

Supplementary Appendix

Table S1. List of covariates evaluated within the generalised linear regression analysis of the primary outcomes. EOPD, early-onset Parkinson's Disease.

Variable
Age at index, years
≤ 50 years
51 ~ 60 years
61 ~ 70 years
71 ~ 80 years
> 80 years
Age at onset of Parkinson disease
> 50
≤ 50 (EOPD)
Male (vs. Female)
Duration of Parkinson disease, years
0 ~ 5 years
5 ~ 10 years
10 ~ 15 years
15 ~ 20 years
20 ~ 25 years
> 25 years
Baseline HCRU
> 2 neurology outpatient department visits per patient-year (vs. ≤ 2)
> 5 non-neurology outpatient department visits per patient-year (vs. ≤ 5)
Any neurology department, elective inpatient admission (yes vs. no)
Number of admissions: neurology department, elective inpatient admission
Any neurology department, non-elective inpatient admission (yes vs. no)
Any non-neurology department, elective inpatient admission (yes vs. no)
Number of admissions: non-neurology department, elective inpatient admission
Any non-neurology department, non-elective inpatient admission (yes vs. no)
Number of admissions: non-neurology department, non-elective inpatient admission
Any A&E attendance (yes vs. no)
Number of A&E attendance
Baseline medications
Sleep medication (yes vs. no)
Painkillers (yes vs. no)
Antidepressants (yes vs. no)
Amantadine (yes vs. no)
Anticholinergics (yes vs. no)
Antihypotensives (yes vs. no)
Antidiarrheal (yes vs. no)
Anti-nausea/emetic (yes vs. no)
Sleep medication at 6 months post-index
Dose decrease
Discontinue
Dose increase

Table S2. Baseline outcomes characteristics (120 days prior to index date) in the matched opicapone and entacapone populations.

Variable	Statistic	Post-Matching			
		First-line opicapone (N=173)	First-line entacapone (N=433)	Standardised Difference	P value
Outpatient Visit: Neurology Dept					
Patients who had ≥ 1 visit	N (%)	163 (94.2%)	313 (72.3%)	0.61	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	24.86 (23.22)	16.74 (18.15)	0.24	<0.001
	Median (Q1, Q3)	16.67 (8.33, 33.33)	16.67 (0.00, 25.00)		
	Min, Max	0.00, 158.33	0.00, 133.33		
	95% CI	21.37, 28.34	15.03, 18.46		
Outpatient Visit: Any Dept					
Patients who had ≥ 1 visit	N (%)	164 (94.8%)	341 (78.8%)	0.52	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	65.75 (60.22)	41.38 (45.87)	0.27	<0.001
	Median (Q1, Q3)	50.00 (25.00, 91.67)	25.00 (8.33, 58.33)		
	Min, Max	0.00, 266.67	0.00, 275.00		
	95% CI	56.71, 74.79	37.05, 45.71		
Outpatient Visit: Non-Neurology Dept					
Patients who had ≥ 1 visit	N (%)	120 (69.4%)	238 (55.0%)	0.30	0.002
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	40.90 (50.83)	24.63 (36.39)	0.33	<0.001
	Median (Q1, Q3)	25.00 (0.00, 58.33)	8.33 (0.00, 33.33)		
	Min, Max	0.00, 233.33	0.00, 200.00		
	95% CI	33.27, 48.52	21.20, 28.07		
A&E attendances					
Patients who had ≥ 1 attendance	N (%)	58 (33.5%)	109 (25.2%)	0.18	0.007
Number of attendances per 100 treatment-months (for all patients)	Mean (SD)	5.39 (9.41)	4.52 (13.38)	-0.34	0.008
	Median (Q1, Q3)	0.00 (0.00, 8.33)	0.00 (0.00, 0.00)		
	Min, Max	0.00, 50.00	0.00, 150.00		
	95% CI	3.98, 6.81	3.26, 5.79		
LEDD (mg)					
All drugs	N	171	432		
	Mean (SD)	964.2 (480.6)	946.7 (519.3)	-0.01	<0.001
	Median (Q1, Q3)	881.7 (618.3, 1190.0)	868.3 (568.7, 1180.8)		
	Min, Max	83.3, 2792.7	23.3, 3625.0		
	95% CI	892.1, 1036.4	897.7, 995.8		
Levodopa therapy	N	170	432		
	Mean (SD)	763.3 (430.2)	746.9 (400.7)	0.09	<0.001
	Median (Q1, Q3)	670.8 (490.7, 938.3)	678.3 (466.7, 979.2)		
	Min, Max	37.5, 2602.1	8.8, 2576.7		
	95% CI	698.5, 828.0	709.1, 784.8		
Dopamine agonists	N	87	199		
	Mean (SD)	245.0 (170.4)	245.7 (215.8)	-0.07	0.089
	Median (Q1, Q3)	210.0 (140.0, 300.0)	198.0 (112.0, 304.0)		
	Min, Max	9.3, 1125.0	14.0, 2000.0		
	95% CI	208.7, 281.4	215.0, 276.4		

