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The future of medicine: Strategic insights into drug repurposing

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Abstract

The future of medicine is increasingly being shaped by innovative strategies that maximize the efficacy of existing therapeutics, one of the most promising being drug repurposing. Drug repurposing involves the identification of novel therapeutic applications for approved or investigational drugs, thereby circumventing the lengthy and costly processes associated with traditional drug development. This approach not only accelerates the delivery of treatments to patients but also optimizes existing resources, making it a compelling strategy in the face of rising healthcare costs and the urgent need for novel therapies.

Recent advancements in genomics, bioinformatics, and high-throughput screening have revolutionized our ability to identify potential candidates for repurposing. These technologies facilitate the exploration of drug-target interactions across various diseases, enabling researchers to uncover unexpected therapeutic potentials. For instance, well-known medications originally developed for one condition have been found effective in treating others, such as the use of thalidomide for multiple myeloma and the repurposing of antifungal agents for cancer therapy.

Keywords: Future of medicine; Drug Repurposing; Cimetidine; Aspirin; Mefipristone; Amantadine; Zonisamide; Mebendazole

1 Introduction

The field of medicine is seeing a significant transformation due to swift technological breakthroughs, increasing healthcare costs, and a pressing need for innovative solutions to combat emerging health threats. Among the most promising strategies in this evolving landscape is drug repurposing, a practice it entails discovering novel therapeutic applications for established pharmaceuticals. This method not only expedites the pharmaceutical creation procedure but also capitalizes on the wealth of data already available from previously conducted clinical trials, safety profiles, and established manufacturing processes.

1.1. Understanding drug repurposing

Medication repurposing, alternatively referred to as medication repositioning or re-profiling, leverages existing medications for new therapeutic indications. Historically, serendipitous discoveries, such as the use of sildenafil (originally developed for hypertension) as a treatment for erectile dysfunction, have paved the way for this approach. However, the systematic exploration of drug repurposing has gained traction in recent years, fuelled by advancements in genomics, bioinformatics, and artificial intelligence.

The advantages of drug repurposing are manifold. Firstly, it significantly reduces the both duration and expense associated with bringing a new drug to market. Traditional drug development can take over a decade and cost billions

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of dollars; however, repurposed drugs can often bypass early-stage clinical trials, as their safety profiles are already established. Secondly, drug repurposing can provide prompt action in the event of a public health emergency, like the COVID-19 pandemic, where existing medications were swiftly evaluated for efficacy against a novel virus.

1.2. The strategic importance of drug repurposing

In the context of rising healthcare costs and increasing demand for effective treatments, drug repurposing offers a strategic advantage. Pharmaceutical companies are increasingly looking to diversify their portfolios and mitigate the risks associated with traditional drug development. By investing in repurposing efforts, they can unlock new revenue streams from established products.

Moreover, drug repurposing plays a crucial role in addressing unmet medical needs, particularly for rare diseases or conditions with limited treatment options. The ability to find new applications for existing drugs can provide relief to patients who may have otherwise faced grim prognoses. Furthermore, this approach aligns with the principles of precision medicine, as it allows for the tailoring of treatments based on individual patient profiles and specific disease mechanisms.

1.3. Technological advancements facilitating drug repurposing

The rise of big data analytics and artificial intelligence (AI) has revolutionized the field of drug repurposing. By harnessing vast amounts of clinical data, researchers can identify potential new uses for existing drugs more efficiently. Machine learning algorithms can scrutinize intricate datasets, uncovering correlations and trends that may remain obscured through conventional study methodologies. Additionally, advancements in genomics have enhanced our understanding of disease mechanisms at a molecular level. By identifying shared biological pathways between diseases, researchers can target existing drugs that act on these pathways, thereby repurposing them for new indications. This systems biology approach fosters a more holistic understanding of how drugs interact with biological systems, paving the way for innovative therapeutic strategies.

1.4. Challenges and considerations

While the potential of drug repurposing is immense, several challenges remain. One of the primary hurdles is the regulatory landscape, as repurposed drugs must still undergo rigorous evaluation to ensure their safety and efficacy for new indications. Navigating the complexities of regulatory requirements can be daunting, particularly for smaller companies or academic institutions with limited resources.

Furthermore, the intellectual property landscape poses additional challenges. Original patent holders may be reluctant to allow the repurposing of their drugs, fearing market competition or dilution of their brand. Collaborative efforts between pharmaceutical companies, academic institutions, and regulatory bodies will be crucial to overcoming these obstacles and fostering a more conducive environment for drug repurposing.

1.5. Future directions and potential

Looking ahead, the future of medicine is poised for a paradigm shift driven by drug repurposing. As we continue to navigate the complexities of global health challenges, the ability to adapt and innovate will be essential. The integrating of machine learning and artificial intelligence into drugs discovery processes promises to streamline the discovery of novel uses for already-approved medications, expediting the repurposing pipeline.

Moreover, the collaborative nature of modern biomedical research is likely to enhance the success of drug repurposing initiatives. By fostering partnerships among academia, industry, and regulatory agencies, stakeholders can share knowledge, resources, and expertise, ultimately leading to more effective therapeutic solutions.

