trial discontinuation due to adverse events appear to favour opicapone (discontinuation rates of 5%–14% with open-label opicapone treatment [24, 25] versus 14%–24% with open-label entacapone treatment [26, 27]).

In the longer-term, the reduced HCRU with opicapone use is further supported by the UK population of the OPTIPARK study, where the sustained effectiveness of opicapone on PD symptoms and overall health allowed for a significant reduction in total treatment costs

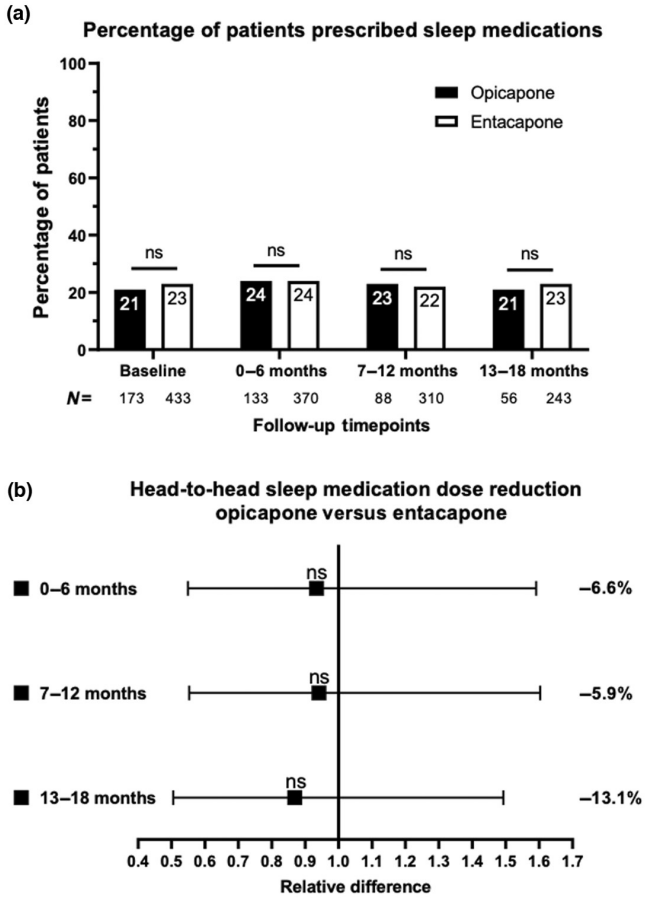

FIGURE 5 Use of sleep medications. (a) Percentage of patients on sleep medications. (b) Generalized linear regression analyses. ns, non-significant, $^{*}p < 0.05$. *p* values in 5a are derived from Wilcoxon rank-sum tests; *p* values in 5b are derived from logistic regressions. Sleep medications included alprazolam, clobazam, clonazepam, diazepam, loprazolam, nitrazepam, temazepam, zolpidem and zopiclone. For the logistic regression analyses, mean (95% confidence interval) relative difference is shown. Entacapone outcomes are normalized to 1, points to the left of this line favour treatment with opicapone. Covariates included: sex, age in 10-year intervals, young onset of PD (first diagnosis at <50 years of age), years from PD diagnosis to index in 5-year intervals, baseline healthcare resource utilization and baseline medications including painkillers and antidepressants.

[28]. In that study, hospital and residential services costs accounted for almost a quarter (23%) of total service costs and the cost savings following opicapone initiation were mainly driven by reductions in these services [28]. To the best of our knowledge, our data are the first to indicate a difference in the number of A&E attendances (as well as the other parameters) following initiation of opicapone versus entacapone. Interestingly, A&E attendances with opicapone are consistently reduced at any time point analysed, including at the additional >18-month time point. Conversely, entacapone-treated patients had an increase in the normalized number of A&E attendances per patient immediately after initiation (0–6 months) and after the 18-month time point. Common reasons for A&E attendance in pwPD typically include falls, fractures, infections, and neuropsychiatric symptoms [29, 30], and the differences between the two COMT inhibitors on this outcome merits further study.

In line with other studies [10, 28], patients in the opicapone group reduced their LEDD by approximately 20% in the first 6 months (a mean reduction of 186 mg in this study) and by 26% (254 mg) at 13–18 months. While the initial decrease in levodopa dosing to adjust for tolerability is expected with COMT inhibition, the observation that pwPD could better maintain their long-term levodopa dosing regimen with opicapone use than with entacapone confirms and extends observations from the open-label phase of the BIPARK-2 study where 63% of opicapone-treated pwPD continued to receive the same dose of levodopa over 1 year [31]. However, our data somewhat differ from the NOMESAFE open-label entacapone study where LEDD decreased over the 12 months of treatment but then (as in the present study) tended to increase thereafter [26]. Reasons for the discrepancy in the earlier months may include the differing time points for evaluation. No significant impact nor differences between treatment groups were observed regarding concomitant sleep medication usage. This is perhaps not surprising as most of the sleep medications were for insomnia (sleep fragmentation, onset, etc.) and not for reducing night-time disability where there is evidence of benefit of bedtime dosing of a COMT inhibitor [25, 32, 33].

