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Does Viagra really prevent Alzheimer's disease?

Ever since it was launched in 1998, sildenafil has had the capacity to capture headlines in the world's popular press. In the early days, the headlines related to worries about the supposed cardiac risks associated with using sildenafil and subsequently there have been scares relating to visual and auditory changes. In reality sildenafil, which was originally supposed to be a new treatment for hypertension or angina was "repurposed" as the first effective oral treatment for erectile dysfunction (ED) and has been followed onto the market by a number of other PDE5 inhibitors, most notably tadalafil and vardenafil. The early worries around safety have proved unfounded. Additional indications for this class of drugs have been identified, with sildenafil being licensed for the treatment of pulmonary hypertension in 2005 and tadalafil being licensed for male LUTS in 2011.

The very recent headlines reflect data which suggests that sildenafil might also reduce the risk of Alzheimer's disease. The basic pharmacological effect of these drugs is to inhibit the enzyme PDE5, thereby resulting in raised intracellular cyclic GMP levels and previous studies have suggested that there are raised levels of PDE in the brains of people with Alzheimer's disease that is also associated with low levels of cyclic GMP. Furthermore, animal studies have demonstrated a possible neuroprotective action for this class of drugs.

The first publication suggesting that sildenafil might be a candidate drug for Alzheimer's disease appeared in *Nature Aging* in 2021. Using a retrospective case control epidemiological methodology based around insurance claims data from over 7 million individuals, the authors found that sildenafil usage was associated with a 69% reduced risk of developing Alzheimer's disease. The authors backed this up with *in vitro* data suggesting that sildenafil increased neurite growth and decreased phosphorylated-tau protein expression (one of the cellular hallmarks of Alzheimer's disease) in stem cell derived neuronal models, providing a mechanistic explanation for the potential benefit of sildenafil.

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While a subsequent paper, using different methodology, reached the opposite conclusion, the most recent publication used data from pseudonymised electronic primary care data from over 16 million UK patients. The investigators identified all those patients with a diagnosis of ED between January 1st 2000 and March 31st 2017, and compared the exposure to a PDE5 inhibitor with the appearance of a new diagnosis of Alzheimer's disease. They identified over 413 000 men with newly diagnosed ED and after applying appropriate exclusions, over 269 000 men were included in the analysis with over 1.3 million person years of follow-up.

https://www.theguardian.com/society/2024/feb/07/viagra-may-help-to-lower-the-risk-of-alzheimers-disease-study-finds

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* 2021; 1: 1175–88.

Desai RJ, Mahesri M, Lee SB et al. No association between initiation of phosphodiesterase-5 inhibitors and risk of incident Alzheimer's disease and related dementia: results from the Drug Repurposing for Effective Alzheimer's Medicines study. *Brain Commun* 2022; 4: fcac247.

Adesuyan M, Jani YH, Alsugeir D et al. Phosphodiesterase Type 5 Inhibitors in Men with Erectile Dysfunction and the Risk of Alzheimer Disease. *A cohort study. Neurology* 2024; 102: 1–11.

Within the cohort, there were 1119 individuals with newly diagnosed Alzheimer's disease and the authors found that exposure to a PDE5 inhibitor reduced the risk of Alzheimer's disease compared with non-users (HR 0.82, 95% CI 0.72–0.93) with additional analyses suggesting a dose response effect, such that increased exposure to the medication provided additional benefit in terms of risk reduction.

> *"Is the benefit due to the medication or to the sexual activity that it facilitates?"*

The authors accepted that there were a number of limitations with the research; firstly, that the exposure was based upon prescription records and therefore

did not prove that the patient had either collected or used the medication. Secondly, the diagnosis of Alzheimer's disease was made on the basis of records, rather than more definitive methods such as diagnostic brain imaging or lumber puncture. Thirdly, given the "on demand" use of the PDE5 inhibitors, the true dose response relationship is difficult to prove. Finally, there is the very obvious issue that men who seek a PDE5 inhibitor, are by their nature likely to be more active, both physically and sexually than patients who do not. Is the benefit due to the medication or to the sexual activity that it facilitates?

Certainly research such as this would potentially support a randomised controlled trial, including both men and women, to explore whether this class of medication truly can contribute to the prevention of Alzheimer's disease. But it raises a wider question that is increasingly relevant to the management of other conditions that has gained significant interest in recent years, specifically "*Can drugs that have a proven role in the management of one disease, be re-purposed for use in another?*"

Repurposing of established drugs for additional indications… even in urology

This question has arisen most commonly in relation to the management of cancer and of rare, so called "orphan" diseases. Indeed, even in urology, there is no shortage of drugs that have been developed for other conditions that have subsequently gained a greater or lesser role in urological practise. Examples include the use of selective serotonin reuptake inhibitors for premature ejaculation and the potential use of ketoconazole and metformin in prostate cancer.

One of the problems with new drug development is that it is estimated that it costs around 2–3 billion US Dollars to take a new pharmaceutical compound from the test tube to the patient. Much of the development process (and cost) relates to understanding the kinetics, dosage, tolerability and safety of the new compound. One advantage of repurposing is that much of this information is already known, such the costs of development can be mitigated, potentially by as much as 30%. Set against that, no pharmaceutical company is going to undertake research into the potential efficacy of a drug that is near to, or past its patent date. Accordingly, the responsibility for such research will inevitably lie with others, including the traditional funding organisations.

The good news is that, perhaps encouraged by the plethora of such research that accompanied the Covid-19 pandemic (and indeed those trials contributed considerably to the fight against the virus), there is considerable interest in such research, as evidenced, for example, by the number or trials registered on ClinicalTrials.gov to explore the role of metformin in the treatment of prostate cancer.

So while we, as urologists, might be amused to see newspaper headlines regarding the potential role of sildenafil in preventing Alzheimer's disease, the principle of drug repurposing is an active area of academic research that might benefit our own patients in the future.

https://clinicaltrials.gov/search?cond=PROSTATE%20CANCER&intr=metformin

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