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Drug Management and the Global Crisis

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ABSTRACT

Medication management is reflected in patients' quality of life. The therapy of infectious diseases is going through a major crisis, due to the magnitude of the antibiotic resistance (AR) phenomenon which has reached alarming levels. The design of new (classes of) antibiotics are difficult to achieve, so efforts are being made to stop and reduce the phenomenon, however, monitoring studies do not report the effects of these policies; numerous studies report the isolation of multidrug-resistant and even pan-resistant strains. Moreover, it is estimated that in 2050, mortality from infectious diseases will outpace that of various types of cancer. Antibiotic resistance (AR) is a global public health problem, that requires concerted action plans. The quality of medicines is not reflected in their price. There is currently a mismatch between new medicinal products launched on the market and their effectiveness as well as a rapid rise in prices from the time of launch to the end of the year.

INTRODUCTION

Drug use is an important indicator in the management of diseases. The increase in drug use is proportional to the increase in the number of people with health problems and the inefficiency of drug treatment. The quality of a drug is determined by its effectiveness in a short time. The biggest complications of drug use are the side effects that are not detected immediately but after a long period. At present, the health problems that patients face are aggravated by the cost of medicines, which are inaccessible to people with modest earnings. Drug management statistics show that the prices of prescription drugs have "exploded," growing steadily by about 12% a year from 2004 to 2016. In 2004 alone, the cost of drugs in the United States was 200 billion dollars. The increase in drug spending reflects the fact that people are taking more drugs than before, that new drugs are probably more expensive, and that the prices of prescription drugs are usually high. Prices for new drugs have risen sharply until the end of the year they were launched on the market. A spokesman for a pharmaceutical company explained that these increases are justified, and necessary for reinvestment in research and development [Angell, 2005].

Sun et al (2008) researched China's pharmaceutical policy in cross-profit management of drug sales, and subsidizing public hospitals which has undermined public health. This has been reflected in the aberrant rise in drug prices, the prescription of inappropriate (but much more expensive) medicines and the unavailability of essential medicines or their questionable quality. Pharmaceuticals account for 41% of total health care spending in China and 51% are outpatient visits [Sun et al., 2008].

According to the Organization for Economic Co-operation and Development (OECD), total per capita health expenditure was roughly the same for Germany, the United Kingdom, Sweden and Japan [https://www.statista.com/statistics/1245261/value-share -of-pharmaceutical-subsectors-worldwide /].

MATERIALS AND METHODS

To obtain the necessary and accurate information, we searched for publications in Pubmed, Medlife, the World Health Organization's (WHO's) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not

approved by governments, reference books and other sources of information about withdrawn medicines, which can be found in the References.

Profitability of large pharmaceutical companies

Swedish policies have been mainly aimed at prescribing and delivering high-priced medicines, while the Japanese have addressed several stakeholders to promote the use of generic medicines [Imai et al, 2016]. From 2016 to 2020, drug manufacturers increased the prices of branded drugs by 36%, almost four times the rate of inflation at the time, according to a report detailing the findings of an investigation by the US House Oversight and Reform Commission. The list of the most expensive medicines in the world includes: Humira (diagram 1), Imbruvica, Enbrel, Sèpar, Revlimid, Acthar Gel, Gleevec, Lyrica, Copaxone, NovoLog products, Humalog products, and Lantus products now have an average price almost 500 percent higher than when they were launched on the market. Nearly a decade after Abbott Laboratories first launched Humira in 2003, the list price rose from $ 522 per 40-milligram syringe to $ 1,024 by 2013, with 13 price hikes, before spinning off AbbVie as a separate company. Under AbbVie, the price of Humira spiked another 14 times, including by 30% within a 10-month window. Producătorii de medicamente au obținut peste 600 de brevete pentru 12 medicamente, prelungindu-și perioadele de monopol cu aproape 300 de ani [Adams, 2021].