The process of using a drug that has already received approval for a medical condition or treatment that has not before been advised for new medicinal conditions is known as "drug repurposing."It was first created to address a distinct medical issue. It has been characterized as an unforeseen, serendipitous procedure. In this procedure, a drug's unwanted side effects may also serve as a cue to investigate whether it might be useful for a completely unrelated medical problem. Typically, medications with proven human safety records are also tested and produced for a specific condition other than the one for which they were intended. By bypassing the drug development process and by moving directly to preclinical as well as clinical studies, this strategy reduces the risk and expenses related to medication development.

The strategic insights into drug repurposing encompass several key elements. First, a multidisciplinary approach that integrates clinical expertise, pharmacology, and computational biology is essential for successful identification and validation of new indications. Collaboration among academia, industry, and regulatory bodies can enhance the efficiency of repurposing efforts, allowing for shared data and resources.

Second, the importance of real-world evidence (RWE) in guiding repurposing strategies cannot be overstated. Information from patient registries, insurance claims, and electronic health records can provide invaluable insights into treatment outcomes, thereby informing decision-making processes. Leveraging RWE facilitates the identification of patient populations that may benefit from repurposed drugs, optimizing treatment pathways and outcomes.

Third, addressing regulatory challenges is critical to the successful implementation of drug repurposing initiatives. Streamlined pathways for approval and clear guidelines on the evidentiary standards required for new indications can significantly reduce barriers to market entry. Regulatory agencies are beginning to adapt their frameworks to accommodate these innovative approaches, fostering an environment conducive to rapid translation of scientific discoveries into clinical practice.

Moreover, the economic implications of drug repurposing are profound. With the potential to reduce development costs and timeframes, repurposing offers a cost-effective alternative to traditional drug development. This is particularly relevant in the context of global health challenges, where rapid responses to emerging diseases are imperative.

2 Cimetidine

2.1. Introduction

Cimetidine (CIM) is a histamine H2-receptor antagonist, belonging to the same class as famotidine, ranitidine, and nizatidine. The H RAs can decrease the gastric acid synthesis; in fact, CIM was the inaugural medicine in its category produced for the management of dyspepsia. CIM is utilized clinically for the treatment of dyspepsia, peptic ulcers, and gastro esophageal reflux disorder (GERD). Originally marketed under the brand-name Tagamet (GlaxoSmithKline) is now widely available as a generic drug and can be purchased over-the-counter (OTC) medication in certain nations, encompassing the United States of America [1]. Numerous cell groups make up the tumor microenvironment (TME), including immune cells, T lymphocytes, B lymphocytes, fibroblasts, endothelial cells, adipocytes, neutrophils, dendritic cells (DCs), tumor-associated macrophages, and malignant and non-cancerous cell[2]. Cancer cells are able to avoid immune monitoring in the TME because of the production immunosuppressive cells, including regulatory T cells, M2 macrophages, and myeloid-derived suppressor cells [3]. Tumor growth is suppressed in part by other immune cells, including DCs, cytotoxic T cells, M1 macrophages, and natural killer cells, or NK cells[4]. The TME is complicated and heterogeneous because of the presence of the relationships between extracellular matrix, soluble mediators, and cell lineages.

2.2. History

An international group of scientists at Smith, Kline & French Laboratories (now a part of GlaxoSmithKline) in the United Kingdom first synthesized cimetidine, a histamine H2-receptor antagonist, in 1969. This is a synopsis of the past:

- In 1964, the business started looking into how histamine affects the formation of stomach acid.
- 1969: A group under the direction of Dr. James Black, who would go on to win the 1988 Nobel Prize in Physiology or Medicine, synthesized cimetidine for the first time.
- Cimetidine began clinical studies in 1971 and showed promise in the treatment of peptic ulcers.
- 1976 saw the UK approve cimetidine, which was sold under the Tagamet brand.
- 1977: Cimetidine was approved by the US FDA and immediately gained widespread usage.
- 6.1980s: The first medicine to sell $1 billion in a year was cipridine.

2.3. Pharmacokinetics

CIM has a 60–75% bioavailability and a 2-3 hour elimination half-life. The kidneys are primarily responsible for elimination, excreting 60% to 40% of the unmodified medication, depending on the dosage and mode of administration[5]. If taken without food, plasma concentrations peak after about an hour; if taken with food, they peak after two hours. After around three hours, when administered in a fasting state, there is a further increase in plasma concentration. Following an oral administration of 200 mg, the peak plasma concentration is minimally influenced by

food, yielding amounts of 1.18 µg/ml and 1.09 µg/ml, accordingly. For nine out of twenty-four hours of the continuous 1.0 g/day therapy, plasma concentrations were higher than 1.0 µg/ml[6].

2.4. Mechanism of action

2.5. Dosage

Quantity Oral CIM can be administered intravenously and is available as a liquid suspension in tablet form. Typically, tablets come in dosages of 200 mg, 400 mg, and 800 mg. Adults with stomach or duodenal ulcers should take 800–1600 mg daily, either in one dose or in smaller doses spread out over the course of 4–8 weeks. For four to eight weeks, the dosage 400 mg four times a day is recommended for reflux oesophagitis. At a daily dosage of 400 mg, CIM is utilised as a maintenance treatment for short bowel syndrome and stomach ulcers; in several cases, this treatment is given for longer than ten years[7].