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables. LEDD, Levodopa Equivalent Daily Dose. N in the LEDD calculations represents the number of patients in each cohort who had data available for the specific variable (all drugs, levodopa and dopamine agonist therapy)

Table S3: Neurology department outpatient visits over 18 months of follow up

Outpatient Visits: Neurology Dept	Statistic	Post-Matching		
		First-line opicapone (N=173)	First-line entacapone (N=433)	P value
Baseline				
Patients who had ≥ 1 visit	N (%)	163 (94.2%)	313 (72.3%)	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	24.86 (23.22)	16.74 (18.15)	<0.001
Number of visits per 100 treatment-months (for all patients)	Median (Q1, Q3)	16.67 (8.33, 33.33)	16.67 (0.00, 25.00)	
	Min, Max	0.00, 158.33	0.00, 133.33	
	95% CI	21.37, 28.34	15.03, 18.46	
	95% CI	12.62, 20.64	17.78, 22.84	
0-6 months post-index				
Number of patients with a follow-up length ≥ 0 months, N		173	433	
Patients who had any visits	N (%)	76 (43.9%)	272 (62.8%)	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	16.63 (27.73)	20.31 (26.77)	0.002
	Median (Q1, Q3)	0.00 (0.00, 16.63)	16.63 (0.00, 33.27)	
	Min, Max	0.00, 166.33	0.00, 216.22	
	95% CI	12.62, 20.64	17.78, 22.84	
7-12 months post-index				
Number of patients with a follow-up length ≥ 6 months, N		133	370	
Patients who had any visits	N (%)	62 (46.6%)	226 (61.2%)	0.003
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	13.99 (29.05)	15.84 (24.18)	0.003
	Median (Q1, Q3)	0.00 (0.00, 16.72)	16.72 (0.00, 16.72)	
	Min, Max	0.00, 217.41	0.00, 234.13	
	95% CI	9.63, 18.34	13.56, 18.13	
13-18 months post-index				
Number of patients with a follow-up length ≥ 12 months, N		88	310	
Patients who had any visits	N (%)	38 (43.2%)	172 (55.5%)	0.041
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	8.37 (21.50)	11.33 (20.92)	<0.001
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 16.63)	
	Min, Max	0.00, 133.06	0.00, 182.96	
	95% CI	5.14, 11.60	9.35, 13.31	
After 18 months post-index				
Number of patients with a follow-up length ≥ 18 months, N		56	243	
Patients who had any visits	N (%)	37 (66.1%)	166 (68.3%)	0.746
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	9.67 (24.51)	13.31 (29.63)	<0.001
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 16.63)	
	Min, Max	0.00, 146.94	0.00, 351.20	
	95% CI	5.99, 13.35	10.51, 16.11	

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.

Table S4: List of covariates which caused a significant impact on generalised linear regression outcomes at all timepoints assessed for the primary outcomes

Variable Category	Variable	Follow-ups length	Estimate	95% CI		P value	+/- for Interpretation
				Low	High		
Neurology outpatient visits							
Baseline HCRU	> 5 non-neurology outpatient department visits per patient-year (vs. ≤ 5)	0 -6 months	1.442	1.177	1.766	0.0004	+44.2%
		7 -12 months	1.689	1.294	2.206	0.0001	+68.9%
		13 - 18 months	1.462	1.101	1.941	0.0086	+46.2%