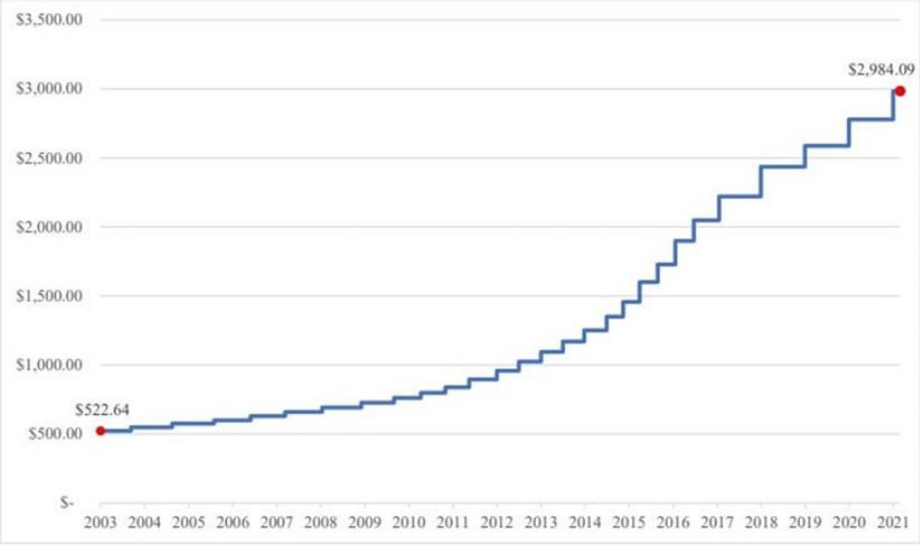

Diagram 1. Humira is now priced at $2,984 per syringe, or $77,586 annually — a 470% increase from when the drug entered the market [Brennan, 2021]

Drug makers have obtained more than 600 patents for 12 drugs, extending their monopoly periods by almost 300 years [Adams, 2021]. In 2016-2020, the top 14 drug manufacturers spent $ 577 billion on share buybacks and dividends, $ 56 billion more than in previous periods [Adams, 2021]. In 2020, research and development spending in the pharmaceutical industry totaled nearly $ 200 billion globally. For comparison, research and development spending totaled $ 137 billion in 2012. Pharmaceutical research and development includes all the steps from the initial research of disease processes, compound testing, pre-clinical testing, and all stages of clinical trials. From 2000 to 2018, the profitability of large pharmaceutical companies was significantly higher than other large, public companies, but the difference was less pronounced when considering the size of the company, or the annual research and development costs [Ledley et al, 2020]. From 2012 to 2020, the expenditure allocated to research and development in the pharmaceutical industry increased by 68.5%, continuously increasing, it is estimated that by 2025 the expenditures will double (Chart 2).

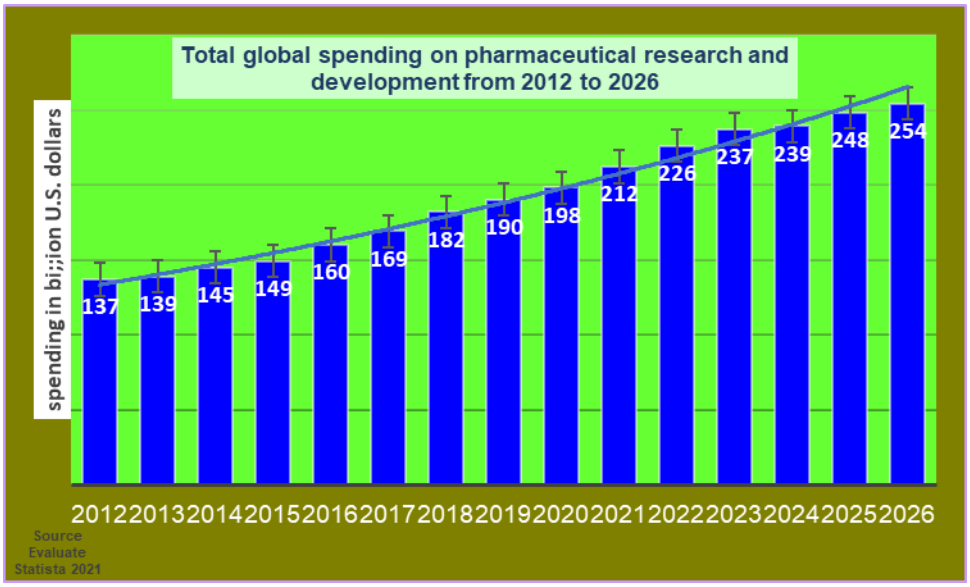

Diagram 2. In 2020, research and development spending in the pharmaceutical industry totaled nearly 200 billion U.S. dollars globally. For comparison, R&D expenditures totaled 137 billion dollars in 2012. Pharmaceutical R&D includes all steps from the initial research of disease processes, the compound testing over pre-clinical, and all clinical trial stages [https://www.statista.com/statistics/1245261/value-share-of-pharmaceutical-subsectors-worldwide/].

