



50 Years of Drugs

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50 years is a long time in publishing, and we at Adis (a Springer Nature imprint) are delighted to be celebrating 50 years of our flagship journal *Drugs*. Looking back at how the world of publishing has changed since 1971, there are many improvements that could be noted, but the biggest is obviously the transition from print to digital and all the ease and speed of use that brings. More important though, and of interest to our readership, are the phenomenal advances made during that time in drug treatment.

The current team of therapeutic section editors and I have selected what we think are the most significant advances in drug treatment over the last five decades, and I think it's safe to say that in 1971 no one could have imagined the progress that would be made.

The last 50 years have witnessed several major advances in the drug treatment of cardiovascular (CV) disorders resulting in a significant decrease in CV mortality. The discovery of the antiplatelet effects of aspirin established its place in the secondary prevention of CV disorders. Identification of the pivotal role of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase in cholesterol metabolism led to the establishment of HMG-CoA reductase inhibitors (statins) in the primary and secondary prevention of CV disorders. A paradigm shift in the understanding of the pathophysiology of heart failure with reduced ejection fraction (HFrEF) from being a hemodynamic disorder to a neurohormonal disorder led to the introduction of several drugs that have been proven to prolong life, prevent adverse cardiac events, and improve quality of life. So, from being contra-indicated in patients with HFrEF, beta-blockers have become first-line therapy along with inhibitors of the renin-angiotensin-aldosterone system (RAAS), e.g., the 'prils' and the 'sartans'.

The development of novel insulins with more predictable and stable time-action profiles, a switch to human

insulins from previous animal insulins, and the introduction of both rapid/short acting for mealtime control and longer-acting recombinant insulins for basal control are some of the successes for those with type 1 diabetes mellitus. Novel agents were developed for type 2 diabetes mellitus (T2DM) targeting various mechanisms, of note the incretin-based therapies (glucagon-like peptide [GLP]-1 receptor agonists and dipeptidyl peptidase [DPP]-4 inhibitors [gliptins]) and sodium-glucose co-transporter (SGLT)-2 inhibitors (gliflozins). The past decade has seen a concerted shift in focus away from glucocentricity towards hard clinical outcomes in T2DM. SGLT-2 inhibitors and GLP-1 analogs in particular have been the first agents to demonstrate beneficial effects on cardiovascular outcomes and renal outcomes in patients with T2DM. In addition, there was the discovery that RAAS inhibitors could significantly delay the progression of nephropathy in patients with T2DM, and thus reduce the risk of end stage renal disease.

In oncology, one of the most important developments has been the introduction of molecularly targeted drugs in the early 2000s to allow for personalized cancer treatment as opposed to chemotherapy. For a number of tumour types, small molecule inhibitors or monoclonal antibodies that target specific proteins and inhibit their essential roles in tumorigenesis are now in routine use. Prominent examples are BRAF inhibitors for the treatment of malignant melanoma, or epidermal growth factor receptor (EGFR) inhibitors for the treatment of small-cell lung cancer. Recently, several targeted drugs have received so-called tumour site-agnostic regulatory approvals across different tumour types that are positive for certain oncogenic changes. The other major development has been the introduction of immune checkpoint inhibitors from 2011 onwards. These monoclonal antibodies target the patient's immune system rather than the tumour cells, allowing immune cells to recognize and fight the tumour, resulting in previously unheard of durable responses in a number of indications that used to have a median survival of mere months.

Targeted therapies have also been the major advance in autoimmune/inflammatory disorders such as rheumatoid

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arthritis, inflammatory bowel disease and psoriasis, starting with anti-tumour necrosis factor (TNF)-alpha agents. The rational development of targeted agents, both biologics and small molecule inhibitors, has allowed more specific therapy and with fewer side effects than the conventional treatment options that were previously used. Another key advancement in this area has been a change in the treatment paradigm to 'treat-to-target', particularly in those diseases that used to be managed symptomatically but where disease progression still occurred. This early, strategic treatment to minimize damage accumulation is now the norm.

The development of disease-modifying therapies is also a significant advance for relapsing forms of multiple sclerosis (MS). The first such therapy – interferon-beta-1b – was approved in 1993, and this century has seen the first oral medication for MS (a sphingosine-1-phosphate-receptor modulator), the first humanized monoclonal antibody (mAb), and finally the first approval for primary progressive MS with another more targeted mAb.

