

EDITORIAL

Drug repurposing: Landmark achievements in translational medicine

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Drug repurposing is finding new medical uses for drugs that are already approved and in use. Over the past decade, it has become one of the most practical and productive strategies in translational medicine. As these drugs already have known safety profiles and established manufacturing processes, repurposing saves considerable time and cost compared to developing entirely new medicines. By leveraging the known safety profiles, pharmacokinetics, and manufacturing processes of established compounds, repurposing significantly shortens the path from laboratory observation to clinical application.¹⁻³

Several examples illustrate the clinical impact of this approach. Metformin, introduced decades ago as an antidiabetic agent, has attracted substantial attention for its antiproliferative and senolytic properties, with growing evidence suggesting it may reduce cancer incidence and delay aging-related pathologies.⁴⁻⁶ Thalidomide, once withdrawn from the market due to severe teratogenic effects, was successfully repositioned as an effective treatment for multiple myeloma and leprosy-related complications.⁷⁻⁹ Thalidomide repurposing demonstrates that even controversial compounds can find legitimate and life-saving second applications. Aspirin, one of the oldest drugs in clinical use, has shown meaningful chemopreventive potential in colorectal cancer, prompting ongoing trials to define its role in oncological prevention.¹⁰ More recently, immune checkpoint inhibitors originally developed for melanoma have been repurposed across a wide range of solid tumors, transforming the treatment landscape in ways that would have been difficult to anticipate from the original indication alone. The COVID-19 pandemic accelerated interest in drug repurposing as a rapid-response strategy. Dexamethasone, a corticosteroid that has been used in clinical settings for over half a century, significantly reduced mortality in hospitalized patients with severe COVID-19 in the RECOVERY trial,¹¹ making it one of the most impactful translational findings of the pandemic period. Baricitinib, a Janus kinase inhibitor developed for rheumatoid arthritis, was similarly repurposed for severe COVID-19 based on its anti-inflammatory mechanism, receiving emergency authorization within months of the pandemic onset.^{12,13}

Sildenafil, marketed by Pfizer under the brand name Viagra, is perhaps the most well-known example of accidental drug repurposing in the history of modern medicine. Originally investigated as a therapy for cardiovascular conditions, its trajectory shifted when an unexpected effect revealed a far more impactful clinical application. Its subsequent adoption as a treatment for erectile dysfunction not only transformed patient care but also marked a defining moment in translational medicine.

In the late 1980s, Pfizer scientists were investigating new compounds to treat angina pectoris and hypertension. Sildenafil was developed as an inhibitor of phosphodiesterase type 5 (PDE5), an enzyme involved in regulating smooth muscle tone in blood vessel

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walls.¹⁴ By inhibiting PDE5, the compound was expected to promote vasodilation in coronary arteries and reduce cardiac workload, thereby relieving the chest pain associated with angina. Early clinical trials, conducted in the early 1990s in Merthyr Tydfil, Wales, yielded disappointing results for its primary cardiovascular indication. The compound did not perform well enough as an antianginal agent, and further development in that direction was postponed.¹⁴

However, an unexpected observation emerged from these trials. Male participants were notably reluctant to return their unused tablets at the end of the study. When investigators looked more closely, they discovered that a substantial proportion of participants were reporting spontaneous penile erections as a side effect. This initially anecdotal observation was taken seriously by researchers who redirected the study. The underlying mechanism, once understood, proved biologically coherent. Penile erection depends on the relaxation of smooth muscle in the corpus cavernosum, a process mediated by nitric oxide and cyclic guanosine monophosphate. PDE5 breaks down cyclic guanosine monophosphate, terminating the erection response. By inhibiting PDE5, sildenafil effectively prolonged and enhanced the natural erectile mechanism in response to sexual stimulation.¹⁵ This meant the drug was not inducing erections independently, but amplifying a physiological process already in motion. Such distinction proved important both clinically and regulatorily.

Pfizer rapidly modified its development strategy. Clinical trials in men with erectile dysfunction showed strong efficacy and an acceptable safety profile. In 1998, the United States Food and Drug Administration approved sildenafil as the first oral treatment for erectile dysfunction, under the brand name Viagra. The drug rapidly achieved widespread clinical and societal recognition and, within a few years, had generated billions of dollars in revenue. It transformed both Pfizer's commercial position and the clinical management of a condition that had previously been neglected or incurable.

Subsequent investigations further expanded its clinical applications. Sildenafil was later investigated for pulmonary arterial hypertension, a serious and often fatal condition characterized by elevated pressure in the pulmonary circulation. Since PDE5 is highly expressed in pulmonary vascular smooth muscle, the same vasodilatory mechanism proved therapeutically relevant in this entirely different clinical context.¹⁶

In 2005, sildenafil received Food and Drug Administration approval for pulmonary arterial hypertension under the brand name Revatio, completing a notable development trajectory from failed heart drug to

dual-indication blockbuster.

The sildenafil story delivered several key lessons for translational medicine: the value of attentive clinical observation, the importance of understanding mechanism over indication, and the recognition that unexpected findings in clinical trials, rather than being dismissed, can open entirely new therapeutic avenues. It remains a key example of how repurposing, whether planned or serendipitous, can deliver transformative benefits to patients.