2.6. Adverse effects

Hazardousness The most prevalent adverse reactions of CIM includes headache and dizziness, diarrhoea, and rash. It has a low toxicity. Gynaecomastia, reversible erectile dysfunction (particularly observed in patients receiving too high doses, such as in the management of Zollinger-Ellison Syndrome), and, extremely infrequently, galactorrhea are unusual adverse effects. In rare cases, CIM has also been linked to thrombocytopenia and reversible leukopenia, side effects that may be especially crucial to monitor in cancer patients who might be receiving chemotherapy[8]. It is not recommended to use CIM when pregnant. Oral CIM may be administered in divided doses to children older than one year should get a daily dosage of 25-30 mg/kg of body weight. A daily dosage of split dosages of 20 mg/kg body weight has been recommended for children under the age of one[9]. It is uncommon to overdose on cimetidine. On the other hand, keeping the cardiovascular and airway health is crucial in cases of poisoning. Gastric lavage with the administration of activated charcoal to lower medication absorption are two methods of decontaminating cimetidine[10].

Negative Results High cimetidine dosages (over 5g/day) may result in gynecomastia or reversible impotence[11]. Cimetidine's anti androgenic potential, which is dependent on the elevation in prolactin levels due to histamine H2 receptor blockage seems to be the underlying source of this effect. Additionally, cimetidine has non-specific effects that increase prolactin production and cause dose-related patterns of galactorrhea in men[12][13]. The effects might potentially be associated with a suppression of estradiol's 2-hydroxylation. However, the alternative H2 receptor antagonists, famotidine, ranitidine, and nizatidine, do not cause gynecomastia in men.

2.7. Drug repurposing

It involve oral administration of CIM (daily 800 mg) to mitigate the negative impacts of para-aortic lymph node radiation therapy in the management of cervical carcinoma [14], as well as the use of intravenous CIM[15] to avoid vinorelbine, induced phlebitis. A major side effect of cisplatin is nephrotoxicity, which is caused by the drug's absorption in the proximal tubules being regulated via means of OCT2, an organic cation transporter 2. Robust OCT2 inhibitor CIM was demonstrated to have no effect on cisplatin absorption or cytotoxicity within a cell line (IGROV-1) for ovarian cancer that expressed elevated OCT2 levels in vitro. The anti tumor efficacy of cisplatin was not diminished in experiments conducted later in a mouse model. For those suffering from head and neck cancer, agree-rent CIM (800)[16].

3 Aspirin

3.1. Introduction

Many medical specialities have used aspirin, or acetylsalicylic acid, for many years. The primary source of this substance willow bark has provided numerous benefits to humanity since its benefits were recognised thousands of years ago. Historically, willow bark has been utilised in various regions worldwide. The initial recorded usage dates to around 500 BC. Chinese doctors employed willow barks to address a range of ailments. Hippocrates, the father of medicine, is

reported to have compelled his patients to masticate willow bark or consume the powder he derived from it, specifically to mitigate fever and alleviate discomfort. Hippocrates lived from 430 to 377 BC. Willow leaves were found to alleviate inflammation by the Greek scholar Discorides around the year 100 AD. In 200 AD, Galen is reported to have utilised these leaves as medicinal agents. Furthermore, when European settlers arrived in America in the 1700s, they saw that the natives were using willow barks to cure various ailments. Still, the bark's ability to lower fever wasn't recorded in medical literature until July 2, 1763, when priest Edward Stone did so.

3.2. History

Worldwide acceptance of aspirin as a safe and efficient treatment for headaches in 1923, arthritis in 1933, and backaches began in 1903. Aspirin was made available without a prescription starting in 1915. The 1919 Treaty of Versailles, signed following Germany's defeat in the First World War, mandated that Bayer give up the aspirin trademark. Dr. Lawrence Craven recommended his patients and associates receive one tablet of aspirin daily after learning in 1948 that patients who took the medication he prescribed experienced fewer heart attacks. Children's chewable aspirin was first made available in 1952. The Apollo astronauts' self-medication kits included aspirin tablets since it was shown to be highly effective in treating the headaches and muscle aches that usually followed extended periods of immobility. This was done in 1969. The pharmacological function of aspirin was elucidated by British pharmacologist Sir John Vane in 1971. He showed that aspirin suppressed the creation of prostaglandins. In 1982, Sir John Vane received a Nobel Prize for his research on prostaglandins[17]. Toleraid® micro coating (transparent coat) was introduced to aspirin tablets in 1984 with the purpose of facilitating easier swallowing.

