Towards the end of 2014 a 66-year-old British man named Alistair had a seizure. A scan revealed shocking news. He had an inoperable brain tumour—a glioblastoma—that was likely to kill him in a few years. Soon afterwards, he read a newspaper article suggesting that a cocktail of cheap, everyday drugs, chosen for their anti-cancer effects, had helped a patient with the same disease. His doctors were unimpressed but said: “We can’t stop you.”

Four years on Alistair is still taking this drug regimen alongside the “standard-of-care” treatment. The drug cocktail is prescribed by Care Oncology, a private clinic in London, which recommends a statin (a cholesterol-lowering drug), metformin (used to treat type-2 diabetes), doxycycline (an antibiotic) and mebendazole (an anti-worming agent). These may sound radical, but are actually safe, cheap, generic
medicines with evidence of some anti-cancer effects. Nonetheless, their labels do not say they treat glioblastoma—nor any other cancer for that matter.

This lack of clinical interest is not unusual. There is a huge untapped medicine chest of generic drugs with unexploited uses. Originally approved for one disease, these drugs went off-patent and now show promise in other diseases. Thalidomide, a morning-sickness drug forever linked with scandal and disaster, found new uses in leprosy and a blood cancer. An acne medicine is now part of an effective treatment for a form of leukaemia. Viagra, famously, came from failed work in angina.

The scale of the opportunity for “drug repurposing” is vast. Bruce Bloom, boss of Cures Within Reach, an American repurposing charity, says 9,000 generic drugs have been approved. Pan Pantziarka, of the Anticancer Fund, another charity, says his group has found evidence in almost 260 non-cancer drugs of anti-cancer activity. Most have lost patent protection. The science that has piqued interest in these drugs comes from pre-clinical lab work in animals, case reports, small clinical trials and large-scale observational studies.

Increasingly, large-scale screening studies are plucking options from oblivion. After screening thousands of approved drugs, the National Institutes of Health (nih), an American research agency, identified 25 molecules that might fight drug-resistant bacteria, half of which are already approved drugs. The California Institute for Biomedical Research in San Diego has a library of 12,000 drug compounds it is testing against disease-causing pathogens. Two drugs are in trials as a result: an anti-rheumatic treatment called auranofin for tuberculosis; and clofazimine, a leprosy drug, to treat the parasite Cryptosporidium.
Drugs like these—off-patent, cheap and already approved—are relatively quick to develop to treat new diseases. New molecular entities can cost hundreds of millions of dollars to test, and safety and toxicity problems mean that 45% of drugs fail clinical trials. Repurposed drugs, with well-established safety profiles, can save about five to seven years in development time. Approval rates are higher, and some think overall costs are 60% of those of new drugs.

**Multiple choice**

Interest in drug repurposing has been rising, particularly for medicines that could treat neglected diseases in poor countries, and rare diseases, cancer and mental health. A recent study in *JAMA Psychiatry* said that statins, metformin and blood-pressure drugs had potential for treating mental illnesses such as schizophrenia and bipolar disorder. Minocycline, an antibiotic, is already being tested as a treatment for autism. Ammar Al-Chalabi, a neurologist at Kings College, London, wants to repurpose Triumeq, an HIV drug, to fight motor neurone disease.

There is a problem, however. Katherine Arline of Shepherd Therapeutics, a biotech firm that works in rare cancers, says that, because the costs are high and may not be recouped, firms have little incentive to run clinical trials on generic drugs. Once the costs of testing and registering have been paid, the lack of patent protection means that any firm can make the drug. Some describe generics as “financial orphans”.

One approach is to change the generic drug to create something patentable. This is how the American drug firm, Johnson & Johnson (J&J), approached ketamine, an anaesthetic with a stack of evidence to support its use in treatment-resistant depression. J&J tweaked the molecule to create a variant that could also be inhaled. Reformulation is costly and risks reducing the efficacy of the drug. But J&J seems likely to receive approval from the Food and Drug Administration, the FDA.
For years, like many off-label medicines, ketamine has been a valuable but hard-to-obtain therapy. This has driven the growth of ketamine clinics in America and Europe. In Britain Oxford Health, a unit within the National Health Service (nhs), will provide it. But the nhs as a whole does not cover it because it is not approved for this use, so patients must pay £795 ($1,058) for three infusions; j&j’s esketamine is likely to be far more costly.

