Comparative Efficacy, Safety and Discontinuation of Inhaled Levodopa for Patients with Parkinson's disease: A Network Meta-Analysis

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INTRODUCTION

- Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterised by motor symptoms including bradykinesia, akinesia, tremors, rigidity, postural instability, gait dysfunction, and freezing.[1,2]
- PD is the most common neurodegenerative movement disorder, affecting approximately 108-257 per 100,000 individuals in Europe.[2] As PD progresses, fluctuations in response to treatment occur, with alternative episodes of good (ON episodes) and poor (OFF episodes) symptom control.[3]
- The rapid discontinuation of apomorphine results in patients moving to more costly and invasive treatments, showing that inhaled levodopa (IL) can be a cost saving therapy.
- IL is indicated for the intermittent treatment of OFF episodes in adults with Parkinson's disease (PD) treated with carbidopa/levodopa. There is no direct clinical evidence comparing IL with other on-demand treatment (ODT) options, hence an ITC was necessary.

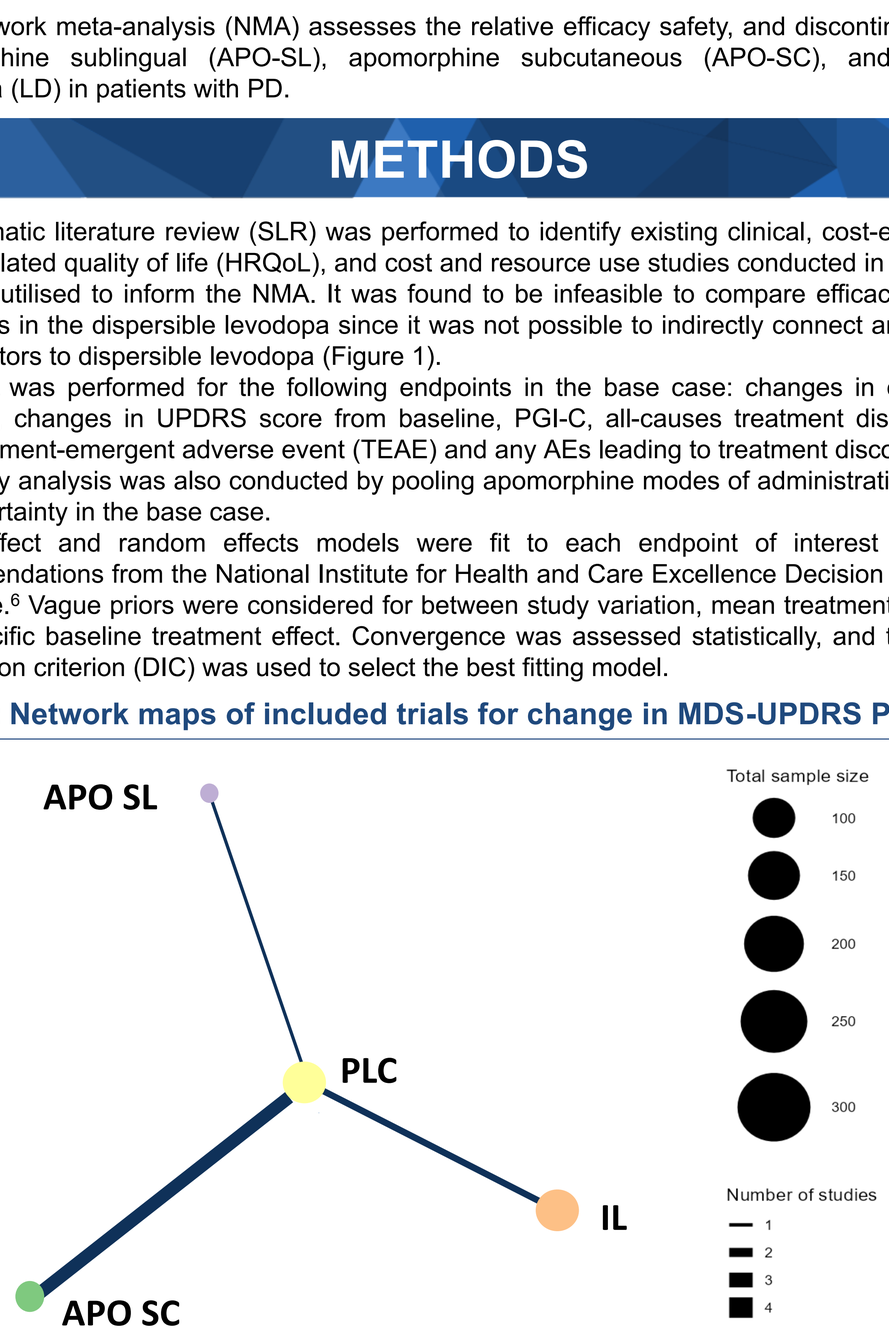
OBJECTIVE

- This network meta-analysis (NMA) assesses the relative efficacy safety, and discontinuation of IL, apomorphine sublingual (APO-SL), apomorphine subcutaneous (APO-SC), and dispersible levodopa (LD) in patients with PD.