Table S5: Any department outpatient visits over 18 months of follow up

Outpatient visits: Any dept	Statistic	Post-Matching		
		First-line opicapone	First-line entacapone	P value
Baseline				
Patients who had ≥ 1 visit	N (%)	164 (94.8%)	341 (78.8%)	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	65.75 (60.22)	41.38 (45.87)	<0.001
Number of visits per 100 treatment-months (for all patients)	Median (Q1, Q3)	50.00 (25.00, 91.67)	25.00 (8.33, 58.33)	
	Min, Max	0.00, 266.67	0.00, 275.00	
	95% CI	56.71, 74.79	37.05, 45.71	
	95% CI	164 (94.8%)	341 (78.8%)	
0-6 months post-index				
Number of patients with a follow-up length ≥ 0 months, N		173	433	
Patients who had any visits	N (%)	114 (65.9%)	351 (81.1%)	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	49.63 (72.86)	59.29 (71.57)	0.014
	Median (Q1, Q3)	16.63 (0.00, 66.53)	33.27 (16.63, 83.16)	
	Min, Max	0.00, 615.40	0.00, 453.32	
	95% CI	38.70, 60.57	52.53, 66.05	
7-12 months post-index				
Number of patients with a follow-up length ≥ 6 months, N		133	370	
Patients who had any visits	N (%)	81 (60.9%)	277 (75.1%)	0.002
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	35.83 (59.15)	47.07 (71.74)	0.002
	Median (Q1, Q3)	0.00 (0.00, 50.17)	16.72 (0.00, 66.90)	
	Min, Max	0.00, 301.03	0.00, 702.40	
	95% CI	26.95, 44.70	40.29, 53.84	
13-18 months post-index				
Number of patients with a follow-up length ≥ 12 months, N		88	310	
Patients who had any visits	N (%)	45 (51.1%)	218 (70.3%)	<0.001
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	21.83 (54.21)	37.87 (67.61)	<0.001
	Median (Q1, Q3)	0.00 (0.00, 16.63)	0.00 (0.00, 49.90)	
	Min, Max	0.00, 316.02	0.00, 515.61	
	95% CI	13.70, 29.97	31.48, 44.25	
After 18 months post-index				
Number of patients with a follow-up length ≥ 18 months, N		56	243	
Patients who had any visits	N (%)	44 (78.6%)	207 (85.2%)	0.224
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	24.39 (57.83)	45.07 (150.23)	<0.001
	Median (Q1, Q3)	0.00 (0.00, 16.63)	0.00 (0.00, 49.90)	
	Min, Max	0.00, 316.02	0.00, 2728.88	
	95% CI	15.71, 33.07	30.88, 59.26	

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.

Table S6: Non-Neurology department outpatient visits over 18 months of follow up

Outpatient Visits: Non-neurology Dept	Statistic	Post-Matching		
		First-line opicapone	First-line entacapone	P value
Baseline				
Patients who had ≥ 1 visit	N (%)	120 (69.4%)	238 (55.0%)	0.002
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	40.90 (50.83)	24.63 (36.39)	<0.001
Number of visits per 100 treatment-months (for all patients)	Median (Q1, Q3)	25.00 (0.00, 58.33)	8.33 (0.00, 33.33)	
	Min, Max	0.00, 233.33	0.00, 200.00	
	95% CI	33.27, 48.52	21.20, 28.07	
	95% CI	120 (69.4%)	238 (55.0%)	
0-6 months post-index				
Number of patients with a follow-up length ≥ 0 months, N		173	433	
Patients who had any visits	N (%)	89 (51.4%)	241 (55.7%)	0.347
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	33.00 (62.50)	38.98 (62.45)	0.267
	Median (Q1, Q3)	16.63 (0.00, 49.90)	16.63 (0.00, 49.90)	
	Min, Max	0.00, 615.40	0.00, 453.32	
	95% CI	23.62, 42.38	33.08, 44.88	
7-12 months post-index				
Number of patients with a follow-up length ≥ 6 months, N		133	370	
Patients who had any visits	N (%)	63 (47.7%)	195 (53.3%)	0.243
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	28.41 (45.15)	36.94 (65.74)	0.190
	Median (Q1, Q3)	0.00 (0.00, 33.45)	16.72 (0.00, 50.17)	
	Min, Max	0.00, 217.41	0.00, 702.40	
	95% CI	20.67, 36.15	30.18, 43.70	
13-18 months post-index				
Number of patients with a follow-up length ≥ 12 months, N		88	310	
Patients who had any visits	N (%)	31 (35.2%)	153 (49.4%)	0.019
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	26.46 (51.16)	37.07 (64.59)	0.039
	Median (Q1, Q3)	0.00 (0.00, 33.27)	0.00 (0.00, 49.90)	
	Min, Max	0.00, 282.75	0.00, 461.17	
	95% CI	15.62, 37.30	29.85, 44.28	
After 18 months post-index				
Number of patients with a follow-up length ≥ 18 months, N		56	243	
Patients who had any visits	N (%)	31 (55.4%)	142 (59.5%)	0.533
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	45.45 (61.58)	58.02 (183.56)	0.938
	Median (Q1, Q3)	22.33 (0.00, 75.78)	16.63 (0.00, 66.53)	
	Min, Max	0.00, 282.75	0.00, 2623.92	
	95% CI	28.96, 61.94	34.53, 81.51	