In 2020, member companies' R&D spending has reached around the US $ 91 billion. It costs about $ 2.6 billion to develop a new drug and can take up to 15 years. In terms of sales, the pharmaceutical sector invests more money in research and development than many other industries: PhRMA members spent 21 percent of their combined global revenue on research and development in 2020 - a share of more than 23 percent if we only consider the sales and research and development expenditures of the U.S. domestic market [https://www.statista.com/statistics/1245261/value-share-of-pharmaceutical-subsectors-worldwide/].

In Norway, both the value of imports and exports of basic pharmaceutical products and preparations have increased every year since 2011. The value of imports of these products has exceeded the value of exported products (Diagram 3).

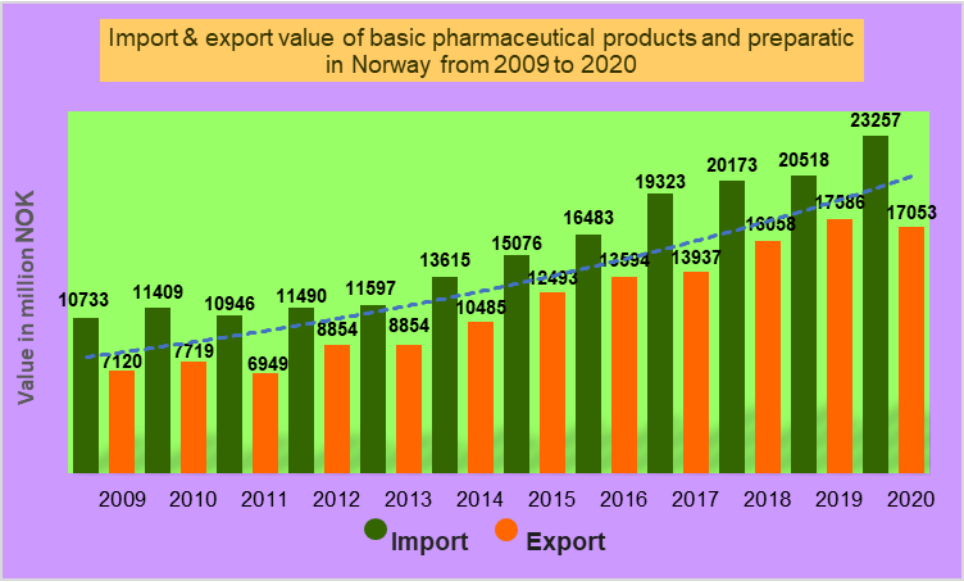

Diagram 3. Overall, both the import and export value of basic pharmaceutical products and preparations in Norway increased every year since 2011. The import value of these products in 2020 was around 23.3 billion Norwegian kroner, and the export value was around 17 billion Norwegian kroner [https://www.statista.com/statistics/1245261/value-share-of-pharmaceutical-subsectors-worldwide/].

While the UK industry has seen a significant increase in drug exports, Japan has always imported more drugs than it has exported. Japan has the largest trade deficit for pharmaceuticals of any

other country in the world. The export of pharmaceuticals has been almost constant since 1950, ranging from 2.5 to 3.0 percent of total pharmaceutical production. Government statistics suggest that only 7.5% of all medicines sold in Japan are imported, a figure that underestimates the importance of foreign drug companies [Neary, 1994]. However, life expectancy and longevity in Japan are the highest compared to the group of seven countries (Canada, France, Germany, Italy, Japan, the United Kingdom (UK), and the United States of America (USA) in alphabetical order from a World Health Organization (Diagram 4).

