Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Cummings et.al. Lancet 2013.*

Summary created by Abhishek Lenka, M.D.

Background: >50% of the PD patients experience psychotic symptoms at some point in the disease course. Psychosis is a debilitating non-motor symptom that is associated with a higher rate of nursing home placement, caregiver distress, dementia, and mortality among PD patients. Unfortunately, the therapeutic options that could ameliorate the psychotic symptoms without worsening parkinsonian symptoms are limited. Among antipsychotics, quetiapine and clozapine have been used to treat PD-associated psychosis (PD-P); however, the former's efficacy was never proved in any of the controlled trials in the past, and the latter is associated with several serious side effects in the elderly. Hence, this trial explored pimavanserin, a selective inverse agonist of 5HT2A, which does not have any dopamine receptor blocking property.

Study design (sponsored by the drug manufacturer, ACADIA pharmaceuticals)
Type of study: Randomized double-blinded placebo-controlled trial
Site of study: 54 centers in North America (USA: 52, Canada: 2)
Inclusion criteria: Age >40 years, diagnosis of PD as per UK brain bank criteria (at least one year of disease), diagnosis of PD-P as per NINDS-NIMH criteria, at least a score of 3 in the scale for assessment of positive symptoms (SAPS), MMSE >21/30
Exclusion criteria: non-PD causes of psychosis, serious medical illness (recent MI, stroke, heart failure), Long QT.
Discontinuation of other antipsychotics: at least for >5 half-lives
Intervention: Pimavanserin 40 mg/d
Assessment days: Baseline, day 15, day 29, day 43
Primary outcome: Change in total SAPS-PD score from baseline to day 43.

Key results:

- Patients on pimavanserin had a 37% improvement in the SAPS-PD score (vs. placebo 14%, p=0.0006).
- Treatment with pimavanserin was effective irrespective of age (65–75 years vs. >75 years), sex, and
- screening MMSE score (<25 vs. ≥25).
- Pimavanserin was also associated with improved caregiver burden, nighttime sleep, and daytime wakefulness.
- There was no worsening of motor symptoms in the treatment arm of the trial.
- There was no difference in the mean △QT interval of the two groups.

Conclusion:
Pimavanserin improves psychotic symptoms in PD-P at least till the 6th week of therapy, without significantly worsening the motor symptoms/QT interval.

- Pimavanserin remains the only FDA-approved drug for treating psychosis in PD.
- There are some controversies related to the association of long-term treatment with pimavanserin (and other antipsychotics as well) and increased mortality in PD patients *(Pimavanserin: A Friend or Foe in Parkinson Disease Psychosis. https://n.neurology.org/content/97/13/613).*
- For details regarding treatment of psychosis in PD- *Lenka A, Gomathinayagam V, Bahroo L. Approach to the management of psychosis in Parkinson's disease. Ann Mov Disord 2019. https://www.aomd.in/text.asp?2019/2/3/83/272289*