METHODS

- A systematic literature review (SLR) was performed to identify existing clinical, cost-effectiveness, health-related quality of life (HRQoL), and cost and resource use studies conducted in patients with PD was utilised to inform the NMA. It was found to be infeasible to compare efficacy and safety outcomes in the dispersible levodopa since it was not possible to indirectly connect any of the key comparators to dispersible levodopa (Figure 1).
- An NMA was performed for the following endpoints in the base case: changes in off-time from baseline, changes in UPDRS score from baseline, PGI-C, all-causes treatment discontinuation, any treatment-emergent adverse event (TEAE) and any AEs leading to treatment discontinuation. A sensitivity analysis was also conducted by pooling apomorphine modes of administration to assess the uncertainty in the base case.
- Fixed effect and random effects models were fit to each endpoint of interest in line with recommendations from the National Institute for Health and Care Excellence Decision Support Unit guidance.[6] Vague priors were considered for between study variation, mean treatment effects, and trial-specific baseline treatment effect. Convergence was assessed statistically, and the deviance information criterion (DIC) was used to select the best fitting model.

Figure 1: Network maps of included trials for change in MDS-UPDRS Part III



RESULTS

Table 1: Summary of efficacy and safety endpoints from the studies included in the NMA

Endpoint	Trials included in NMA
Change in off-time	(PLC | APO SC): Katzenschlager 2018[7], Dewey 2001[8] (PLC | IL): Lewitt 2016[9], Lewitt 2019[10]
Change in MDS-UPDRS Part III	(PLC | APO SC): Katzenschlager 2018[7], Dewey 2001[8], Nomoto 2015[11], Pfeiffer 2007[12] (PLC | APO SL): Olanow 2020[14] (PLC | IL): Lewitt 2016[9], Lewitt 2019[10]
Change in PGI-C	(PLC | APO SC): Katzenschlager 2018[7], (PLC | APO SL): Olanow 2020[14] (PLC | IL): Lewitt 2019[10]
All-causes treatment discontinuation	(PLC | APO SC): Katzenschlager 2018[7], Dewey 2001[8], (PLC | APO SL): Olanow 2020[14] (PLC | IL): Lewitt 2016[9], Lewitt 2019[10]
AEs	(PLC | APO SC): Katzenschlager 2018[7], Dewey 2001[8], Nomoto 2015[11], Pfeiffer 2007[12] (PLC | APO SL): Olanow 2020[14] (PLC | IL): Lewitt 2016[9], Lewitt 2019[10], Lewitt 2018[13]
AE leading to treatment discontinuation	(PLC | APO SC): Katzenschlager 2018[7], Dewey 2001[8], (PLC | APO SL): Olanow 2020[14] (PLC | IL): Lewitt 2016[9], Lewitt 2019[10], Lewitt 2018[13]

- The SLR identified 21 relevant randomised controlled trials (RCTs) suitable for inclusion in an NMA (Table 1). A feasibility assessment retained 11 studies for the NMA.
- For all endpoints, the results of the random effects analyses were selected for the base case as the feasibility assessment for this NMA demonstrated some heterogeneity amongst the studies included in the analyses. However, there was limited data to estimate the tau/heterogeneity parameter in the sparse networks of this NMA. Moreover, the DIC and residual deviance statistics were within three points for both the random effects and fixed effect models.
- Fixed effect models do not account for heterogeneity thus they are usually not realistic and lead to artificially narrow credible intervals.

Table 2: The pair-wise comparison of standardized mean difference (SMD) for the change in off-time (h/day) and UPDRS/MDS-UPDRS III scores

SMD [95% CI] change in UPDRS/MDS-UPDRS III scores	IL	APO SC	APO SL	PLC
IL		0.740 [-2.015, 3.484]	NA	-0.133 [-3.052, 2.889]
APO SC	-1.989 [-4.522, 0.453]		NA	-0.908 [-3.657, 1.837]
APO SL	-0.963 [-3.581, 1.664]	0.583 [-1.975, 3.231]		NA
PLC	0.695 [-1.649, 3.030]	3.609 [1.557, 5.789]	1.664 [-0.895, 4.204]	

SMD of change in off-time (h/day) [95% CrI]

- Reduction in OFF-time was not significantly different between IL and APO-SC (Standardized mean difference [SMD] = 0.740, 95%CrI [-2.015, 3.484]).
- Changes in UPDRS III were not significantly different between IL and APO-SC (SMD = 1.989, 95%CrI [-0.453, 4.522]) and APO-SL (SMD = 0.963 [-1.664, 3.581]) (Table 2).