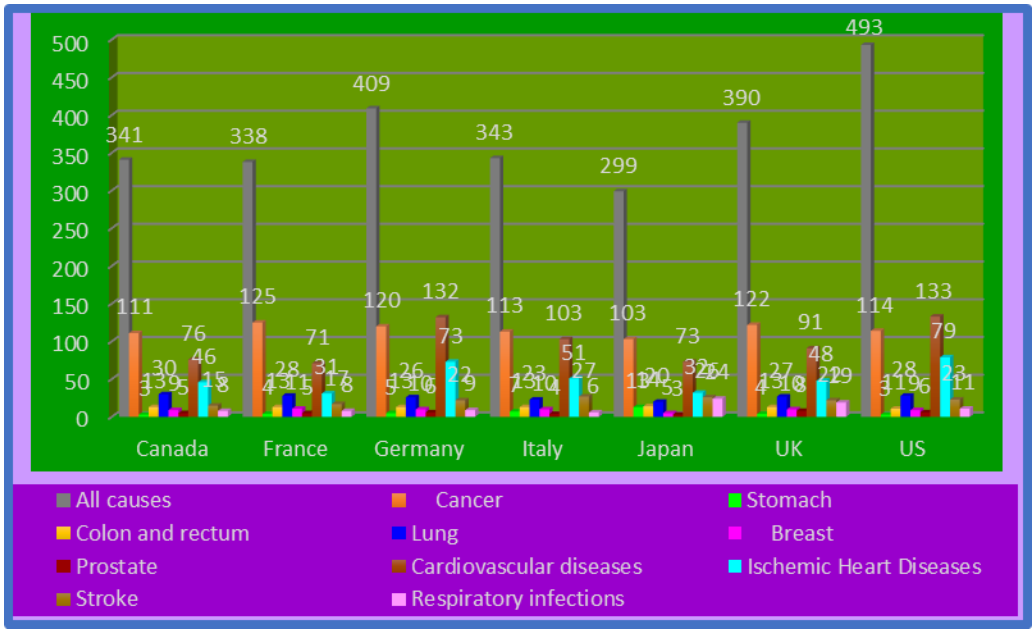

Diagram 4. Mortality statistics in selected countries. Life expectancy is the longest in Japan for both men and women. The mortality rate compared to the USA is about 75% lower. Breast and prostate cancer as well as ischemic heart disease have the lowest mortality rate in Japan. In contrast, mortality from infectious and cerebrovascular diseases is relatively high. Most deaths from various diseases are in the United States.

The longest life expectancy in the world is due to the significant decrease in mortality caused by infectious diseases, which have been increased in the past while maintaining mortality from cancer and low vascular disease [Tsugane, 2021]. Traditional Japanese medicine has remained the same for more than a thousand years. It is divided into folk medicine and Chinese medicine (or Kampo medicine). Traditional medicinal plants are considered by Japanese society to be safe in the treatment of diseases [Zang, 1998; Eguchi et al., 2000; Saito, 2000]. The Japanese

Pharmacopoeia is used as a guide in the use of herbs. In the evaluation of a Chinese medicinal product, "pharmacological facts or experience" shall be taken into account rather than the pharmacological action of each ingredient. In the United States, more than 2.8 million antibiotic-resistant infections are reported each year. More than 35,000 people are dying from infections, according to a 2019 report by the CDC (Center for Disease Control and Prevention) on threats to antibiotic resistance (AR). Thus, the US balance sheet for all threats in the report exceeds 3 million infections and 48,000 deaths [https://www.cdc.gov/drugresistance/biggest-threats.html].

Antibiotic-resistant infections that require the use of second and third-line treatments can harm patients, causing serious side effects such as organ failure and prolonging care and recovery, sometimes for months. The emergence of multiple drug resistance among pathogenic bacteria is a worldwide danger. Antibiotic resistance attributed to the misuse of these agents, which has facilitated the development of new genes that increase virulence, unavailability of new classes of drugs (attributed to demanding regulatory requirements and reduced financial incentives), have all led to the global crisis. [Aslam et al, 2018].

Paradoxically, although research and development spending has almost doubled in the last 20 years, we are facing one of the biggest new drug crises in the world. Antibiotics (Greek etymology ἀντί- contra, βίος- life) are produced from microorganisms such as bacteria or saprophytic fungi, or are obtained synthetically (eg quinolones, sulfamides, and nitrofurans) or semi-synthetic being the most important medicinal substances involved in the treatment and prophylaxis of bacterial infections of different types. For this reason, antibiotic resistance may simply describe the Darwinian competition between microbial-derived natural antimicrobial elements [Forsberg et al, 2014; Aminov, 2009]. In this competition it seems that the microbes are stronger, their adaptation and evolution in the development of new resistance genes go beyond the developmental stage of antibiotics. According to analysts at Research and Development Corporation by 2050, it is estimated that approximately 444 million people will face serious problems due to untreatable infections.

