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A Systematic Review and Network Meta-Analysis of Pharmacological Therapies Used for Patients with Advanced Parkinson's Disease

Shijie Ren,[1] Katy Cooper,[1] James Cooper,[2] Helen Smith,[2] Soraya Shaikh[2]

[1] School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

[2] GlaxoSmithKline, Brentford, Middlesex, United Kingdom

Objectives

To assess the relative efficacy and safety of modified-release levodopa (IPX066), controlled-release levodopa and add-on therapy to immediate-release levodopa (including dopamine agonists, monoamine oxidase-B inhibitors (MAOBI), and catechol-O-methyl transferase inhibitors (COMTI)) using network meta-analysis (NMA).

Methods

A systematic literature search was conducted in MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, DARE and HTA. A random effects NMA was used to determine the relative efficacy and safety of treatments on off-time reduction, three Unified Parkinson's Disease Rating Scale (UPDRS) scores, patient withdrawals, and six adverse events in WinBUGS. An additional analysis was conducted to assess treatment class effects. Node-splitting approach was used to assess the assumption of consistency when direct and indirect evidence was combined.

Results

Forty-three trials with 9,453 patients were identified. Immediate-release levodopa plus pramipexole produced the greatest reduction in off-time relative to immediate-release levodopa plus placebo (-1.71 hours a day; 95% CrI: -2.11, -1.35), followed by IPX066 (-1.40; 95% CrI: -2.19, -0.67). The greatest improvement on UPDRS ADL score was given by add-on ropinirole (-2.33 points; 95% CrI: -3.53, -1.06); on UPDRS motor and total score was given by add-on pramipexole (-5.88 points; 95% CrI: -7.22, -4.63 and -10.09 points; 95% CrI: -13.75, -6.56, respectively). Dyskinesia was increased with IPX066 and adjuvant therapy classes except for MAOBIs. Patient withdrawals were also increased with IPX066 and controlled-release levodopa.

Conclusions

The NMA showed that all treatments except controlled-release levodopa were associated with a statistically significant reduction in off-time. Dopamine agonist class as adjunctive to levodopa therapy had the greatest reduction. IPX066 was broadly comparable with add-on dopamine agonists on off-time reduction, and comparable with add-on MAOBIs and COMTIs on UPDRS scores. However, the treatments were associated with an increase in the risk of having dopaminergic side effects, particularly dyskinesia.