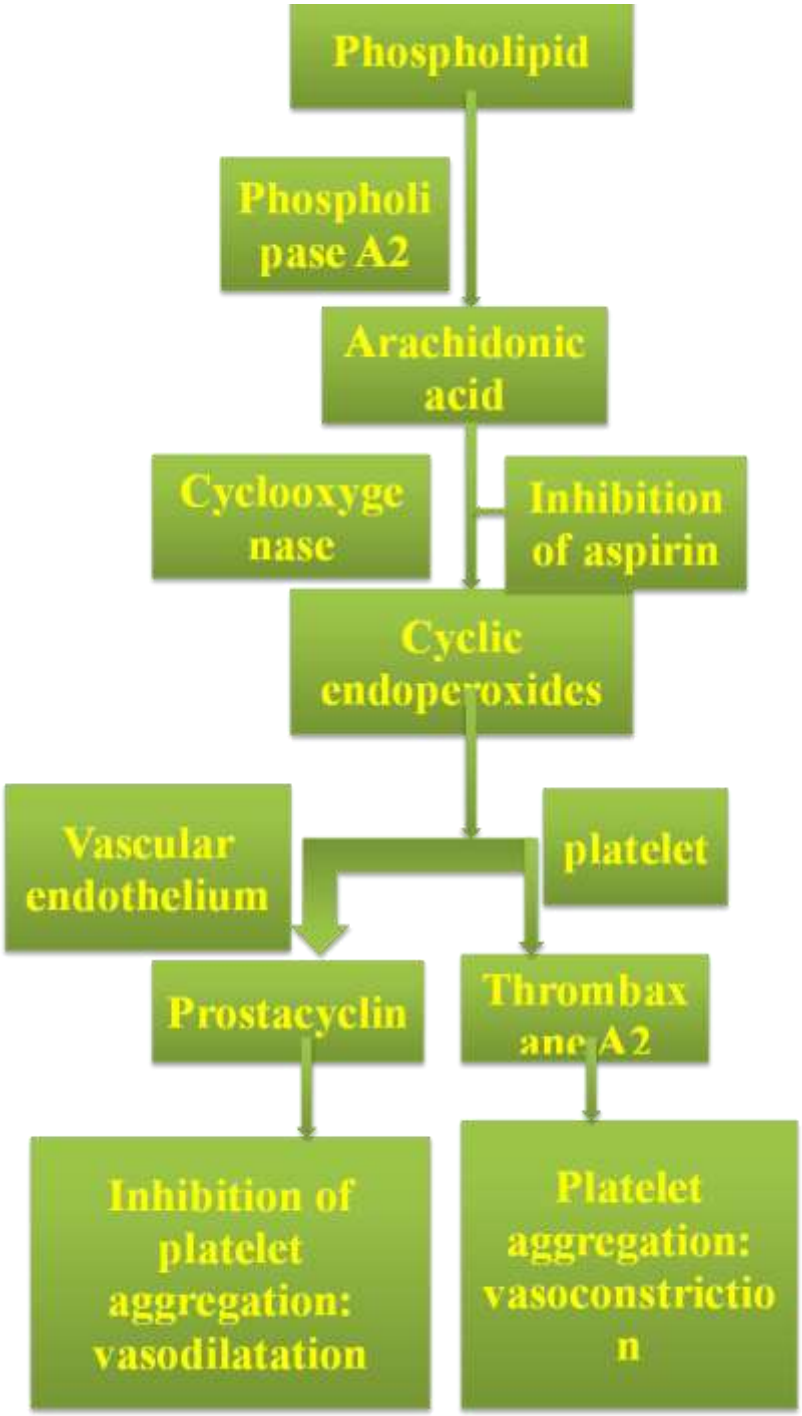
3.3. Dosage

The therapeutic and detrimental effects of aspirin may be significantly influenced by the relationship correlation between aspirin dosage and their body weight, according to recent findings[18]. Aspirin at a low dose (75–100 mg) is advantageous for patients under 70 kg, while greater doses of aspirin are more effective for heavier patients, according to a meta-analysis comprising over 117,000 patients from eleven primary prevention studies. Based on these findings, the generalisation that aspirin can be used at any dose may not be valid. The intriguing theory of weight-based aspirin dosage has been generated by this and will probably have an impact on future aspirin-related research plans. An ongoing secondary prevention trial called "The interaction of body weight with aspirin dosing: a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE)" is examining two different aspirin doses (81 mg and 325 mg) and could provide more information on this topic[19].

3.4. Pharmacokinetics

Less than 75 mg of aspirin per day is more beneficial than greater dosages since it has no impact on prostacyclin, platelets anti-aggregant and vasodilator that also results in fewer gastrointestinal problems[20]. While suppression of thromboxane A2 synthesis by platelets transpires in the portal (pre-systemic) circulation, while the systemic bioavailability of oral aspirin is necessary for the suppression of prostacyclin formation by vascular endothelium[21]. A meta-analysis of randomised research indicates that in high-risk individuals[22], there is no discernible difference between the daily aspirin doses of less than 75 mg and more than 75 mg in terms of preventing vascular events. Major extra cranial the bleeding risk was similar across all daily aspirin dosages below 325 mg, with odds ratios of 1.7 (95% confidence interval 0.8-3.3) for dosages under 75 mg, 1.5 (1.0-2.3) for 75-150 mg, and 1.4 (1.0-22.0) for 160-325 mg when compared to the control group. It is unclear how changed platelet function in diabetic individuals may affect the aspirin dosage for cardio protective outcomes in this patient population[23].

