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Natural experiments with sildenafil and stiffness

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In August 2020, I found myself being taken by ambulance to the intensive care unit (ICU) at the Royal Brompton Hospital. For the preceding year I had been getting progressively more fatigued and breathless. I was periodically put on antibiotics to treat what was presumed to be a chest infection, but my symptoms had continued. Shortly after the first lockdown ended, my GP suggested that I go to the emergency department to be seen by a doctor in person. The attending doctor at my local emergency department then made the decision to transfer me to an ICU for the treatment of suspected infective endocarditis.

This decision was the first of many that undoubtedly saved my life. Within a week, I had gone into multiple organ failure and was in a chemically induced coma while on extra corporeal membrane oxygenation (ECMO). I remained on ECMO for six weeks and in hospital for nearly 100 days. The medical details have been written up in a case study for those interested.[1] Luckily, I made it out alive and I am eternally grateful to the doctors and nurses who saved me.

The only lasting issue was a diagnosis of chronic thrombotic pulmonary hypertension. To reduce my pulmonary pressure, I was put on a dual medication treatment of macitentan and sildenafil. Like many people in their mid-20s, I found that the tedium of the UK's second lockdown in 2020 caused my mind to wander. Learning more about the broader context for which sildenafil is prescribed, and how that might alleviate my lockdown blues, my curiosity and slight anxiety then turned to thinking about the long term effects of being put on a medication largely prescribed to treat erectile dysfunction.

Many people probably would have been tempted to "experiment" about the effects with someone else once covid-19 restrictions were lifted. But this is a scientifically suboptimal approach for learning about drug effects: any good epidemiology textbook should explain that such an "experiment" would be difficult to interpret causally because of the small sample size and lack of control group. In addition to the risk of catching an infectious disease, a practical limitation of "experimenting" is having to wait in real time to find out what the long term effects would be. These could all be avoided by instead analysing existing epidemiological data.

Before being admitted to hospital, I had been working on my PhD thesis applying mendelian randomisation to study the intergenerational effects of exposures such as second hand smoking on health outcomes. Given the methods used in my thesis, I considered a potentially obvious alternative was to use a "natural experiment" to study the consequences of long term exposure to sildenafil. Specifically, I could leverage the random inheritance of genetic variants that mimic sildenafil's effect in a drug target mendelian randomisation study.

The design and analyses of drug target mendelian randomisation studies can differ from the epidemiological applications of mendelian randomisation that I had previously worked on. Fortunately, my friend Dipender Gill had been trying to stoke my interest in the pharmacological applications of mendelian randomisation. Our linked article in the Christmas issue therefore emerged as a personally pertinent exercise, and one that gives insight into the consequences—serious and otherwise—of the potential effects of PDE5 inhibitors such as sildenafil.[2]

Competing interests: Please see the linked research paper for a full declaration of competing interests.

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1 Ibrahim W, Hoschtitzky A, Thakuria L, etal. Follow the Lead: The Challenges of Cardiogenic Shock in Device-Related Infective Endocarditis. *JACC Case Rep* 2021;3:-9. doi: 10.1016/j.jaccas.2021.05.012 pmid: 34401751

2 Woolf B, Rajasundaram S, Cronjé HT, Yarmolinsky J, Burgess S, Gill D. A drug target for erectile dysfunction to help improve fertility, sexual activity, and wellbeing: mendelian randomisation study. *BMJ* 2023;383:e076197. doi: 10.1136/bmj-2023-076197. pmid: 38086555