We must mention the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the mid-1980s, representing a new approach to the treatment of depression and subsequently anxiety disorders, and the development of the 'atypical' antipsychotics in the mid-1990s, which provided a new approach to treating schizophrenia and related psychotic disorders. The opioid epidemic has had profound effects across the world but many lives have been saved by the use of naloxone, such that the drug is now the agent of choice for reversing opioid overdoses both within emergency departments and outside the hospital setting. On the flip side, the introduction of new formulation and delivery methods for opioids has made a significant impact on pain management, particularly for cancer and chronic pain, and the addition of the third major class of analgesics, colloquially known as 'neuropathic' agents, has had an important role in chronic neuropathic pain conditions.

One of the major drug developments in asthma and chronic obstructive pulmonary disease (COPD) was the beta-adrenoceptor agonists and later the long-acting beta-adrenoceptor agonists (LABAs), as well as long-acting muscarinic receptor antagonists (LAMAs). This led to the introduction of maintenance and reliever combination therapies that allow better control for both asthma and COPD patients. Understanding that asthma is a spectrum of diseases has led to the development of targeted therapies for particular phenotypes, including various monoclonal antibody therapies targeting inflammatory molecules or specific cell receptors. The development of highly effective CFTR-directed therapeutics following the identification of mutations in the CFTR gene underlying cystic fibrosis in the late 80s early 90s has resulted in significant improvements for patients with appropriate mutations in the CFTR gene.

There are now several classes of drugs that can markedly reduce fracture risk in osteoporosis. The 1970s and 1980s saw the clinical introduction of the first generation of the anti-resorptive bisphosphonates with the later introduction of more potent and less frequently administered versions. More recent developments also include analogues of parathyroid hormone, RANK-L targeted treatment, and most recently an anti-sclerostin monoclonal antibody. The past decade has also seen the advent of recombinant enzyme replacement therapies for many metabolic disorders caused by enzyme deficiencies, e.g. lysosomal storage disorders, where previous treatments were predominantly symptomatic.

Vascular endothelial growth factor A inhibitors have resulted in significant improvements in a range of eye disorders that can result in vision loss, including wet age-related macular degeneration, diabetic macular oedema, retinal vein occlusion and retinopathy of prematurity.

The identification in the 1980s that *Helicobacter pylori* was the cause of peptic ulcer disease rather than stress or lifestyle factors meant that they could be treated by a combination of antibacterials and proton pump inhibitors (the latter first approved in the late 1980s). The first antiretroviral therapy (ART) was approved by the US FDA a mere 6 years after the AIDS epidemic was formally recognised in 1981. The continued development of different classes of ART allowing for highly effective combination ART from 1996 means that the current almost 40 million people living with HIV receiving treatment have a life expectancy approaching normal. This rapid development of antiviral agents was replicated this century with the success of direct acting antivirals against hepatitis C virus and the possibility of cure for those with chronic HCV infection.

Although the development of vaccines started much earlier, 1971 saw the licensure of the first combination vaccine for measles, mumps and rubella (MMR). Over the rest of the 20th century, the first recombinant DNA vaccine was developed against hepatitis B virus (HBV), the first bacterial conjugate vaccine was developed against *Haemophilus influenzae* type B (HiB) in children, and the first vaccines to prevent human papillomavirus (HPV)-related cancers were developed. By the start of this century genome sequencing and 'reverse vaccinology' were being used to develop the first vaccine for serogroup B meningococcal infection, and in the last decade synthetic biology techniques enabled the development of vaccine platforms capable of producing pandemic influenza vaccines ready for preclinical testing within a week of genome sequencing and mass production within months.

Antibiotic resistance has been declared by the WHO to be one of the biggest threats to global health, food security, and development today. The scarcity of novel antimicrobial development over the last 50 years has certainly not helped,

and the appropriate use of existing antibiotics has never been more important.

Drug treatment has certainly come a long way in the last half century, and I am incredibly grateful to all the previous Editors-in-Chief before me who have guided the journal through some challenging times as well as great successes, and to all the editors, in-house writers, production and support staff who have helped to bring independent reviews to you the readers. I must also acknowledge the considerable contribution of our Editorial Director, Diana Faulds. She continually looks for ways to improve the reader experience, introducing new article types, figures and digital features, and we are all thankful she encourages us to do the same, always with the overriding mantra ‘the science must be correct’. Finally, my sincere thanks to our Honorary Editorial Board members, past and present. Many have been with the journal for a very long time, and their ongoing support and advice has proved hugely important over the years.

I was delighted Sir Graeme Avery was able to provide insight into how it all started in an accompanying editorial

in this issue (<https://doi.org/10.1007/s40265-020-01451-4>). His vision and hard work saw Adis grow into an international publisher of considerable repute with a suite of journals as well as a database of drug information that remains today as AdisInsight™, now within Springer Nature with all the advantages of being a part of one of the top 10 largest publishers.

Whatever the next 50 years brings, we remain committed to being a respected source of authoritative and independent drug information, and to promoting optimum drug therapy.

Declarations

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