OLD DRUGS, NEW TRICKS

Allen Shaughnessy explains how computer power is expanding our pharmaceutical armoury

A meta-analysis last year linking aspirin to reduced death rates from certain types of cancer signalled the latest reinvention of this well established drug.[1] Developed as an analgesic, greater understanding of its properties has led to it being used to treat stroke and reduce the risk of cardiovascular disease, and it has also been suggested to help prevent pre-eclampsia and dementia.

Aspirin is just one of many drugs that have found new uses, some before they even get to market (see table). Raloxifene, for osteoporosis, was a failed oral contraceptive found to increase bone density. The antidepressant fluoxetine flunked hypertension trials but affected mood. The erectile dysfunction treatment sildenafil was ineffective for angina. All three medicines were repurposed to great effect.

Discovering new uses for old drugs offers great promise for quickly bringing new therapeutic options to patient care; the lag between drug discovery and availability, often 10 years or longer, can be shortened by dusting off drugs already marketed and repurposing them. But the discoveries are not simply down to serendipity. New uses are increasingly being discovered not by pharmacologists but by computer scientists in university departments of computational drug discovery or biomedical informatics.

Serendipity and science

Many of the new uses result from better understanding of the drugs' method of action. Sildenafil, for example, has its roots in zaprinast, an analogue of theophylline that was never marketed but investigated as a treatment for allergy. The drug was also found to potentiate the effect of nitrates by inhibiting breakdown of cyclic guanosine monophosphate (cGMP), an intracellular messenger that causes vasodilatation and hypotension. Although the drug was promising in laboratory studies, its results in angina were disappointing, but some men reported an increase in erectile function. Pursuing this side effect resulted in the development of an explanation of erectile function as a function of cGMP as well, and a new drug market was opened.[2 3] Sildenafil and its cousins are more potent chemical variations of this shelved drug.

Similarly, the monoclonal antibody bevacizumab was originally developed to treat patients with metastatic colon cancer and non-small cell lung cancer by inhibiting angiogenesis, preventing vascularisation of the tumour. It is now being used, alongside other angiogenesis inhibitors, to slow or reverse abnormal vascularisation of the retina in exudative (wet) macular degeneration.[4]

Perhaps one of the most unexpected examples of new uses is that of the sedative thalidomide, prescribed for morning sickness in the 1950s.[5] Although it was withdrawn from the market in 1961 after over 10 000 children were born with phocomelia,[5] a small supply remained on the pharmacy shelves of a French hospital several years later. Desperate to find relief for a critically ill patient with erythema nodosum leprosum, a doctor prescribed it. The patient, "slept soundly for 20 hours, and, on waking, felt well enough to get out of bed without assistance."[6] Later research found that thalidomide worked in leprosy by inhibiting tumour necrosis factor alpha. Its antiangiogenesis activity was subsequently identified, leading to its use for treatment of multiple myeloma.

Examples of repurposed medicines

Drug	Original use	Repurposed use
Allopurinol	Antineoplastic	Gout
Amantadine	Antiviral	Essential tremor
Atomoxetine	Antidepressant	Attention deficit hyperactivity disorder
Bimatoprost	Glaucoma	Eyelash growth
Bromocriptine	Parkinson's disease	Type 2 diabetes
Colchicine	Gout	Post-pericardiotomy syndrome
Colesevelam	Cholesterol lowering	Type 2 diabetes
Doxepin	Antidepressant	Sleep
Metoclopramide	Gastro-oesophageal reflux	Migraine
Thalidomide	Sedation	Multiple myeloma

Prospecting for gold in the literature

Identification of new uses for old drugs has become a science in itself. Forget in vitro and in vivo research—the new frontier is "in silico" research using computer applications.

Drug-disease interactions are usually thought of as occurring in patients, but they also occur in vast databases. Hidden relations in the literature can be found by computer analysis of great mountains of text for biomedical concepts (drugs, diseases, or genes) occurring in close proximity to one another. Called "co-occurrence," this method assumes that biomedical concepts occurring in the same body of text in a database are in some way related. Using a database of around 250 000 keywords called CoPub, researchers connected the antidepressant milnacipran to obsessive compulsive disorder through research connecting both to several genes. Animal research subsequently showed that milnacipran had an effect on obsessive compulsive disorder as predicted by this computer based connecting of the dots.[7]

Another method is to compare side effects of marketed drugs, creating complex networks to discover new receptor targets and pharmacological action. Using algorithms and statistical probability mapping, one approach analysed the likelihood of common targets among 277 885 pairs of 746 marketed drugs. After several nervous system drugs and the proton pump inhibitor rabeprazole were noted to have similar side effects, rabeprazole was found to inhibit a specific dopamine receptor and stimulate a particular serotonin receptor.[8]

Even more complex is the "similarity ensemble approach" that starts with pharmacological targets—receptors, proteins—and clumps them into specific targets by the drugs that are known to bind to them. This technique captures similarities across disparate drug receptors. This approach discovered, for example, that fluoxetine and paroxetine have ß adrenergic blocking activity and that the reverse transcriptase inhibitor delavirdine has antihistamine effects.[9]

The connections can also be made in the other direction. In fragile X syndrome emotional and intellectual disabilities occur as a result of the physical alteration of neuronal synapses due to a missing protein encoded by a missing or inactive gene. However, researchers found that the neuronal malformation can

be avoided by blocking a second gene in the dendrite.

