Nelotanserin is a serotonin 2A and 2C (5-HT2A/5-HT2C) inverse agonist that was previously tested in the clinic for rapid-eye-movement sleep behavior disorder and psychosis in patients with Parkinson's disease dementia. Its effect on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia has however not been investigated. As 5-HT2A antagonism/inverse agonism is a validated approach to alleviate dyskinesia, Kwan et al. undertook a study to evaluate the anti-dyskinetic potential of nelotanserin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset. Parkinsonism was induced in six common marmosets (Callithrix jacchus, three females, and three males) that were then chronically treated with L-DOPA to induce dyskinesia. On experimental days, they were administered L-DOPA in combination with vehicle or nelotanserin (0.1, 0.3 and 1 mg/kg) subcutaneously, in a randomized fashion. Dyskinesia and parkinsonism were rated post hoc by a blinded observer. In comparison to the vehicle, the addition of nelotanserin 0.3 and 1 mg/kg to L-DOPA diminished peak dose dyskinesia by 47% ($P < 0.05$) and 69% ($P < 0.001$). Nelotanserin 0.3 and 1 mg/kg also reduced the severity of global dyskinesia, by 40% ($P < 0.01$) and 55% ($P < 0.001$), when compared to vehicle. Nelotanserin 0.1 mg/kg did not alleviate peak dose or global dyskinesia severity. Nelotanserin had no impact on the anti-parkinsonian action of L-DOPA. Our results highlight that nelotanserin may represent an efficacious anti-dyskinetic drug and provide incremental evidence of the potential benefit of 5-HT2A/2C antagonism/inverse agonism for drug-induced dyskinesia in PD [1].

1)
Kwan C, Frouni I, Bédard D, Hamadjida A, Nuara SG, Gourdon JC, Huot P. The 5-HT2A/2C inverse agonist nelotanserin alleviates L-DOPA-induced dyskinesia in the MPTP-lesioned marmoset. Eur J Neurosci. 2023 Jul 28. doi: 10.1111/ejn.16104. Epub ahead of print. PMID: 37515363.