Strengths of the study lie in its pragmatic, real-world setting, the use of the nationally curated, well-established CPRD/HES-linked database and the matched sampling approach, which was used to reduce variability and align baseline characteristics of the two treated cohorts. Recent audits of UK PD services indicate that only 1.9% of patients are managed in the community by nurses without consultant input [34], thereby supporting the generalizability of the hospital-based data to the wider population of pwPD. As an additional strength, the results were supported by a consistent trend when analysing pre-matched cohort data. However, the size of the available opicapone cohort limited the overall study sample size and a larger sample size of the same patient population would be expected to increase the power of statistical analyses, which were only considered exploratory in this study. The study is also limited by duration which was constrained by launch of opicapone at one end and by the COVID pandemic at the other end. Future evaluations would not be constrained in the same way and would presumably include more pwPD as experience with using opicapone continues to grow in the United Kingdom. Other limitations lie in the databases and type of information recorded, for example, a lack of granularity in the precise reasons for hospital visits (e.g., reasons for A&E attendance), which would have helped us understand if the reasons for each visit were associated with PD progression, PD medication, or something else. Likewise, we do not know the rates of COMT inhibitor discontinuation in either group. In the United Kingdom, a proportion of pwPD are managed by geriatricians and it was not possible to differentiate between PD and non-PD-related geriatric visits; consequently, the databases used for this evaluation may have fluctuating quality and low internal validity. Finally, it should be noted that, while the

longitudinal post-18-month analyses support the continued trend to reduced HCRU with opicapone versus entacapone, the analyses are based on varying durations of follow-up which had an impact on the variance observed.

In summary, this retrospective observational cohort study is the first to indicate, using head-to-head 'real-life' data, that initiating COMT inhibition with opicapone as first-line COMT inhibitor therapy is likely to decrease the need for post-treatment HCRU, as well as lowering the LEDD, versus initiation of COMT inhibition with entacapone. Since hospital costs are a key driver for PD-associated costs, this suggests that the current secondary position of opicapone to entacapone in local PD algorithms due to basic prescribing costs should be reconsidered. The study design provides an additional framework for cost-effectiveness modelling and this analysis will be published separately.

AUTHOR CONTRIBUTIONS

Valentina Di Foggia and Glynn Harrison-Jones conceived the study and were involved in execution, analysis and interpretation of results. K. Ray Chaudhuri and Francesca Morgante provided initial feedback on the study protocol. Guillermo Castilla-Fernández assisted with statistical planning of the study and Xiaocong Li Marston was involved in data analysis. Valentina Di Foggia wrote the first draft of the manuscript. All authors were involved in interpretation of the data and in critical review and approval of the manuscript and take accountability for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Glynn Harrison-Jones, Guillermo Castilla-Fernández and Valentina Di Foggia are employed by BIAL. Xiaocong Li Marston is employed by OPEN Health who were contracted by BIAL for this work. K. Ray Chaudhuri reports advisory board for AbbVie, UCB, GKC, Bial, Cynapsus, Lobsor, Stada, Zambon, Profile Pharma, Sunovion, Roche, and Therevance, Scion, as well as honoraria for lectures for AbbVie, Britannia, UCB, Zambon, Novartis, Boehringer Ingelheim, Bial, Kyowa Kirin and SK Pharma, and grants (Investigator Initiated) from Bial, EU Horizon 2020, Parkinson's UK, the National Institute of Health Research (NIHR), Parkinson's Foundation and the Wellcome Trust, and royalties or licences (ongoing) from Oxford (book), Cambridge publishers (book) and the MAPI institute (KPPS, PDSS 2), and payment for expert testimony for the General Medical Council (UK). Francesca Morgante has received speaking honoraria from Abbvie, Medtronic, Boston Scientific, Bial, Merz, travel grants from the International Parkinson's disease and Movement Disorder Society, advisory board fees from Abbvie, Merz and Boston Scientific, consultancy fees from Boston Scientific, Merz and Bial, research support from the NIHR, UKRI, Boston Scientific, Merz and Global Kinetic, and royalties for the book '*Disorders of Movement*' from Springer. She is member of the Editorial Boards of *Movement Disorders*, *Movement Disorders Clinical Practice* and the *European Journal of Neurology*.

DATA AVAILABILITY STATEMENT

Raw data were obtained from the CPRD and NHS (HES) under licence and are not publicly available. Copyright© 2023, re-used with the permission of The Health & Social Care Information Centre. All rights reserved. These data are provided under licence via Harvey Walsh Ltd from NHS Digital (Data Sharing Agreement: DARS-NIC-05934-M7V9K). All available analyses are provided in the supplementary appendices.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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