**Prescription sequence symmetry analysis of glucagon-like peptide-1 receptor agonist and neuropsychiatric conditions**

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**Introduction.** Glucagon-like peptide-1 receptor agonist (GLP1Ra) use has surged since its expanded use for weight management, beyond the original indication of type 2 diabetes. Recent preclinical evidence suggests GLP1Ra may have neuroprotective, antidepressant, and anxiolytic properties through direct effects on the CNS and indirect effects on the gut-brain axis, thereby opening the possibility of using GLP1Ra to treat neuropsychiatric conditions.

**Aim**. To examine the association between GLP1Ra initiation and a range of neuropsychiatric conditions using prescription sequence symmetry analysis (PSSA) on prescription claim records.

**Methods**. Prescription claims data (Jul 2013 – Dec 2024) from a 10% sample of the Australian Pharmaceutical Benefits Scheme were analysed to determine whether GLP1Ra initiation was associated with initiation of marker medications for depression, substance use disorder, schizophrenia, attention-deficient hyperactivity disorder, epilepsy, migraine, Alzheimer’s, and Parkinson’s disease. The PSSA was used to estimate adjusted sequence ratios (aSRs), accounting for underlying temporal trends in medication use. The aSRs compared the number of initiators of GLP1RA followed by marker medications to those initiating in the reverse order within a one-year exposure window, excluding those who initiated both within a 14-day blackout period. Sensitivity analyses varied the exposure and blackout windows.

**Results.** 32,429 individuals initiated GLP1Ra and one of the marker medications within one year. An inverse association between GLP1Ra and antidepressants (aSR: 0.85, 95%CI 0.76 - 0.94), and medications for substance use disorders (aSR: 0.70, 95%CI 0.51 - 0.88) was observed. No associations were observed for other marker medications. Using a longer two-year exposure window, we additionally observed inverse associations for antipsychotics (aSR: 0.76, 95%CI 0.60–0.92), antiepileptics (aSR: 0.83, 95%CI 0.70–0.96), and antimigraine agents (aSR: 0.83, 95%CI 0.70–0.96).

**Discussion.** Initiation of medications for depression and substance use disorder was less likely in the year after GLP1Ra initiation, suggesting a protective association. This finding is consistent with preclinical evidence that GLP1RAs may modulate reward pathways and related behaviours. Future well-designed cohort studies and randomised trials are needed to confirm causality.