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POSSIBILITY FOR USE OF OLD DRUGS IN THE THERAPY OF NEW DISEASES

Assist. Prof. Nadya Agova - PhD, MPharm
Department of Pharmaceutical Sciences, Faculty of Pharmacy,
Medical University-Varna "Prof. Dr. Paraskev Stoyanov"
E-mail: Nadya.Agova@mu-varna.bg

Stanislava Georgieva, MPharm
Mariya Koleva, Mpharm
Department of Pharmacology, Toxicology and Pharmacotherapy,
Faculty of Pharmacy, Medical University of Varna
E-mail: stassy.s@abv.bg, Maria.Koleva@mu-varna.bg

Assist. Prof. Momchil Lambev, MPharm
Assist. Prof. Plamen Bekyarov, MPharm
TRS "Assistant Pharmacist", Medical College,
Medical University - Varna, Bulgaria
E-mail: momchil.lambev@mu-varna.bg, Plamen.Bekyarov@mu-varna.bg

Abstract: *In the context of a global pandemic, it is important for the medical and pharmaceutical community to find effective drugs for socially significant diseases, which in turn is connected with the possibility of their rapid release on the market. However, the development of new drugs involves a lengthy process. The entire process – from concept through preclinical testing in the laboratory to clinical trial development, including Phase I–III trials – to the approved drug typically takes more than a decade. This enables medical professionals to use already known drugs in the treatment of new or rare diseases for which no conventional treatment has been established. The repurposing drugs have a number of advantages and represent a promising direction in the treatment of a number of diseases.*

Keywords: *pandemic, development of new drugs, repurposing drugs, rare diseases.*

INTRODUCTION

Drug repurposing (also called drug repositioning, reprofiling, or re-tasking) is a strategy for new uses that are outside the scope of the original medical indication. (Ashburn T.T., Thor K.B. 2004). This approach becoming more widespread in view of the global COVID-19 pandemic. Although the most popular example for placing a medicinal product on the market with different indications from those initially studied is sildenafil (Viagra®). The drug was originally marketed to treat high blood pressure but in 1998 is approved to treat erectile dysfunction, and very quickly became a blockbuster drug. However, this is not the only example of such an application. Some of the most successful and well-known examples are minoxidil, acetylsalicylic acid, valproic acid, methotrexate, etc. (Aggarwal S, Verma S, Aggarwal S, Gupta SC. 2020).

The many advantages make repurposing an attractive and pragmatic concept for the pharmaceutical industry. In 2012, drug repurposing was included in the New Pharmaceutical Strategy for Europe and is part of Europe's Beating Cancer Plan.

This article discusses some well-known drugs that have received a new application profile and the various advantages that result from this.

EXPOSITION

Sildenafil

In 1985, the pharmaceutical company Pfizer developed a new drug for the treatment of hypertension. Subsequently, the drug made a real revolution in the market, but not in the treatment of high blood pressure. (Boolell M., 1996) It induces vasodilation and inhibits platelet aggregation by inhibiting phosphodiesterase type-5 (PDE5), the enzyme that breaks down cGMP. Unexpected

side effect - erection of the penis occurred during clinical trials. For this reason, sildenafil is the main indication for the treatment of men with erectile dysfunction, also called impotence. Its structural formula is shown in Figure 1.

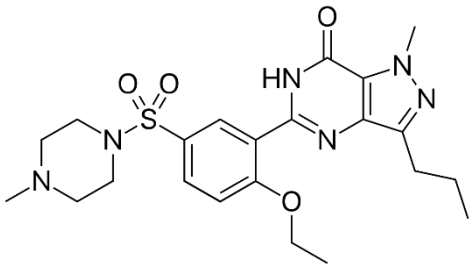

Fig. 1. Structural formula of Sildenafil

Famotidine

Famotidine is one of the strongest H_2-receptor blockers, which suppresses the increased acid secretion of the gastric glands. Famotidine is used to treat the symptoms of reflux (return of gastric juice to the esophagus) such as burning, heartburn, and pain behind the sternum.

There are data on the use of famotidine in the treatment of COVID-19. Famotidine could significantly reduce the risks of death or intubation. A lower level of certain serum markers was also observed. However, it is necessary to evaluate the effects of famotidine on improving the outcome of COVID-19 sufferers by meta-analysis. Its structural formula is shown in Figure 2.

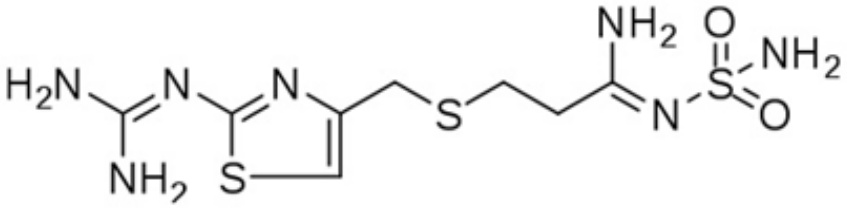

Fig. 2. Structural formula of Famotidine

There is evidence that some pneumocytes may respond to the local release of histamine, therefore the use of antihistamines may modulate the development of the pathological process. It has been reported that a combination of famotidine and cetirizine may have a positive effect on disease progression in hospitalized patients. (Chenyu Sun et. All. 2021)

Schizophrenia drug could potentially be used to treat tuberculosis.

Chlorpromazine, trifluoperazine, and thioridazine are parts of the typical antipsychotic drugs. Chemically, they are phenothiazine ring-containing drugs. They mainly use for some mental illnesses, mainly affecting hallucinations and psychotic disorders such as schizophrenia. The general structure of phenothiazine drugs is shown in Figure 3.

