**Treatment Modifiers and Predictors of Risperidone Response in Dementia: An Individual Participant Data Meta-Analysis of Six Randomised Controlled Trials**

Hieu T. Le1, Edward C.Y. Lau1, Christine Y. Lu1,2, Tuan A. Nguyen3, Lee-Fay Low1, Sarah N Hilmer1,2, Yun-Hee Jeon1, and Edwin C.K. Tan1,2.

1Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia.

2Kolling Institute, Royal North Shore Hospital, St Leonards, NSW, Australia.

3National Aging Research Institute, Parkville, VIC, Australia.

**Background and aims.** Although risperidone is the only antipsychotic approved for behaviours and psychological symptoms of dementia (BPSD) in some countries, its efficacy is modest and varies by symptom1. Given its known risks, identifying individuals most likely to benefit is essential for personalised care. This study aimed to: (1) identify BPSD most responsive to risperidone, (2) explore subgroups with differing responses, and (3) investigate predictors of therapeutic response.

**Methods.** An individual participant data meta-analysis (IPD-MA) was conducted from six clinical trials. Data on baseline characteristics, symptoms, treatment-emergent factors, and outcomes at weeks 4 and 8 were captured. Symptoms were assessed using the Behavioural Pathology in Alzheimer’s Disease (BEHAVE-AD) scale, and therapeutic response was defined as ≥30% reduction in total score. Mixed-effects logistic and linear regression evaluated treatment effects, modifiers, and predictors.

**Results.** Among 1,720 participants (711 placebo, 1,009 risperidone), risperidone showed modest benefit over placebo (Week 8 odds ratio [OR]: 1.30; 95% CI: 1.01–1.67). Statistically significant improvements were observed for aggression (Week 8 standardised mean difference [SMD]: -0.61; 95% CI: -0.95 to -0.26), psychosis (Week 8 SMD: -0.9; 95% CI: -1.46 to -0.34), and anxieties/phobias (Week 8 SMD: -0.19; 95% CI: -0.35 to -0.04). Factors influencing pharmacokinetics and pharmacodynamics (e.g., body mass index, endocrine diseases, race, gender) potentially modified treatment effects. Early response at week 2 predicted outcomes at weeks 4 (OR: 9.04; 95% CI: 6.10–13.39) and 8 (OR: 4.46; 95% CI: 3.00–6.62).

**Conclusion/Discussion.** Risperidone provided symptom-specific benefits, especially for aggression, psychosis, and anxiety/phobia with no effect on activity, affective, or sleep disturbances. Subgroup analyses identified potential pharmacokinetic-related factors influencing treatment efficacy, while early response predicted sustained improvement. This study provides potential evidence for individualised treatment in people with BPSD; however, further research is needed to balance risks and benefits across subgroups.

**References:**

1. Yunusa, I., & El Helou, M. L. (2020). The Use of Risperidone in Behavioral and Psychological Symptoms of Dementia: A Review of Pharmacology, Clinical Evidence, Regulatory Approvals, and Off-Label Use. Frontiers in pharmacology, 11, 596.