The Lancet 2014; 383:533-540

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| **CATEGORY** | **DATA/ANALYSIS** |
| Does the RCT state a clear primary hypothesis? | Fair. The idea was to test the efficacy and safety of pimavanserin in treating psychosis in Parkinson’s and there is discussion as to why pimavanserin might cause fewer motor side-effects. |
| Does the hypothesis seem implausible? If so, discount any support the RCT creates for the hypothesis. | No, with respect to motor side-effects because pimavanserin does not block dopamine receptors. No with respect to psychosis because pimavanserin is an inverse agonist at 5-HT2 receptors and increased activity at 5-HT2A receptors may be related to Parkinson’s psychosis. |
| Equivalence to my patients | INCLUDE: 40 years old or older, idiopathic Parkinson’s Disease for at least one year, Parkinson’s psychosis for at least one month, score of at least 6 on the Neuropsychiatric Inventory (NPI) or score of 4 or more on either the delusions or hallucinations sub-tests of the NPI, Mini-Mental Status Exam Score > 21EXCLUDE: delirium, psychosis secondary to toxic or metabolic disorders, dementia concurrent with or pre-existing diagnosis of Parkinson’s psychosis, psychosis after stereotaxic surgery, CVA, serious medical illness |
| Blinding | Triple-blind, parallel group |
| Ratings scales (validated)Scale for the Assessment of Positive Symptoms-Parkinson’s Disease (SAPS-PD) derived from SAPS by somewhat arbitrary methodology. No studies on inter-rater reliability. A number of the developers were current or former employees or paid consultants of the maker of pimavanserin.Maximum score on SAPS-PD is 45. | NPIUnified Parkinson’s Disease Rating ScaleClinical Global Impression ScaleOthers |
| Randomization | Yes, programmed randomization schedule, block sizes of 4 |
| Similarity at baseline | Yes, see table 1 |
| Equal treatment post-randomization | Yes |
| Follow-up duration | 43 days |
| Sample size | 199 randomized185 completed |
| Intent-to-treat?*Drop-out rate.* *Imputation method(s)?* | No. Measured completers of all patients who took at least one dose and completed one post-baseline Scale for the Assessment of Positive Symptoms. Missing values not imputed. |
| Statistical significance: p value set at what level? One- or two-sided? (Don’t overvalue statistical significance.) | 0.05 is mentioned in discussion of the power calculation, but not explicitly specified as the level of statistical significance for the study. P values should be specified as one- or two-sided. |
| Bonferroni or other correction for multiple statistical comparisons | No |
| Effect sizes and how they were measured*Absolute change in a biological parameter or rating scale**Percent change in a biological parameter or rating scale**Percentage of subjects reaching a prospectively defined outcome, e.g., absolute or percentage change in a biological parameter or rating scale or a particular benchmark with respect to a biological parameter or rating scale (might then be converted into a number needed to treat, risk ratio or odds ratio)**Standardized mean difference**Number needed to treat**Risk ratio**Odds ratio**Hazard ratio**How heterogeneous are the effect sizes? For the primary outcome, did the study report a prediction interval? The 95% PI = M ± 1.96SD with M being the mean effect size and SD being the standard deviation of the effect size. If so, what does the PI suggest about whether the effect is clinically meaningful and whether I should offer the treatment to a given patient?* | **PRIMARY OUTCOME****SAPS-PD**Difference between pimavanserin and placebo was 3.06 points, p = 0.001.However, of the 199 randomized patients, 45 met at least 1 of 2 exclusion criteria regarding use of concomitant medications. When these patients are excluded from the calculation of the SAPS-PD differential, it falls to 2.2 points. This difference could be explained by resolution of a mild delusion.**SOME OF THE SECONDARY OUTCOMES****STANDARDIZED MEAN DIFFERENCE**SMD = 0.5(Not excluding the 45 patients who were improperly included in the study.)**CLINICAL GLOBAL IMPRESSION SCALE**0.67, p = 0.0011 (not corrected for multiple statistical comparisons; corrected p value is 0.002)**SAPS-PD**3.06 (1.22-4.9)**CGI**0.67 (0.28-1.06)No prediction interval |
| Bottom line*After considering costs and benefits, should I offer the treatment to a given patient?* | Probably not. Study has many flaws, effects sizes are small and drug is expensive. Cost is about $5,000 per month. |