3.5. Mechanism of action



3.6. Adverse effects

Like every medication, aspirin has possible side effects in addition to its advantages. Due to its connection to Reye's syndrome, a potentially lethal illness that impacts many organs, particularly the liver and brain, aspirin must be strictly avoided in children under 12 with inflammatory disorders such as influenza and the common cold[24,25]. Additionally, since aspirin might precipitate asthma attacks, it is not advised for certain asthmatic patients. Aspirin should be avoided during the lactation phase and the final trimester of pregnancy. When taking aspirin, people with individuals with bleeding and blood clotting disorders must take utmost caution. Individuals suffering from gastric distress and peptic ulcers must abstain from using aspirin while unwell and seek professional advice regarding its usage following recuperation. People who do not have the enzyme glucose-6-phosphate dehydrogenase should not take aspirin. Aspirin may contribute to chronic illnesses and worsen liver and renal damage in individuals who drink too much alcohol.

Remember that aspirin contains salt if you're following a low-sodium diet[26,27]. Tinnitus is another common aspirin adverse effect [28]. Close observation of the patients is necessary. Bicarbonate, glucose, potassium chloride, and salt should be given in that order to treat hypokalaemia, neutralise salicylate in the blood, control acidity, and treat hypoglycemia. Blood gases should be drawn often, blood pH should be assessed, and metabolic acidosis and ventilatory alkalosis should be closely monitored [29,30].

3.7. Repurposing

Given aspirin's great efficacy in treating acute coronary syndromes[31] and myocardial infarction, as well as its importance when it comes to secondary cardiovascular event prevention, it seemed sense to assume that it might also be beneficial in primary prevention. Previous randomised research have demonstrated this advantage. More recent research, though, such the ASPREE study[32] and the ARRIVE trial[33], did not demonstrate this benefit. That failure might have been caused in part by the extremely low event rate. These days, doctors have a far lower aim for managing low-density lipoprotein, and the Western population strives for better sugar control when they are diabetic. The incidence of cardiovascular events have decreased as a result of these advancements as well as the notable advancements in medical therapy. Treatments with established advantages are now not received by the majority of patients, especially those residing in the lower and middle classes nations[34]. In the context of primary prevention, aspirin has a negligible, if not negative, benefit-risk analysis; as such, it should not be prioritised. In the United States, aspirin use reduced for primary prevention are a recent trend that reflects this unfavourable benefit-risk trade off[35].

4 Mefipristone

4.1. Introduction

Since its US approval in 2000, mifepristone has seen a remarkable journey. The drug's proponents had thought that it would address the disparities in access to abortion care. In developing countries, unsafe abortion results in nearly 70,000 deaths and 5 million either long-term or temporary disabilities[36]. However, in affluent nations, the practice of abortion is safe, legal, and accessible, the mortality rate from early surgery for a first-trimester abortion is 0.1/100,000 [37]. The global death rate might drop to 50, if extrapolated to the 50 million abortions anticipated by the World Health Organisation worldwide! Using mifepristone has been done early abortion by millions of women globally. The data disproves the worry that access to medical abortion would lead to a rise in abortions, with the number of abortions declining in the US[38], France[39], and Sweden[40]. While mifepristone has been listed by the World Health Organisation as one of the key medications for developing nations, the promise for medical abortion to substantially enhance accessibility to safe abortion services in regions where unsafe practices persist has not yet been realised.

4.2. History

The two main areas of abortion care where mifepristone has been used recently are medical abortion, referred to as the medical termination of a pregnancy prior to nine weeks of gestational period [41], and induction, which is the medical abortion of a pregnancy during the second trimester. Females tried in various ways to limit having children for generations by having abortions. Hippocrates prescribed "jumping up and down so that the feet touch the buttocks" in order to cause an abortion. The dosages of poisons used by Americans in the 19th century were intended to kill the foetus while sparing the woman[42]. Despite its long history, medical abortion has solely been studied scientifically for the past five decades, with only the past two decades being relevant have methods comparable to Hoover aspiration become accessible. Three primary categories include the agents of scientific focus: uterotonics, which mostly consist of prostaglandins and their equivalents; antiprogestins; and methotrexate is an antimetabolite. The sole antiprogestin that had been utilised in clinical settings is mifepristone.

4.3. Dosage

4.3.1. Medical abortion (up to 10 weeks gestation)

A solitary oral administration of 200 mg mifepristone, succeeded 24 to 48 hr afterwards by 800 mcg of misoprostol (given vaginally, buccally, or sublingually). This combination is highly effective with a success rate over 95% in early pregnancy terminations.

4.3.2. Medical abortion (13-24 weeks gestation)

A solitary administration of 200 mg mifepristone, succeeded by successive administrations of 400 mcg misoprostol every 3 hours, often for a maximum of 5 doses. Dosage adjustments may be necessary based on clinical response.

4.3.3. Management of early pregnancy loss (missed miscarriage)

200 mg of mifepristone, succeeded by 800 mcg of misoprostol delivered 24 to 48 hours subsequently.

