Viagra-like drugs may play role in treating dementia

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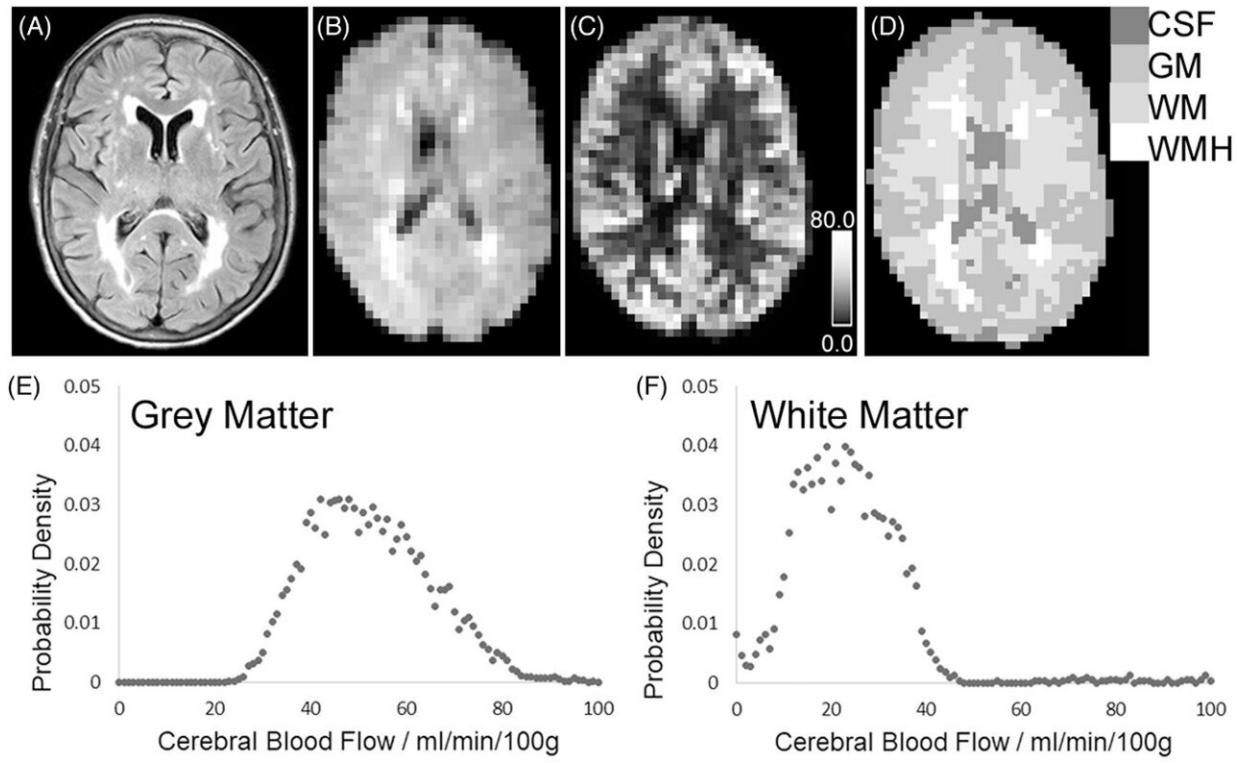

Example of anatomical and cerebral blood flow (CBF) mapping, with tissue segmentation. A, Fluid-attenuated inversion recovery (FLAIR) image at full resolution. B, FLAIR image co-registered to the CBF map, with voxels re-sized to be equivalent to the pseudo-continuous arterial spin labeling (pCASL) map. C, CBF map, derived from pCASL. Calibration bar shows 0.0–80.0 mL/min/100 g. D, Tissue segmentation map for CBF computation. Each voxel has been defined as either: cerebrospinal fluid (CSF), gray matter (GM), normal-appearing white matter (WM), or white matter hyperintensity (WMH). E, F, Probability density functions of CBF values in voxels assigned as gray matter (E) or normal-

appearing white matter (F). For this participant, median CBF was 51.3 mL/min/100 g in gray matter and 21.8 mL/min/100 g in normal-appearing white matter. Credit: DOI: 10.1002/alz.12559

A new study, published today in *Alzheimer's & Dementia*, tested whether tadalafil, a drug closely related to Viagra, may be effective in treating people with vascular dementia.