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.

Table S7: Any accident and emergency (A&E) attendances over 18 months of follow up

Number of A&E attendances	Statistic	Post-Matching		
		First-line opicapone	First-line entacapone	P value
Baseline				
Patients who had ≥ 1 visit	N (%)	58 (33.5%)	109 (25.2%)	0.18
Number of visits per 100 treatment-months (for all patients)	Mean (SD)	5.39 (9.41)	4.52 (13.38)	-0.34
Number of visits per 100 treatment-months (for all patients)	Median (Q1, Q3)	0.00 (0.00, 8.33)	0.00 (0.00, 0.00)	
	Min, Max	0.00, 50.00	0.00, 150.00	
	95% CI	3.98, 6.81	3.26, 5.79	
	95% CI	58 (33.5%)	109 (25.2%)	
0-6 months post-index				
Number of patients with a follow-up length ≥ 0 months, N		173	433	
Patients who had any visits	N (%)	29 (16.8%)	112 (25.9%)	0.017
Number of A&E attendances per 100 treatment-months (for all patients)	Mean (SD)	5.01 (14.00)	9.76 (21.78)	0.005
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 16.63)	
	Min, Max	0.00, 99.80	0.00, 160.20	
	95% CI	2.91, 7.11	7.71, 11.82	
7-12 months post-index				
Number of patients with a follow-up length ≥ 6 months, N		133	370	
Patients who had any visits	N (%)	24 (18.0%)	79 (21.4%)	0.410
Number of A&E attendances per 100 treatment-months (for all patients)	Mean (SD)	2.90 (7.69)	5.04 (14.85)	0.189
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
	Min, Max	0.00, 33.45	0.00, 167.24	
	95% CI	1.75, 4.06	3.64, 6.44	
13-18 months post-index				
Number of patients with a follow-up length ≥ 12 months, N		88	310	
Patients who had any visits	N (%)	12 (13.6%)	66 (21.3%)	0.110
Number of A&E attendances per 100 treatment-months (for all patients)	Mean (SD)	1.92 (8.19)	5.00 (15.04)	0.005
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
	Min, Max	0.00, 66.53	0.00, 133.16	
	95% CI	0.69, 3.15	3.58, 6.42	
After 18 months post-index				
Number of patients with a follow-up length ≥ 18 months, N		56	243	
Patients who had any visits	N (%)	7 (12.5%)	88 (36.2%)	<0.001
Number of A&E attendances per 100 treatment-months (for all patients)	Mean (SD)	1.35 (7.91)	8.56 (23.45)	<0.001
	Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
	Min, Max	0.00, 66.53	0.00, 199.59	
	95% CI	0.16, 2.53	6.34, 10.77	

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.

Table S8: Mean levodopa equivalent daily doses (LEDD)