Withdrawal of medicines for safety reasons

Between 1990 and 2010, a total of 133 medicines were withdrawn from the market for safety reasons. Withdrawal time has been shortened in recent years due to serious side effects. Adverse drug reactions have not improved in the last 60 years. The delay between the introduction of the drug and its subsequent withdrawal for safety reasons, as well as the methodologies used to identify previously unknown risks, are still a major concern and there is no gold standard described in the literature [Onakpoya et al, 2016]. Between 82-90% of the safety issues identified in withdrawn drugs were recognized as adverse reactions.

Diagram 5 shows the main reasons why drugs were withdrawn between 1990 and 2010. The main reasons were hepatotoxicity (n = 36, 27.1%), heart disorders (n = 25, 18.8%), hypersensitivity (n = 17 , 12.8%) and nephrotoxicity (n = 14, 9.8%). %), representing 69.2% of all withdrawn drugs [Craveiro et al, 2020].

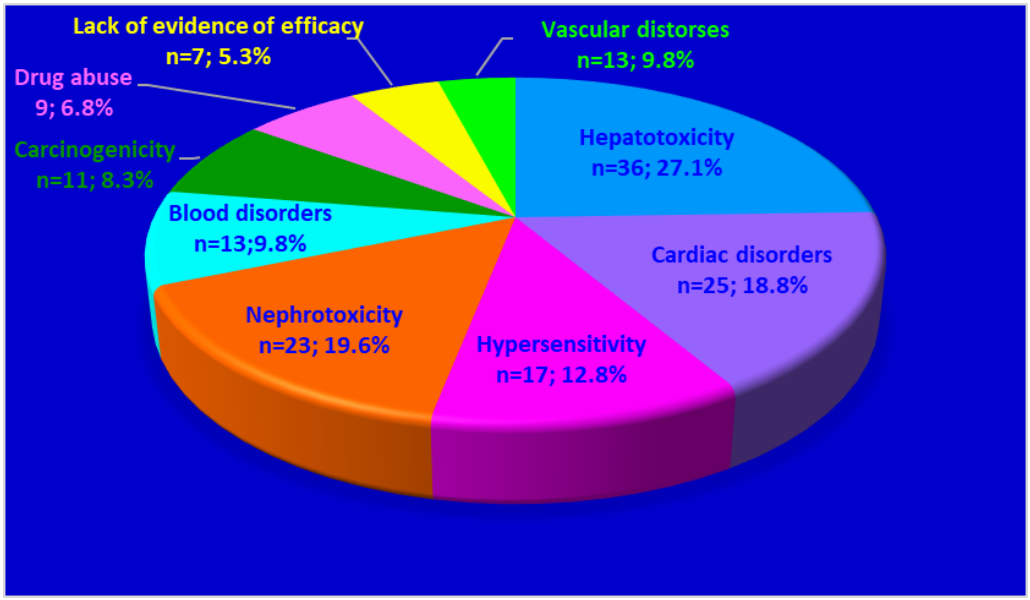

Diagram 5. the main safety concerns identified for medicines withdrawn between 1990 and 2010.

It is estimated that less than 5% of adverse reactions are reported, the average underreporting rate by healthcare professionals was 94%.

Rare side effects of medicines may go undetected for years, exposing patients to unforeseen risks. Examples of major drug withdrawals include lumiracoxib (associated with severe hepatotoxicity), which occurred only after thousands of patients in Australia were exposed. Montelukast-associated neuropsychiatric adverse reactions and euglycemic ketoacidosis associated with sodium-glucose co-transporter inhibitors are rare adverse reactions detected only by careful pharmacovigilance analysis. The Australian Pharmacovigilance System has detected an outbreak of toxicity, hyoscine hydrobromide, due to large variations in the concentration of the active ingredient. Recognizing an adverse effect is a key issue, however, even when it is recognized, it may not be reported [Martin & Lucas, 2021].

Between 2002 and 2011, 19 medicines were withdrawn from the EU for pharmacovigilance reasons (Table 1).

