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Sildenafil is a candidate drug for Alzheimer's disease: Real-world patient and RNA-sequencing data observations in patient-induced pluripotent stem cells-derived neurons

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Background: Alzheimer's disease (AD) is the main form of dementia and become one of the most expensive burdening diseases in the United States. As the traditional anti-tau or anti-amyloid selective drug discovery approaches did not benefit the AD patients, we developed an endo-phenotype disease module-based methodology for AD drug repurposing and identified sildenafil (a phosphodiesterase type 5 (PDE5) inhibitor) as a candidate drug for AD.

Method: We performed new patient data analyses using both the MarketScan® Medicare Supplemental database (n = 7.23 million older [>65 years] subjects) and the OPTUM database (n=11.52 million older subjects). We selected a new calcium channel blocker (nifedipine) and three diuretics (bumetanide, furosemide, and spironolactone) as comparator drugs and conducted propensity score-matched observations. In total, we generated an AD patient-induced pluripotent stem cells (iPSC)-derived neuron models in this study. iPSC from six AD patients were induced to neural progenitor cells (NPCs). Neuronal precursors were generated from NPCs and matured to neurons. The AD patient-iPSC-derived neurons were treated with a concentration gradient of sildenafil and the effects were studied using ELISA, Western blotting and RNA-seq.

Result: We adjusted sex, age, race, and 13 comorbidities in the OPTUM analyses, as well as sex, age, geographic location, and 18 comorbidities in the MarketScan analyses. We found sildenafil usage to be associated with reduced likelihood of AD across all four drug cohorts, including bumetanide, furosemide, spironolactone, and nifedipine. Specifically, we found sildenafil vs. spironolactone was associated with a 46% reduced prevalence of AD in MarketScan (HR = 54%, 95% CI 0.32-0.66, p-value = 3.33×10^{-5}) and a 30% reduced prevalence of AD in OPTUM (HR = 70%, 95% CI 0.49-1.00, p-value = 0.05). Subgroup analysis further revealed sildenafil usage in individuals with hypertension to be associated with reduced likelihood of AD across all four drug cohorts. Sildenafil treatment can reduce phosphorylated tau (pTau181 and pTau231), phosphorylated GSK-3b and CDK5 in the AD patient-iPSC-derived neuron model. mechanistically supporting its potential therapeutic effect in Alzheimer's disease. In addition, RNA-sequencing analysis of iPSC-derived neurons after sildenafil treatment revealed new mechanism-of-actions and potential biomarkers to be tested in future clinical trials.

Conclusion: The new patient data provide further support for reduced AD prevalence in patients exposed to sildenafil, and suggest that future experimental and clinical studies are warranted.