Table 3: The pair-wise comparison of odds ratio (OR) of improvement in PGI-C and all-causes treatment discontinuation[15]

Log odds ratio of all-causes treatment discontinuation [95% CrI]	IL	APO SC	APO SL	PLC
IL		-0.587 [-7.262, 6.163]	0.098 [-6.520, 6.831]	0.470 [-4.220, 5.242]
APO SC	0.513 [-1.640, 3.801]		0.685 [-5.971, 7.538]	1.057 [-3.761, 5.883]
APO SL	1.089 [-1.851, 4.149]	0.576 [-3.368, 3.371]		0.373 [-4.440, 5.037]
PLC	0.065 [-1.630, 1.748]	-0.449 [-3.331, 1.153]	-1.024 [-3.540, 1.449]	

Log odds ratio of improvement in PGI-C [95% CrI]

- The log ORs of our NMA demonstrated that IL and apomorphine were generally more effective than placebo for patients expressing improvement in PGI-C; however, the difference was not statistically significant.
- The differences in log ORs for improvement in PGI-C or all-cause treatment discontinuation between IL and APO-SC and APO-SL were not statistically significant (Table 3).

Table 4: The pair-wise comparison of odds ratio (OR) of AEs and AEs leading to treatment discontinuation[15]

Log odds ratio of AEs leading to treatment discontinuation [95% CrI]	IL	APO SC	APO SL	PLC
IL		-0.254 [-1.391, 1.013]	-0.952 [-2.696, 0.830]	0.061 [-0.776, 0.961]
APO SC	**20.712 [1.855, 55.991]**		-0.698 [-2.505, 0.977]	0.315 [-0.586, 1.079]
APO SL	0.734 [-1.689, 3.201]	**-19.978 [-54.909, -0.959]**		1.013 [-0.521, 2.538]
PLC	0.120 [-1.105, 1.396]	**-20.593 [-55.614, -1.755]**	-0.615 [-2.651, 1.499]	

Log odds ratio of AEs [95% CrI]

- IL demonstrated significantly lower odds of treatment discontinuation due to AEs (log OR = -20.712, 95% CrI [-55.991, -1.855]) compared to APO-SC, but no significant difference was observed with APO-SL (log OR = -0.734 [-3.201, 1.689]) (Table 4).
- Scenario analyses confirmed the robustness of the NMA results.
- One limitation is the relatively small sample size of the trials included in the networks. There were 350 patients in the placebo arm, 300 in the IL arm, 150 patients in the apomorphine subcutaneous arm, and 50 in the apomorphine sublingual arm. This meant the estimated endpoints were subject to uncertainty.

CONCLUSIONS

- IL, APO-SC, and APO-SL have comparable efficacy in reduction in OFF time, change in UPDRS-III score, and improvement in PGI-C score. Although the AE rates are comparable, the probability of treatment discontinuation due to AEs is significantly higher for APO-SC compared to IL.

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Abbreviations: AE – adverse event; APO-SC: apomorphine subcutaneous; APO-SL: apomorphine sublingual; CrI: credible intervals; DIC – deviance information criterion; HRQoL: health related quality of life; IH :inhaled levodopa; ITC: indirect treatment comparison; LD: levodopa; NMA – network controlled trials; meta-analysis; ODT: on-demand treatments; OR: odds ratio; PD: Parkinson's disease; PGI-C: patient global impression change; PLC: placebo; QALY: Quality-adjusted life year; RCT: randomised TEAE: treatment emergent adverse event; SLR: Systematic literature review; SMD: standardized mean difference; TEAE: treatment emergent adverse events; UK: United Kingdom; UPDRS: unified Parkinson's disease rating scale; WTP: Willingness to pay

15. Log OR: The numbers on the right upper triangle are Log10 ORs (95% CrI) of reporting improvement in PGI-C (table 3) and AEs (table 4), and Log10 OR values smaller than 0 indicate lower risk. Those on the left bottom triangle represent the Log10 ORs (95% CrI) of discontinuation due to all causes (table 3) and AEs leading to discontinuation (table 4), and Log10 OR values smaller than 0 indicate lower risk. Values represent the row-defining treatment compared with the column-defining treatment. All numbers are shown after rounding off to three decimal places. The bold font indicates significant results.

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