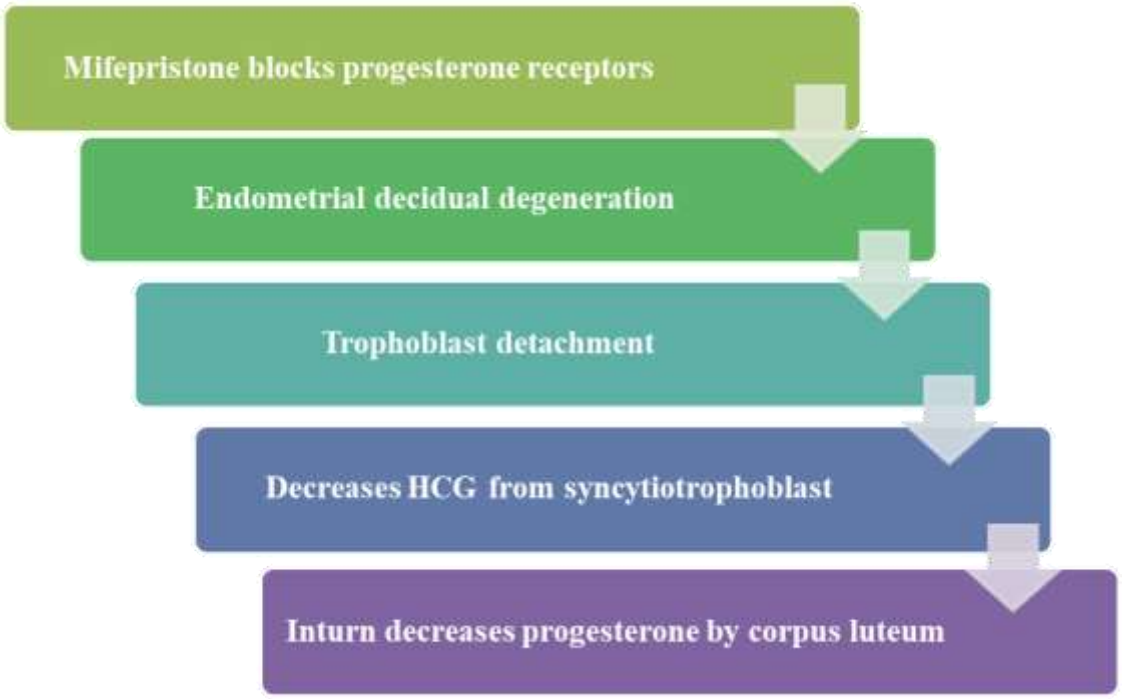
4.3.4. Cushing's syndrome

Initially, 300 mg once day, subject to incremental increases of 300 mg daily based on tolerance and response, with a maximum dose of 1200 mg/day.

4.4. Pharmacokinetics

Maternal women's serum concentration of mifepristone peaks about two hours after oral administration, which is well absorbed. Every dosage above 100 mg has comparable pharmacokinetics, and women administered 100, 200, and 800 mg have similar peak blood concentrations of 2.0 to 2.5 mg/mL. Eighteen Medication for pregnant women possesses a half-life of approximately 19 hours. It predominantly interacts to a-1-acid gylcoprotein, a serum-binding protein[43].

4.5. Mechanism of action



4.6. Adverse effects

Patients must be explicit about their decision to end the pregnancy while using mifepristone and prostaglandin during an abortion. The patient should anticipate that an aspiration operation will be used to complete a failed abortion and that continuing the pregnancy is not a viable option. There is an absence of evidence to suggest that the use of mifepristone causes insults in addition to teratogenic effects from the mediations used to induce abortions. 3452 foetal abnormalities were found in 91,665 pregnancies in France over a two-year period, although No one of the pregnant ladies had administered mifepristone[44]. Misoprostol's teratogenicity has been extensively studied in Brazil, where women attempt to have illegal abortions using the medication. Mobius sequence[45]. Is characterised by mask like facial features, potential micrognathia, and bilateral sixth and seventh nerve palsy in some of these children[46]. The two-drug protocol for medical abortion effectiveness lowers failure rates and raises success rates, which lowers the chance of any related foetal abnormalities[47]. It is imperative that patients and healthcare practitioners comprehend the crucial correlation among effectiveness, failure, and commitment in regards to pregnancy termination.

4.7. Repurposing

Mifepristone has been allowed in several nations for use in reproductive related treatments like contraceptives for emergencies[48], as well as for abortions during the late first trimester (9–14 weeks) and the second trimester (14–22 weeks)[49-52]. Mifepristone is utilised for induce labour at term for foetal death in utero and to remove the uterus for embryogenesis or foetal demise[53,54]. Mifepristone is being studied for its potential to regulate menstruation and

prepare the cervix for surgical abortion[55,56]. Mefipristone's antiglucocorticoid characteristics have shown beneficial in the treatment of acute psychotic depression[57], Cushing's syndrome[58] and high stress-related illnesses like HIV[59]. Other disorders with progesterone receptors that have been treated with Mefipristone include endometriosis, uterine leiomyomas[60], meningiomas[61], leiomyosarcoma[62], and certain types of breast cancer.