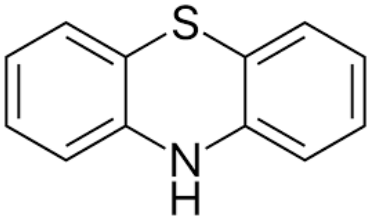

Fig. 3. General structure of phenothiazine preparations

The antipsychotics chlorpromazine, thioridazine, and trifluoperazine have significant anti-tuberculosis effects. Thioridazine stands out with particular importance. Numerous studies have been conducted to clarify the mechanism of action of phenothiazine antipsychotics drugs in the treatment of tuberculosis. For now, it is only clear that a very small dose of thioridazine is needed to kill the tubercle bacteria in the macrophages in the lungs, where the bacteria try to stay and multiply. (J.E Kristiansen et.all. 2015). The use of low doses is devoid of side effects and makes the

preparations suitable for use. The structural formulas of phenothiazine antipsychotics drugs are presented in Figure 4.

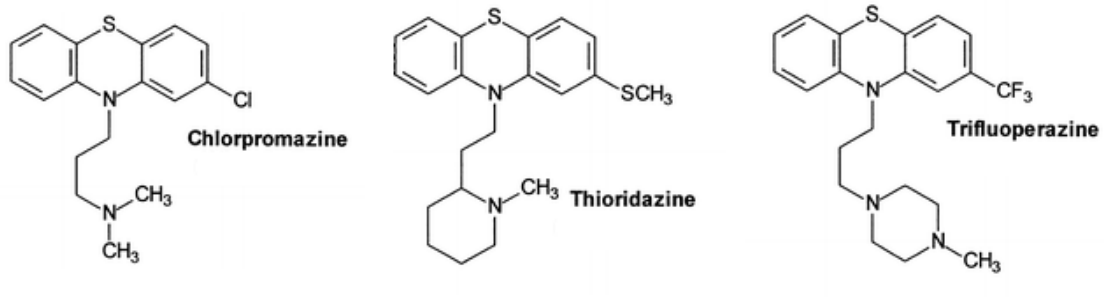

Fig. 4. Structural formulas of phenothiazine antipsychotics drugs - chlorpromazine, trifluoperazine, and thioridazine.

Tamoxifen:

Tamoxifen is a non-steroidal antiestrogenic product with antitumor activity. It is commonly used in the treatment of breast cancer. It is one of the oldest and most prescribed selective estrogen receptor modulators (SERM). Its structural formula is shown in Figure 5.

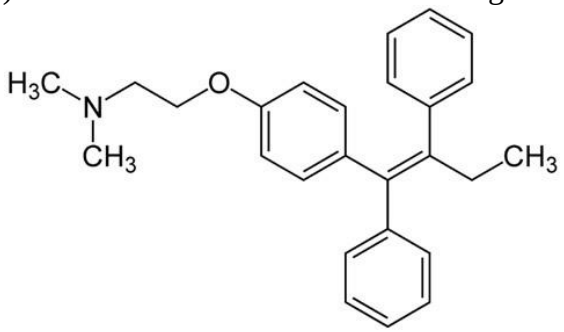

Fig. 5 - Structural formulas Tamoxifen

It was originally approved in 1977. The mechanism of action is related to inhibit the intracellular action of protein kinase C (PKC). However, the possibility for application in the field of mental illness is surprising. Thirty years after its release on the market, researchers discovered that it also helps people with bipolar disorder by blocking the enzyme PKC, which determines its potential for treatment episodes of mania. Future studies could investigate its effects in addition to dopamine antagonists for improved antimanic efficacy and establish its long-term effects on mood, especially depression and relapse. (Jorge Palacios, Ayşegül Yildiz, Allan H Young, Allan H Young 2019).

Methotrexate

Another clear example of drug repurposing is Methotrexate. It is a folic acid antagonist that inhibits the dihydrofolate reductase (DHFR) enzyme. Methotrexate was discovered in the 1940s as a substitute for folic acid due to dietary deficiency. It is designed as a molecule that is ubiquitous antimetabolite for the treatment of cancer. In the 1960s and 1970s, methotrexate was being used as a single cytotoxic agent for advanced breast cancer treatment. Its activity as an immunosuppressant allows it to be in clinical use for treating autoimmune diseases like rheumatoid arthritis. (Michael E. Weinblatt 2013). Its structural formula is shown in Figure 6.

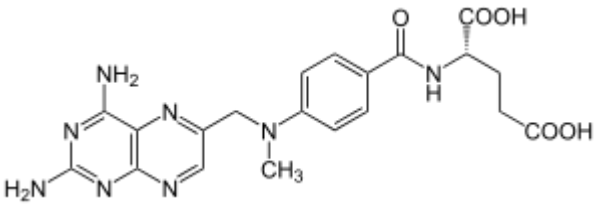

Fig. 6. Structural formula of Methotrexate

Other popular drugs found additional use beyond the indication for which they are lead on the market are presented in Table 1.

Table 1. – Some repurposing drug, their original indication and repurposing use

Drug	Original indication	Repurposing use
Astemizole	Antihistamine drug	Antimalarial drug
Galantamine	Cerebral palsy, mononeuritis, polyneuritis	Alzheimer's disease
Mifepriston	Pregnansi termination	Psychotic major depression
Ropinirol	Hyprtension	Parkinson's disease
Valsartan	Hyprtension	Alzheimer's disease

CONCLUSION

The drug discovery system has been transformed in the last years by the development of processes in chemistry, genetics, and genomics biology. Drug repurposing is a promising strategy that time has proven can lead to new treatment options. This is clear from all the examples presented so far and many more that this work does not consider.

Science has a vast array of chemical, pharmacological, and clinical data on drug use. The challenge for the pharmaceutical industry is to use the knowledge gained so far to enable the treatment of diseases that medicine has not yet overcome.

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