Table 1 Drugs withdrawn from the market with major implications for vital organ dysfunction

Drug name	**Drug class or use**	**Adverse reaction or safety concern**
Rofecoxib	NSAID (COX-2 inhibitor)	Thrombotic events
Thioridazine	Neuroleptic (α-adrenergic and dopaminergic receptor antagonist)	Cardiac disorders
Valdecoxib	NSAID (COX-2 inhibitor)	Cardiovascular and cutaneous disorders
Rosiglitazone	Antidiabetic treatment (PPAR agonist)	Cardiovascular disorders
Sibutramine	Treatment of obesity (serotonin-noradrenaline reuptake inhibitor)	Cardiovascular disorders
Orciprenaline	Sympathomimetic (non-specific β-agonist)	Cardiac disorders
Benfluorex	Anorectic and hypolipidaemic	Heart valve disease—Pulmonary hypertension

Clobutinol	Cough suppressant (centrally acting)	QT prolongation
Buflomedil	Vasodilator (α1 and α2 receptor antagonist)	Neurological and cardiac disorders (sometimes fatal)
Veralipride	Neuroleptic (and dopaminergic receptor antagonist)	Neurological and psychiatric disorders
Rimonabant	Treatment of obesity (cannabinoid receptor antagonist)	Psychiatric disorders
Carisoprodol	Muscle relaxant	Intoxication—Psychomotor impairment—Addiction—misuse
Acepromethazine + Acepromazine + Clorazepate	Hypnotic	Cumulative adverse effects—misuse—a fatal side effect
Dextropropoxyphene	Opioid painkiller	Fatal overdose
Nefazodone	Antidepressant	Hepatotoxicity
Ximelagatran/melagatran	Anticoagulant (thrombin inhibitor)	Hepatotoxicity
Lumiracoxib	NSAID (COX-2 inhibitor)	Hepatotoxicity
Sitaxentan	Antihypertensive (endothelin receptor antagonist)	Hepatotoxicity
Bufexamac	NSAID	Contact allergic reactions

The main reasons why these drugs were withdrawn were cardiovascular disorders, followed by liver disorders, and neurological or psychiatric disorders. The mean time to retirement was 23 years, with an IQR of 4 and 46 (Chart 3) [McNaughton at al, 2014].

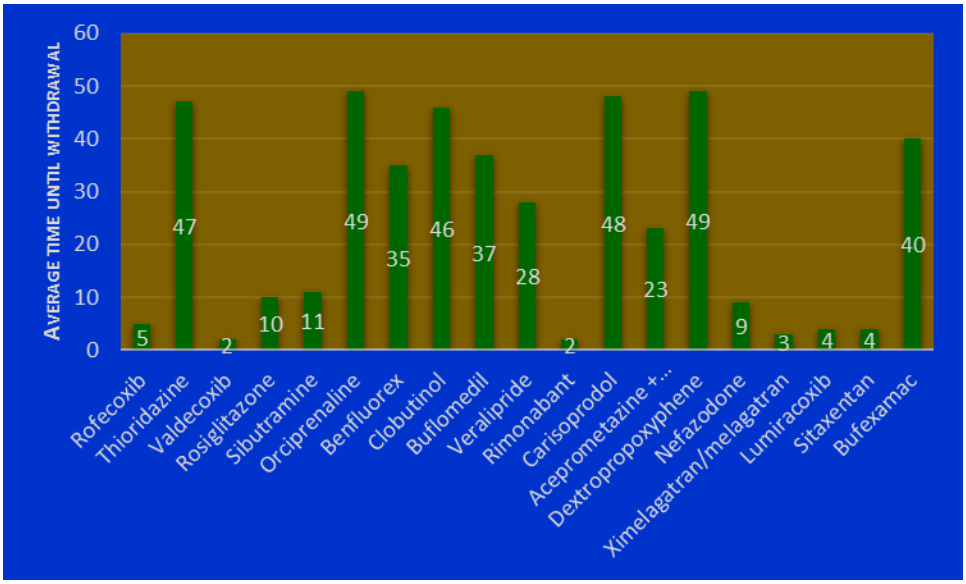

Diagram 6. The average time to market withdrawal was 23 years. The longest time was 49 years for Orciprenaline (a bronchodilator used in the treatment of asthma) and Dextropropoxyphene (analgesic in the opioid category) and the shortest period for Valdecoxib (nonsteroidal anti-inflammatory) and Rimonabant (anorectic antiobesity) [McNaughton et al, 2014].

