getting around, and terms such as "confined to a wheelchair" or "wheelchair bound" are still in common usage.

In *The Lancet Neurology*, Alim Benabid and colleagues[5] discuss the clinical application of a brain–computer interface system developed for patients with tetraplegia with cervical spinal cord injuries, which enabled bilateral control of the arms and legs of an exoskeleton or a computer avatar, for a 24-month period. An originality of this study is showing the control of four limbs, whereas in most previous studies only one limb was controlled. However, autonomous walking with equilibrium is not so far possible. Although this study presents a welcome and exciting advance, we must remember that proof of concept is a long way from usable clinical possibility. A danger of hype always exists in this field. Even if ever workable, cost constraints mean that high-tech options are never going to be available to most people in the world with spinal cord injury. One analysis[6] suggests that only 15% of the world's disabled population have access to the wheelchairs or other assistive technologies that they need.

People with tetraplegia do already have usable solutions, in the form of lightweight wheelchairs with new generation batteries, and controls that can enable users to drive themselves by blow and sip, by micromovements of one hand, and by other means. Although this study suggests the possibility of replacing a joystick by conscious control, why this is a major practical improvement is not obvious. Highly effective control systems for hoists, beds, living areas, cars, and most other areas of daily life are available, benefiting many people with spinal cord injury. Often, making environments accessible or providing appropriate assistive technology is more effective than trying to fix individuals with injury, particularly in low-income settings.[6] However, our dominant medical mindset seems always to have wanted to make the paralysed walk.

Benabid and colleagues' study does not make space for user views, which is disappointing, although apparently the research participant found his added control to be rewarding. Developments in rehabilitation—whether neurosurgical, therapeutic, or technological—are more likely to be taken up if the views of the potential beneficiaries are considered at the outset. Although a newly paralysed patient does indeed dream of walking again, a person who has adapted to their situation might have other priorities—eg, bladder or bowel management, pain control, or avoidance of pressure sores. Indeed, people with spinal cord injury generally enjoy a good quality of life,[7] regardless of the level and degree of lesion.[8] Understanding the life goals of this patient group would be an important step towards collaborating on a genuinely useful medical or technological advance. Ending the focus on moving limbs might assist people who have had trauma in adapting to their situation.

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Glycolysis as a therapeutic target for Parkinson's disease

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A drug licensed in the USA and Europe for the treatment of benign prostatic hyperplasia and hypertension might be neuroprotective in Parkinson's disease. This is the conclusion of a study that assessed the effects of terazosin across a range of experimental models of Parkinson's disease, and explored epidemiological associations in databases.[1] The report follows another study that identified that, in addition to blocking α_1-adrenergic receptors, terazosin acts on phosphoglycerate kinase 1 (PGK1) activity, increasing the product of glycolysis—ie, pyruvate.[2] This action has downstream consequences, increasing oxidative phosphorylation, mitochondrial activity,

and ATP concentrations, all of which might have direct implications for Parkinson's disease pathophysiology.

The more recent study found beneficial effects of terazosin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, the 6-hydroxydopamine (6-OHDA) rat model, fly models of familial disease, and in inducible pluripotent stem cells taken from two patients with the *LRRK2* Gly2019Ser mutation.[1] Even when administered 7 days after MPTP in the mouse model or 2–5 weeks after 6-OHDA in the rat model, terazosin rescued the loss of dopaminergic cells and improved the parkinsonian phenotype in these animals.

In a rotenone fly model of Parkinson's disease, terazosin enhanced ATP concentrations, and its protective effects depended on intact PGK1 activity. By studying the relevance of this activity for flies with *Pink1* or *Lrrk2* mutations, and flies that over-express α-synuclein, the authors showed the potential applicability of PGK1 activation to a broad range of pathophysiological processes of known importance in Parkinson's disease. Furthermore, in dopaminergic cells that were differentiated from inducible pluripotent stem cells from two patients with the *LRRK2* Gly2019Ser mutation, terazosin reduced the rate of α-synuclein accumulation.

The Parkinson's Progression Markers Initiative (PPMI) collects detailed information from patients at early stages of the disease. Within the PPMI cohort, seven people who had used terazosin had a rate of progression of 0·01 Unified Parkinson's Disease Rating Scale (UPDRS) points per year compared with 0·54 UPDRS points per year in a control cohort of 269 individuals. Patients treated with tamsulosin, an α_1-adrenergic receptor antagonist with no effect on PGK1, did not have any advantage in terms of their rate of disease progression. In patients treated with other α_1-adrenergic receptor antagonists, doxazosin and alfuzosin (which might both enhance PGK1 activity), the rate of disease progression was only 0·02 UPDRS points per year.

In a separate database, there were fewer hospital visits, non-motor symptoms, hospital admissions, and motor complications reported among patients taking terazosin, doxazosin, or alfuzosin, than among patients taking tamsulosin. Furthermore, in people without Parkinson's disease taking terazosin, doxazosin, or alfuzosin, 118 (0·15%) of 78 444 developed Parkinson's disease over a 9-month period, compared with 190 (0·25%) of 78 444 individuals taking tamsulosin. Inevitably, the breadth of these findings and the consequent publicity surrounding their publication had an effect on people desperately seeking an intervention to slow down their Parkinson's disease.

Should neurologists prescribe terazosin? The drug should not yet be recommended for use in patients with Parkinson's disease for the following reasons. Many drugs have previously been effective in the animal models of the disease, but have subsequently failed when tested in human trials. Furthermore, patients with Parkinson's disease frequently have autonomic dysfunction, which can lead to postural hypotension. Therefore, the hypotensive effects of terazosin, which could aggravate falls and cognitive dysfunction in susceptible patients, are a potential downside of the treatment.

Alternative explanations for the epidemiological findings of the study of terazosin in Parkinson's disease should also be considered.[1] The relative safety and tolerability of tamsulosin versus terazosin might influence how many individuals continue use of these drugs and, in turn (consciously or unconsciously), the prescribing habits of clinicians. For example, if terazosin has a worse side-effect profile, then only more robust patients will continue on it. In a systematic review, tamsulosin was found to be better tolerated than terazosin in terms of dizziness, hypotension, and dry mouth.[3] Therefore, a possible bias in prescribing habits might have contributed to the epidemiological associations reported.

Independent research teams will have to investigate whether the reported effects of terazosin on the glycolytic pathway are reproducible and compare the efficacy and brain penetration of terazosin, doxazosin, and alfuzosin. Other well-studied cohorts could be usefully explored in a similar way to the studies following the suggestion that the β_2-adrenergic receptor agonists might have neuroprotective properties.[4–6] It is pleasing to note that the authors of the terazosin study[1] have already set up a safety and tolerability trial with 20 participants who will be randomly assigned to take 5 mg of terazosin or placebo at the University of Iowa (NCT03905811).

If this 12-week trial confirms that terazosin has acceptable tolerability, the next step will be an efficacy trial. The authors of the terazosin study speculate that the putative increase in ATP associated with the drug might push the equilibrium of aggregated versus soluble α-synuclein in a beneficial direction, or might have an anti-apoptotic effect. If so, this treatment could have

relevance for a broad population of patients, rather than just the so-called mitochondrial subgroup.

In summary, terazosin has suddenly leapt into a growing pool of drugs that might have a repurposed role in Parkinson's disease, such as exenatide, salbutamol, ursodeoxycholic acid, nilotinib, deferiprone, and ambroxol.[7] Clever approaches to multi-arm neuroprotective trials could improve the efficiency of testing useful verses futile agents. This multi-arm approach is at the core of the Linked Clinical Trials Initiative in Parkinson's disease.[8]

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