Viagra For the Brain

Can the "little blue pill" save our brain from Alzheimer's?

I got a lot of questions regarding this study which of course is all over the media. How was the connection between Viagra (sildenafil) and Alzheimer's prevention made? Could Viagra be a promising drug candidate to help prevent and treat Alzheimer's disease? What's the dose? When can I start?

Abstract

- We developed an endophenotype disease module-based methodology for Alzheimer's disease (AD) drug repurposing and identified sildenafil as a potential disease risk modifier. Based on retrospective case–control pharmacoepidemiologic analyses of insurance claims data for 7.23 million individuals, we found that sildenafil usage was significantly associated with a 69% reduced risk of AD (hazard ratio 0.31, 95% confidence interval 0.25–0.39, $P < 1.0 \times 10^{-8}$). Propensity score-stratified analyses confirmed that sildenafil is significantly associated with a decreased risk of AD across all four drug cohorts tested (diltiazem, glimepiride, losartan and metformin) after adjusting for age, sex, race and disease comorbidities. We also found that sildenafil increases neurite growth and decreases phospho-tau expression in neuron models derived from induced pluripotent stem cells from patients with AD, supporting mechanistically its potential beneficial effect in AD. The association between sildenafil use and decreased incidence of AD does not establish causality, which will require a randomized controlled trial.

Alzheimer's disease is devastating and we don't have any good treatments. There is an urgent need for the development of effective therapeutics. Developing drugs for diseases like Alzheimer's is costly and can take years. Being able to repurpose existing drugs can reduce the time of drug discovery and approval, bringing potential cures out faster. Viagra (sildenafil) is a therapy for erectile dysfunction and pulmonary hypertension. So how did the researchers make the leap to consider using Viagra for Alzheimer's? This research used existing data to construct a network to describe how thousands of proteins interact with proteins associated with Alzheimer's Disease, and then to find drugs that interact with the most closely associated proteins. Researchers used sophisticated statistical methods and computer modeling to combine large, publicly available datasets to generate the hypothesis and then looked at data from insurance claims to look for potential drugs that could be repurposed to prevent Alzheimer's disease. This was followed by cell experiments to establish that sildenafil was having the predicted effect of the biological process identified in the statistics. The model found that sildenafil users were 69% less likely to develop Alzheimer's disease than non-sildenafil users after 6 years of follow-up.

What is the mechanism of the possible effectiveness of sildenafil? The authors suggest that this protective effect occurs by preventing activation of two proteins that affect hyperphosphorylation of tau, and therefore the formation of tangles. Sildenafil was originally developed as a cardiovascular drug, so another mechanism could be the protective effects are from promoting brain blood flow which may stop Alzheimer's disease from developing since a reduction in brain blood flow is one of the first things that goes wrong in the development of Alzheimer's disease, well before symptoms occur.

Although reports have shown that Viagra is protective in animal models of Alzheimer's, this research doesn't prove that sildenafil is responsible for reducing dementia risk, or that it slows or stops the disease, although the 69% number is very compelling. The only way to test this would be in a large-scale clinical trial measuring the sildenafil effect against the usual standard of care so a mechanistic trial and a phase II randomized clinical trial to test causality and confirm sildenafil's clinical benefits for Alzheimer's patients will need to be performed. However, this is a compelling use of data analysis to identify potential repurposed drugs for disease and I look forward to the results of further studies. It appears that there is likely something here so stay tuned. In the meantime, if we look at the pathway by which these potential beneficial effects of sildenafil are being mediated, we can try to duplicate some of this through lifestyle factors (like exercise), which are being shown to reduce risk over the same pathways sildenafil work on and also reduces other risk factors for Alzheimer's such as coronary artery disease, hypertension, and type 2 diabetes.

Fang, J., Zhang, P., Zhou, Y. *et al.* Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease. *Nat Aging* **1,** 1175–1188 (2021). https://doi.org/10.1038/s43587-021-00138-z