The story of Minoxidil is another striking example of serendipitous drug repurposing, sharing surprising parallels with the sildenafil story.^{17,18} Minoxidil was first synthesized in the 1960s by the Upjohn Company in a research program aimed at finding new treatments for severe hypertension. It belongs to a class of compounds known as potassium channel openers. It works by relaxing the smooth muscle in arterial walls, causing blood vessels to dilate and blood pressure to fall. Early clinical trials confirmed that minoxidil was a potent antihypertensive agent, particularly effective in patients with severe or treatment-resistant hypertension who had not responded adequately to other medications. The Food and Drug Administration approved it in 1979 under the brand name Loniten for oral use in this indication.

However, minoxidil exhibited a notable and troublesome side effect profile. Patients taking the oral formulation frequently experienced fluid retention, rapid heart rate, and a condition called hypertrichosis: the excessive and unwanted growth of body hair in areas such as the face, arms, and back.¹⁹

In the context of antihypertensive therapy, this was considered an undesirable complication. However, as later observed with sildenafil, this finding attracted scientific attention from researchers thinking beyond the original indication. In the early 1980s, dermatologists and clinical investigators began asking a logical question: if oral minoxidil stimulated hair growth systemically as a side effect, could a topical formulation applied directly to the scalp produce the same effect locally, without the cardiovascular side effects of the oral drug? This hypothesis was scientifically grounded. Minoxidil, as a potassium channel opener, was known to promote vasodilation, and, thus, it was hypothesized that it could improve blood flow to hair follicles. This, combined with a possible direct stimulatory effect on follicular cells, might slow or reverse hair loss.

Clinical trials in the early to mid-1980s tested a topical solution of minoxidil in patients with androgenetic alopecia, the most common form of hair loss in both men and women,

driven by genetic sensitivity to dihydrotestosterone. The results were encouraging. A meaningful proportion of participants showed visible hair regrowth or a slowing of hair loss, particularly in the vertex region of the scalp. The effect was modest in absolute terms, but in a condition with virtually no approved pharmacological treatment at the time, it represented a genuine breakthrough.

In 1988, the Food and Drug Administration approved a 2% topical minoxidil solution under the brand name Rogaine for the treatment of male pattern baldness. It was the first drug ever approved specifically for this indication.²⁰

The approval was both scientifically and culturally significant. Hair loss, despite affecting millions of people, had long been considered a cosmetic rather than a medical concern. The arrival of a regulated, evidence-based treatment changed that perception. A 5% formulation was later approved for men seeking stronger efficacy, and eventually, a lower concentration formulation was approved for women with female pattern hair loss.

Rogaine became a major commercial success, making it accessible without a prescription and dramatically expanding its reach. Generic versions of topical minoxidil subsequently became widely available, making the treatment affordable.

Despite its clinical success, the precise mechanism by which minoxidil promotes hair growth remained incompletely understood for many years. Current evidence suggests that it acts through multiple pathways. It prolongs the anagen phase of the hair growth cycle, stimulating follicular keratinocytes, promoting vascularization around the hair follicle, and possibly exerting direct effects on follicular stem cells. The potassium channel opening activity that underpins its cardiovascular effects appears to play a role in follicular biology, though the exact molecular pathway is still being investigated.

More recently, interest has grown in oral low-dose minoxidil for hair loss. It was returned to the original formulation, but at doses far lower than those used for hypertension, sufficient to stimulate hair growth with a more manageable side effect profile. This represents an additional translational application of the same compound, as clinicians seek to optimize benefit while minimizing risk.

The minoxidil example highlights several important principles. First, it illustrates that side effects, rather than being purely obstacles to be managed, can contain valuable biological signals pointing toward new therapeutic applications. Second, it demonstrates the power of route of administration innovation. Converting a systemic drug into a topical one opened an entirely new therapeutic niche.

Third, it highlights how a compound initially developed for a serious, life-threatening condition can ultimately have its greatest population-level impact in a quality-of-life indication, affecting far more people.

Together with sildenafil, minoxidil stands as one of the most instructive and widely cited examples of serendipitous repurposing in pharmaceutical history. It shows that in drug development, careful observation and scientific curiosity can transform an unwanted side effect into a treatment used by millions.

The growing integration of artificial intelligence and network pharmacology has given drug repurposing a more systematic and scientifically rigorous foundation. Rather than relying on serendipitous clinical observations, researchers can now screen thousands of compounds computationally, mapping molecular targets, interaction networks, and disease pathways to identify repurposing candidates with a high prior probability of success.^{3,21} This shift positions drug repurposing not as an opportunistic shortcut, but as a deliberate and increasingly central strategy within translational medicine.

In summary, repurposed drugs represent a compelling demonstration of translational medicine. They bridge the gap between established science and unmet clinical need, reducing development timelines and costs. As such, drug repurposing delivers tangible benefits to patients across a remarkably diverse range of diseases.

Conflict of interest

Jacek Z. Kubiak is the Editor-in-Chief of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The author declares that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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