As a result of this co-occurrence of molecular events—a protein that affects neuron formation and a receptor in another part of the cell that can be turned off—the missing gene can be rectified without gene therapy. From this discovery it was simply a matter of finding a drug to block this receptor. Hiding in a database was the knowledge that fenobam, a never marketed anxiolytic, antagonises this receptor, and clinical research is underway to evaluate its effectiveness.[10 11]

Even social scientists have had a role in drug discovery and rediscovery. By analysing research articles and patents they can discover evolving collaboration networks and localised nodes of research activity that cross institutions. These networks are increasingly important as boundaries between drug companies and academic institutions blur and can focus research efforts by connecting researchers and even predicting where drug discovery may occur. The modelled networks also help redistribute closely held industry information that is not commercially exploitable to academic institutions, which are more willing to investigate treatments for non-commercial diseases or for older drugs that are no longer financially viable.[10]

Serendipity: a "rye" effect on diabetes

The serendipitous connection of bizarre behaviour and hallucinations after eating bread led to the discovery of a rye grain fungus that produces ergot, a chemical with effects on dopamine and other receptors in the central nervous system. Bromocriptine is an ergot derivative developed over 30 years ago to treat Parkinson disease and hyperprolactinaemia by this mechanism. When dopamine and other neurotransmitters were found to regulate leptin, ghrelin, insulin, and other hormonal signals that affect hepatic glucose production, bromocriptine was reinvigorated as a treatment for patients with type 2 diabetes.

Incentives to repurpose

Despite the promise of new treatments from old drugs, there is little incentive for drug manufacturers to perform the clinical testing to get approval for a new indication of a drug that is off patent. Patent protection usually does not apply, since it is the drug and not its use that is protected. The financial risk to manufacturers is even higher if the new use is for a rare disease.

The European Union has taken a small step to encourage the investigation of new drug uses by extending patent protection by an additional year for the new use. The value of this concession is questionable, however, because the new use has to be approved within eight years after the first marketing authorisation.

In the United States, a government sponsored National Centre for Advancing Translational Science will open by the end of this year, charged with developing new drugs. The centre will support initial clinical investigation of drugs, serving as a bridge between the basic science research supported by the National Institutes of Health and clinical research sponsored by drug manufacturers. However, this centre may focus on new chemical entities and may not explore new uses for existing drugs.

The industry has tried various approaches to protect its investment in repurposed drugs. The antidepressant bupropion (Wellbutrin) was marketed under a new brand name (Zyban) when repurposed for smoking cessation. Fluoxetine (Prozac) was renamed Sarafem to treat premenstrual dysphoric disorder.

Another approach is to use a previously unmarketed dose to provide market exclusivity. The makers of bromocriptine conquered the generic problem by getting a new licence for diabetes with a tablet size of 0.8 mg, which cannot be achieved by using generically available 2.5 mg tablets. The antidepressant doxepin, remarketed for insomnia, is given as a 6 mg dose, which is unavailable from other manufacturers.

"Chance favours the prepared mind," according to Louis Pasteur, attributing a combination of luck and intellect to explain his string of serendipitous discoveries. Perhaps today he would have added, "and powerful databases." The brute force drug discovery method of testing thousands of chemicals will still have its place, but just as computer generated graphics are replacing actors on the movie screen, so too are researchers finding new uses for old drugs on a computer screen.

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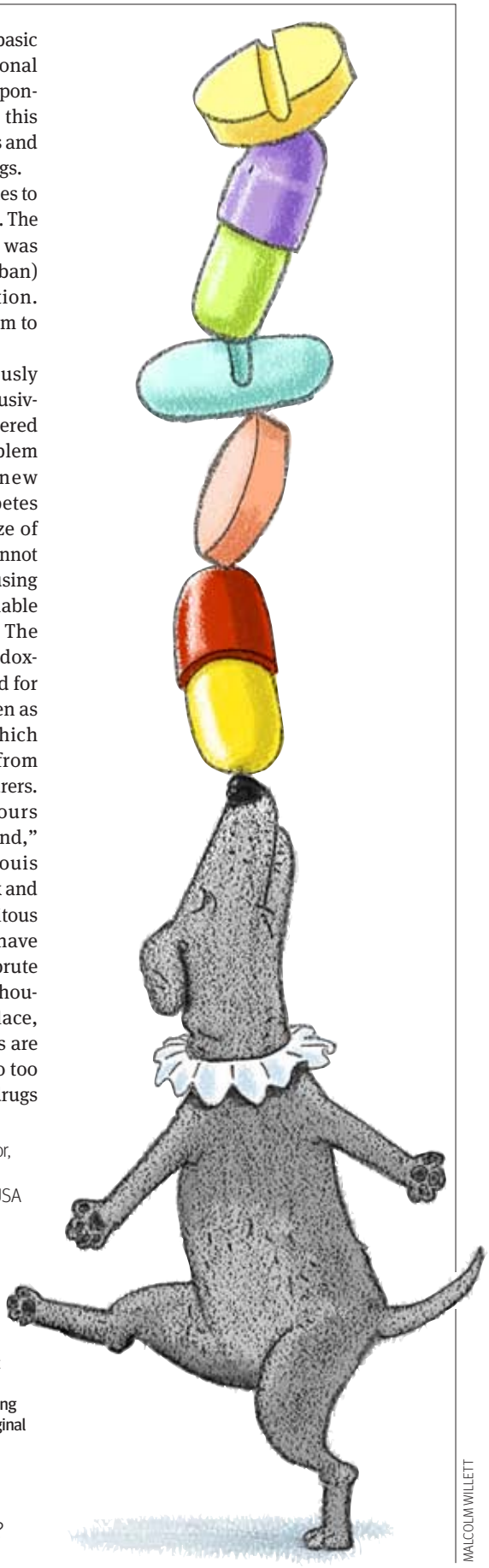

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