5 Zonisamide

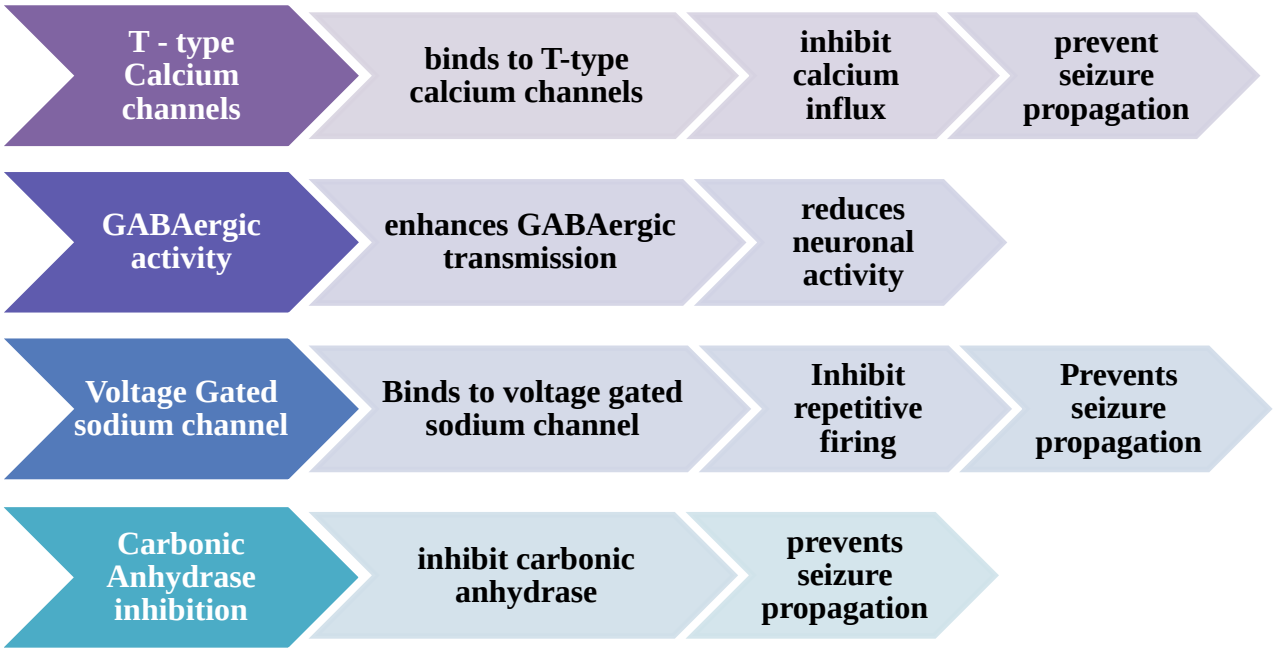
5.1. Introduction

Zonisamide is a 1,2 benzisoxazole derivative and a sulfonamide antiepileptic medication. It is the first drug from this class of compounds to be used for this purpose. It has no chemical connection to other antiepileptic drugs[63]. Japanese physicians have been using the medication to treat epilepsy since at least 1990. The medication was first used in Japan in 1972 to treat mental illnesses[64].

5.2. History

In the US, the FDA approved it in 2000 to treat adult partial seizures as an adjunct treatment. A number of epilepsy types and syndromes, include Lennox-Gastaut syndrome, infantile spasms, progressive myoclonus epilepsy, simple partial seizures, complex partial seizures, and myoclonic seizures, have been shown to respond well to zonisamide, according to small clinical investigations. For the treatment of epilepsy, zonisamide as a monotherapy has only become the focus of a brief number of clinical trials[65,66]. A systematic review states that there is not enough proof to justify zonisamide monotherapy for children experiencing partial seizures. It might work well as a stand-alone treatment for epilepsy. However, before zonisamide monotherapy is advised, larger double-blind clinical trials are required[67,68].

5.3. Mechanism of action



5.4. Repurposing

Patients with mania and acute psychotic disorders have benefited from zonisamide use in clinical trials. additionally, it has been effective for neuropathic pain sufferers.

When combined with other drugs, certain trials have shown improvements in the manifestations of Parkinson's disease. Research indicates that zonisamide may be equally effective as propranolol in treating patients who have essential tremors or head tremors[69].

5.5. Pharmokinetics

After oral treatment, zonisamide is promptly absorbed and distributed evenly. Concentration reaches its peak in two to five hours. The time to maximal concentration is postponed by food but not by bioavailability. It could take up to four or six hours for peak plasma levels if taken with food. Absolute bioavailability in humans is uncertain due to the absence of a parenteral formulation, despite the great bioavailability in animals. The primary metabolite is cytochrome P450 3A4. Oral preparation's lower bioavailability could be explained by intestinal 3A4.The volume of distribution of zonisamide decreases in a dose-dependent manner. It binds to erythrocytes saturably, particularly to intracellular carbonic anhydrase. It is more abundant in red blood cells (RBCs) than in plasma and attaches to them. When the dosage is raised, the concentration of zonisamide in whole blood is not linear, although the concentration of zonisamide in plasma increases linearly. Zonisamide is tethered to plasma proteins, particularly albumin, in amounts of about 40%[70,71].The half-lives of zonisamide after oral administration are predicted to be 50–69 hours for plasma, while red blood cells require 105 hours. After starting zonisamide at a stable dosage, steady-state levels can take up to 14 days to reach. In the urine, less than 30% of it is excreted undisturbed. Most of the medication is extensively processed in the liver.