Several issues dog reusing generic medicines in new indications. Mr Bloom says that, in his experience, between one-third and a half of patients are loth to use drugs outside the current standard of care—even if they have a disease they know is going to kill them. And even if doctors might be willing in principle to prescribe an off-label drug, many feel unable to do so because of worries about their legal liability should something go wrong. Or there may be disputes over whether public health services or insurers will pay for drugs that have not been approved for that disease.

Nonetheless, many non-profit groups see promise in supporting trials into drug repurposing. Epidemiological data can offer enticing leads. An insurance database in Taiwan shows a 76% reduction in the risk of tuberculosis among diabetic patients on metformin, and progressively larger protective effects with higher cumulative doses. However, Udai Banerji, a researcher at the Institute of Cancer Research in London, warns that randomised clinical trials are necessary to prove definitively the value of a drug to treat a new disease.

Trials are costly, but the benefits can be huge. The Drugs for Neglected Diseases Initiative, a Swiss non-profit research group, supported r&d into fexinidazole, which was abandoned by a pharma firm at an early stage but was then found to show anti-parasitic qualities. This January, after years of work, it was approved for sleeping sickness in the Democratic Republic of Congo. It is the first oral medicine for the disease, and works for all stages of it.
When it comes to cancer, some of the most promising generic pills are already well-known. Cancer Research UK, a charity, is testing aspirin to see if it can stop cancer recurring; metformin in a large prostate-cancer trial; and an anti-fungal medication to treat bowel cancer. The Anticancer Fund in Brussels has high hopes for propranolol in treating angiosarcoma—cancers of the inner lining of blood vessels—and for pancreatic cancer. Propranolol is a generic 1960s beta-blocker used for a wide range of ailments such as hypertension, anxiety and migraine. If approved for cancer, its price would be negligible compared with the tens of thousands of dollars a month normally charged for cancer medicines. Mr Banerji estimates that one cancer drug in five that goes off-patent is likely to have uses in treating other cancers. It is “almost free money”, he says.
The Anticancer Fund believes that the path to wider uptake of repurposed drugs is through approval and relabelling by drug
regulators for new treatments. Although difficult and expensive, Mr Pantziarka says it unleashes a cascade of important events. When a regulator licenses a drug, clinical guidelines are updated, drug formularies are changed, reimbursement should follow more smoothly and clinicians gain experience using it. In America Mr Bloom agrees that relabelling will encourage the usage of repurposed drugs.

Money, though, is a crucial constraint. Even governments keen to pump cash into drug development prioritise drugs with patents. Mr Pantziarka says many official funding schemes, such as the eu’s Horizon 2020 programme, want projects that hold intellectual property. In America the National Centre for Advancing Translational Sciences will support research to help drug companies repurpose molecules for which they hold patents.

Finance is not the only obstacle. Only the makers or original developers of a drug are permitted to adjust its label. Sanofi, based in Paris, was the firm that requested regulatory review of fexinidazole for sleeping sickness—although the r&d was a charitable effort. But drug firms are not obliged to support non-commercial efforts to repurpose drugs. And outside the industry it is hard to find the legal expertise to manage the necessary paperwork.

Some of these concerns are under review by an expert group on repurposing within the European Commission. It is looking at how regulatory changes, as well as legal and financial support, could support repurposing by third parties such as charities and foundations. The Anticancer Fund wants the regulator to be able to evaluate evidence on drugs that has been submitted by third parties such as itself.

As non-profits make headway in repurposing, corporate interest may be rising. Mr Bloom says that ten years ago not a single pharma company would have anything to do with his charity. Today he receives calls from at least two or three small- to mid-sized firms every month saying they are interested. In terms of achieving new treatment options, this is good news. But it will not bring cheaper medicines in areas traditionally
neglected by the drug industry. Firms will focus on finding ways to patent the new uses—through reformulation or new combinations of substances—and charge high prices for the finished product.

If governments want cheaper drugs, non-profits will need financial incentives and a helpful regulatory framework. Would-be repurposers have come up with some suggestions. They include making regulators give free advice and waive approval fees, and a public fund to support repurposing. Another idea is a “social-impact bond”—backed by private investors funding a range of drug trials for diseases that cost public-health services a lot of money to treat. When drugs are approved, investors are paid back by the public health service, which makes savings by using the newly approved generic drugs.

**Patiently waiting**

The slow pace of change leaves patients like Alistair stranded. Care Oncology says it will publish results from its glioblastoma patients this spring. Though welcome, this will fall short of the gold-standard trial evidence needed to register a drug. The treatment will be left in limbo. And patients will be left to wonder why governments fail to see the purpose of repurposing drugs.

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