The phase II trial, led by researchers at St George's, University of London and St George's Hospital was joint-funded by the US-based Alzheimer's Drug Discovery Foundation and the UK Alzheimer's Society. The trial tested whether tadalafil increases brain blood flow in older men and women with narrowing of the brain arteries, a condition that can cause strokes and vascular dementia.

Although the trial results found no significant increase in blood flow, the researchers found clues pointing towards a potential use for tadalafil in treating certain groups of patients, warranting further investigation.

Dementia is an escalating global healthcare challenge, estimated to affect 55 million people worldwide, increasing to 139 million by 2050. There are few treatment options for patients, and the new trial explored whether repurposing an existing drug, tadalafil, may have potential for treating vascular dementia—a common type of dementia in which there is reduced blood flow to the brain.

A recent computational analysis identified sildenafil (Viagra) and vardenafil, drugs commonly used to increase blood flow in erectile dysfunction and in pulmonary hypertension (a form of lung disease), as possible candidates for preventing or delaying dementia.

Tadalafil belongs to the same group of drugs, and the researchers hypothesize that the mechanisms that increase blood flow in other parts of the body, may also apply in the brain—providing brain cells with a healthier blood supply and reducing dementia symptoms.

Tadalafil was selected as the drug candidate for the trial because of its longer half-life (remaining in the bloodstream for longer) and evidence that it is better able to enter the brain, than its related drugs.

The trial compared a single dose of tadalafil with placebo, recording brain blood flow using an MRI-based method called arterial spin labeling, which traces blood flow without the need for radioactive tracers.

The investigators did not detect a significant difference in blood flow between those given tadalafil and those given a placebo. However, the results did show a trend for increased blood flow in older participants (those aged over 70) in the white matter of the brain, which is the area most important for vascular dementia.

No serious adverse events were recorded during the trial.

The research team believe further investigation of tadalafil should be considered to explore its effectiveness in older age groups over a longer time period.

Dr. Jeremy Isaacs, principal clinical investigator on the trial and consultant neurologist at St George's Hospital, said: "Narrowing of the brain arteries is a common contributor to cognitive decline in older people and currently has no treatment. This was a landmark study in which we attempted to reverse the reduction in brain blood flow characteristic of this condition. Although we did not find a significant effect following a single dose of tadalafil, we can't rule out the

possibility of benefits from longer term use, for which further research is needed."

Dr. Atticus Hainsworth, lead investigator on the trial and Reader in Cerebrovascular disease at St George's, University of London, said: "Viagra-like drugs merit further investigation for possible use in dementia. Repurposed drugs have the increased benefits of a shorter development time, a known safety profile and low cost, once their original patent has expired. We hope that further investigations will prove fruitful and provide new options for clinicians treating dementia."

Katherine Gray, Research Communications Manager at Alzheimer's Society, said: "Sadly, for the 900,000 people living with dementia in the UK, there aren't any current drugs to stop dementia progressing. Using existing medications, such as Viagra-like drugs, could shave decades off our search for treatments because they are already shown to be safe for people to use.

"Although it's disappointing that tadalafil did not have a significant effect overall, it's promising that people over the age of 70 did have an increase in blood flow to certain areas of the brain, and we now hope to now see further tests for different doses over a longer period of time."

More information: Mathilde M.H. Pauls et al, The PASTIS trial: Testing tadalafil for possible use in vascular cognitive impairment, *Alzheimer's & Dementia* (2022). DOI: 10.1002/alz.12559

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