

A systematic review and network meta-analysis of pharmacological therapies used for patients with advanced Parkinson's disease

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BACKGROUND

Parkinson's disease affects about 110,000 people in the UK and 1.25 million people in Europe.¹

Current options for management of advanced Parkinson's disease include:

- Increased dose or frequency of immediate-release levodopa (IR LD)
- Supplemental controlled-release levodopa (CR LD)
- Adjunctive therapies with levodopa, including dopamine agonists, monoamine oxidase-B inhibitors (MAO-BIs), and catechol-O-methyl transferase inhibitors (COMTIs)

A new modified release form of levodopa (IPX066) is in development.

OBJECTIVE

To update and extend a previous review^{2,3} and explore the efficacy and safety of therapies for management of advanced Parkinson's disease including IPX066 using network meta-analysis

METHODS

Search method

- A systematic literature search to identify relevant studies
- Identified additional relevant studies by checking bibliographies of recent systematic reviews^{2,3}, NCCCC PD guideline, and via contact with clinical experts

Study selection

- Included studies in advanced Parkinson's disease patients with motor fluctuations
- Excluded interventions not recommended as first choice for advanced Parkinson's; open label trials; non-English language studies

Outcome measures

- Off-time reduction, Unified Parkinson's Disease Rating Scale (UPDRS) scores, patient withdrawals, adverse events

Statistical analysis

- A network meta-analysis using WinBUGS⁴ software
- A random effects model to allow for potential heterogeneity in treatment effects between studies
- Class effects taken into account

RESULTS

- Systematic literature review included 43 trials; 9,453 patients were included in the network meta-analysis

Table 1: Results of the network meta-analyses for effectiveness and safety outcomes comparing each intervention with IR LD+placebo, median (95% credible interval)

	IR LD + Entacapone	IR LD + Ropinirole	IR LD + Pramipexole	IR LD + Rotigotine	IR LD + Rasagiline	IR LD + Selegiline	IPX066	CR LD
Off-time reduction ^a (unit hours)	-0.70 (-1.02, -0.39)	-1.39 (-2.05, -0.71)	-1.71 (-2.11, -1.35)	-1.13 (-1.63, -0.61)	-0.79 (-1.40, -0.21)	-0.94 (-1.84, -0.05)	-1.40 (-2.19, -0.67)	-0.84 (-1.77, 0.13)
UPDRS ADL score ^a	-1.06 (-1.55, -0.56)	-2.33 (-3.53, -1.06)	-1.93 (-2.69, -1.35)	-1.84 (-2.68, -1.02)	-1.47 (-2.73, -0.23)	NA	-1.44 (-2.58, -0.44)	NA
UPDRS motor score ^a	-2.49 (-3.41, -1.59)	-4.25 (-6.16, -2.45)	-5.88 (-7.22, -4.63)	-4.94 (-6.14, -3.75)	-2.77 (-4.80, -0.80)	NA	-2.63 (-4.63, -0.67)	NA
UPDRS total score ^a	-2.25 (-4.72, 0.40)	NA	-10.09 (-13.57, -6.56)	NA	-2.05 (-13.00, 9.13)	NA	-4.27 (-7.74, -0.53)	NA
Dyskinesia ^b	2.26 (1.73, 3.00)	3.02 (1.71, 5.57)	2.40 (1.78, 3.44)	2.64 (1.58, 4.71)	1.77 (0.99, 3.12)	0.90 (0.41, 2.00)	7.07 (2.10, 32.72)	NA

a: efficacy outcome: estimates measured by mean difference; b: safety outcome: estimates measured by hazard ratio

CONCLUSION

- Confirmed previous findings^{2,3} regarding class effects of adjuvant therapies that dopamine agonists class was more effective than MAO-BIs and COMTIs
- All therapies with the exception of controlled-release levodopa were associated with benefit (MAO-BIs at borderline)
- IPX066 was broadly comparable with IR LD+dopamine agonists in off-time reduction
- Most therapies were associated with a significant increase in the risk of having dopaminergic side effects, particularly dyskinesia.

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