LEDD (mg) of	Statistic	Post-Matching		
		First-line opicapone (N=173)	First-line entacapone (N=433)	P value
All Drugs				
0-6 months post-index				
Patients who had any treatment data recorded	N	167	420	
	Mean (SD)	778.13 (495.25)	809.88 (437.09)	0.189
	Median (Q1, Q3)	705.03 (508.74, 972.68)	743.93 (504.92, 1017.43)	
	Min, Max	11.48, 4147.76	45.90, 3488.52	
	95% CI	702.46, 853.79	767.96, 851.81	
7-12 months post-index				
Patients who had any treatment data recorded	N	122	349	
	Mean (SD)	711.92 (461.19)	842.53 (452.81)	0.002
	Median (Q1, Q3)	646.15 (386.37, 941.54)	795.05 (530.77, 1076.92)	
	Min, Max	15.38, 3004.84	8.24, 3415.38	
	95% CI	629.26, 794.58	794.86, 890.20	
13-18 months post-index				
Patients who had any treatment data recorded	N (%)	80	285	
	Mean (SD)	709.80 (454.89)	847.37 (462.40)	0.015
	Median (Q1, Q3)	642.08 (387.43, 933.01)	791.80 (535.52, 1142.90)	
	Min, Max	57.38, 1927.87	87.98, 2655.74	
	95% CI	608.56, 811.03	793.45, 901.28	
LEDD (mg) of Levodopa/DDCI therapy				
0-6 months post-index				
Patients who had any treatment data recorded	N	164	420	
	Mean (SD)	635.09 (417.13)	627.79 (329.58)	0.628
	Median (Q1, Q3)	550.82 (380.60, 787.16)	561.20 (413.11, 818.58)	
	Min, Max	69.40, 3462.30	45.90, 2570.49	
	95% CI	570.77, 699.41	596.18, 659.40	
7-12 months post-index				
Patients who had any treatment data recorded	N	122	349	
	Mean (SD)	568.18 (383.54)	651.19 (341.08)	0.006
	Median (Q1, Q3)	524.45 (276.92, 751.65)	609.89 (430.77, 830.77)	
	Min, Max	15.38, 2487.91	8.24, 2492.31	
	95% CI	499.43, 636.92	615.28, 687.10	
13-18 months post-index				
Patients who had any treatment data recorded	N	78	284	
	Mean (SD)	582.60 (391.30)	649.20 (335.86)	0.043
	Median (Q1, Q3)	502.73 (320.87, 765.03)	622.95 (395.63, 885.79)	
	Min, Max	57.38, 1927.87	87.98, 2104.92	
	95% CI	494.37, 670.82	609.97, 688.43	

LEDD (mg) of Dopamine agonists	Statistic	Post-Matching		
		First-line opicapone	First-line entacapone	P value
0-6 months post-index				
Patients who had any treatment data recorded	N	78	212	
	Mean (SD)	213.50 (193.23)	239.65 (192.61)	0.121
	Median (Q1, Q3)	183.61 (97.92, 266.23)	220.00 (108.63, 330.49)	
	Min, Max	9.18, 1229.51	6.12, 1817.70	
	95% CI	169.94, 257.07	213.57, 265.73	
7-12 months post-index				
Patients who had any treatment data recorded	N	58	182	
	Mean (SD)	186.25 (132.11)	242.64 (213.72)	0.087
	Median (Q1, Q3)	156.59 (80.00, 289.23)	196.92 (110.77, 332.31)	
	Min, Max	9.23, 547.47	1.65, 1635.60	
	95% CI	151.51, 220.98	211.39, 273.90	
13-18 months post-index				
Patients who had any treatment data recorded	N	38	151	
	Mean (SD)	204.03 (122.69)	242.21 (191.39)	0.490
	Median (Q1, Q3)	183.61 (116.28, 293.77)	196.72 (110.16, 325.90)	
	Min, Max	24.48, 587.54	12.24, 1370.49	
	95% CI	163.70, 244.35	211.43, 272.98	

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.

Table S9: Percentage of patients undergoing a reduction/in any sleep medication(s) at baseline and all follow-ups

Sleep medications	Statistic	Post-Matching		
		First-line opicapone	First-line entacapone	P value
Baseline				
Patients who had any treatment data recorded	N	173	433	
Patients who had ≥ 1 any sleep medication(s)	N (%)	37 (21.4)	99 (22.9)	0.694
0-6 months post-index				
Patients who had any treatment data recorded	N	173	433	
Patients who had ≥ 1 any sleep medication(s)	N (%)	41 (23.7)	104 (24.0)	0.934
7-12 months post-index				
Patients who had any treatment data recorded	N	133	370	
Patients who had ≥ 1 any sleep medication(s)	N (%)	30 (22.6)	82 (22.2)	0.902
13-18 months post-index				
Patients who had any treatment data recorded	N	88	310	
Patients who had ≥ 1 any sleep medication(s)	N (%)	18 (20.5)	71 (22.9)	0.254
After 18 months post-index				
Patients who had any treatment data recorded	N	56	243	
Patients who had ≥ 1 any sleep medication(s)	N (%)	14 (25.0)	62 (25.5)	0.956

P values are derived from t-tests or Wilcoxon Rank Sum tests for continuous variables and from Chi-square tests for categorical variables.