RESULTS AND DISCUSSION

According to analysts at Research and Development Corporation, a global nonprofit in the United States, the worst-case scenario shortly would be the lack of a strong antimicrobial agent to treat bacterial infections. There is no match between the quality of the drugs and the price. Pharmaceutical profit often takes precedence over health, results that are reflected in prescriptions prescribed to patients which include the most expensive drugs. Side effects of medications are often greater than the disease that could be carried on the legs for a longer period but still safer. Between 82-90% of the safety issues identified in withdrawn drugs were recognized as adverse reactions. The average time between the introduction of a drug and its subsequent withdrawal for safety reasons was 20.3 years. Less than 5% of adverse reactions are reported, and the average underreporting rate by healthcare professionals was 94%. Better coordination between drug regulators and increased transparency in reporting suspected adverse drug reactions are needed.

CONCLUSIONS

The emergence of multiple drug resistance among pathogenic bacteria is a worldwide danger. Although spending on research and development for new antibiotics has almost doubled in the last 20 years, we are facing one of the biggest new drug crises in the world. Although drug use has increased almost exponentially in the last 10 years, we are facing a drug crisis. There is an urgent need for new innovative treatments with new mechanisms of action so that we can treat the infections and implicit pathological complications, involving as much as possible the use of rational combinations selected by new drugs to avoid or overcome drug resistance. An example might be Japan, which relies on empirical natural treatments.

REFERENCES

1. Adams K. 2021. Drug prices soared by nearly 4 times the inflation rate in 5 years, House investigation finds. *Hospital Review*. December:2021.
2. Aminov RI. 2009. The role of antibiotics and antibiotic resistance in nature. *Environ Microbiol.* 2009, 11(12):2970–2988.
3. Angell M. 2005. The Truth About the Drug Companies: How They Deceive Us and What to Do About It. New Your: Random House Trade Paperbacks; 2005.
4. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z. 2018. Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance*. 2018, 11: 1645–1658.
5. Brennan Z. 2021. House committee uncovers how Humira's price spiked by 470% as AbbVie execs cashed bonuses tied to the hikes. *Pharma, FDA +* [https://endpts.com/house-committee-uncovers-how-humiras-price-spiked-by-470-as-abbvie-execs-cashed-bonuses-tied-to-the-hikes/].
6. Craveiro NS, Lopes BS, Tomás L, Almeida SF. 2020. Drug withdrawal due to safety: a review of the data supporting withdrawal decision. Current Drug Safety. 2020, 15 (1):4-12 (9).
7. Eguchi K, Hyodo I, Saeki H. 2000. Current status of cancer patients' perception of alternative medicine in Japan. A preliminary cross-sectional survey. *Sup. Care Cancer*. 2000, 8:28–32.
8. Forsberg KJ, Patel S, Gibson MK, et al. 2014. Bacterial phylogeny structures soil resistomes across habitats. *Nature*. 2014, 509(7502):612–616.
9. Imai S, Sundell KA, Fushimi K. 2016. Comparison of pharmaceutical policies to stimulate use of generics in Japan and Sweden. *Health Policy and Technology*. 2016, 5(2):189-195.
10. Martin JH & Lucas C. 2021. Reporting adverse drug events to the therapeutic goods administration. *Medicine Political Science*. 2021.
11. McNaughton R, Huet G, Shakir S. 2014. An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support decision-making. *BMC Medicine*. 2014, 4 (1): e004221.
12. Neary I. 1994. Japanese Industrial Policy and the Pharmaceutical Industry. Industrial policy and the pharmaceutical industry. *The Proceedings of a Symposium held on 22nd June* 1994, London Edited by Adrian Towse.
13. Onakpoya IJ, Heneghan CJ, Aronson JK. 2016. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Med*. 2016, 14:10.
14. Saito H. 2000. Regulation of herbal medicines in Japan. Pharmacol. *Regul*. 2000, 41:515–519.

15. Sun Q, Santoro MA, Meng Q, Liu C, Eggleston K. 2008. Pharmaceutical Policy In China. HEALTH AFFAIRSVOL. 2008, 27(4): CHINA AND INDIA: REFORM GOES GLOBAL
16. Tsugane S. 2021. Why has Japan become the world's most long-lived country: insights from a food and nutrition perspective. *European Journal of Clinical Nutrition*. 2021, 75:921–928.
17. Zhang X. 1998. Regulatory Situation of Herbal Medicines. A Worldwide Review (WHO/trm/ 98.1), Geneva, World Health Organization
18. https://www.statista.com/statistics/1245261/value-share -of-pharmaceutical-subsectors-worldwide /
19. https://www.statista.com/statistics/1245261/value-share-of-pharmaceutical-subsectors-worldwide/
20. https://www.cdc.gov/drugresistance/biggest-threats.html