5.6. Dosage

For adults, a starting dose of 100–200 mg per day is advised; for children, it is 2–4 mg/kg per day. Doses of one or two times per day are utilized. To reach a goal maintenance dosage of 300–400 mg per day for adults and 4–8 mg/kg for paediatric patients., the dose should be increased every two weeks. Adults have taken doses up to 600 mg daily; however, research has shown that doses over 400 mg daily have more side effects and are not more effective. The suggested dosages correspond to plasma concentrations in the steady-state range of 10 to 38 mcg/mL. It is advised to keep zonisamide concentrations below 30 to 40 mcg/mL[72]. For oral administration, it comes in tablet and capsule form. The zonisamide parenteral formulation is not available.

5.7. Adverse effects

Weight loss by zonisamide can range from low to substantial. Patients who are obese or who gained weight while utilising alternative antiepileptic medications may advantage from adding zonisamide to their treatment plan. People who have administered zonisamide for a minimum of six months, possess a familial predisposition to nephrolithiasis, or are simultaneously receiving other antiepileptic medications are more likely to develop rare renal calculi. While in people with a history of kidney stones, zonisamide is not contraindicated, patients taking this medication should exercise caution and drink enough water to ensure proper urine flow [73]. Although uncommon, allergic responses have been documented. The most common allergic reaction that has been reported is a rash. Since zonisamide and sulfonamide medications share a chemical relationship, individuals who have previously experienced an adverse reaction to sulfa medicines should use caution when using zonisamide. There have been cases of mild, relative neutropenia in certain individuals. Oligohidrosis can happen, which results in heat and less sweating. There have been increasing reports of this in kids. Children using zonisamide shouldn't spend a lot of time in really hot weather. Because zonisamide inhibits carbonic anhydrase, it can cause metabolic acidosis. Before beginning treatment and on a frequent basis subsequently, serum bicarbonate levels should be measured, particularly in people with compromised pulmonary or renal function. In certain people, zonisamide may cause behavioral and cognitive changes[74].

6 Mebendazole

6.1. Introduction

For almost 40 years, mebendazole has been a common broad-spectrum benzimidazole used to treat many types of parasitic infections in people. The FDA has approved its use for treating gastrointestinal infections in patients older than two years old that are either single or mixed infections caused by Necatoramericanus or Ankylostomaduodenale (hookworms), Ascarislumbricoides (roundworms), Enterobiusvermicularis (pinworms), and Trichuristrichiura (whipworms)[75]. Additionally, it has multiple off-label applications for adult intestinal nematodes infections brought on by toxocariasis, trichinellosis (Trichinellaspiralis), capillariasis, and trichostrongyliasis[76].

6.2. History

Synthesized in 1967 by Janssen Pharmaceutica (now Johnson & Johnson) researchers. Developed as a broad-spectrum anthelmintic agent. Initially tested against intestinal parasites in animals.

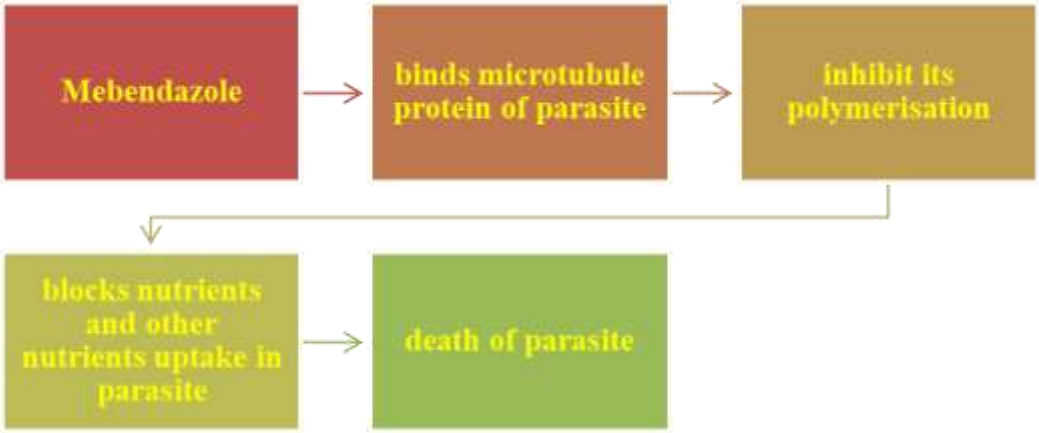
- Granted FDA approval in 1974 for therapeutic use roundworms, hookworms, and whipworms.

- Launched in the US in 1975 under the brand name Vermox.
- Later approved for additional indications, including pinworms and tapeworms.
- 1980s: Mebendazole becomes widely used globally, particularly in developing countries.
- 1990s: WHO includes mebendazole in its Essential Medicines List.

6.3. Pharmacokinetics

Mebendazole is taken orally, regardless of when food is consumed. Before ingesting, the patient needs to chew the tablet thoroughly. Patients who have trouble swallowing the pill should use a dosage syringe to mix it with two to three milliliters of drinking water in a spoon. After absorbing the water, the pill becomes a soft, semi-solid mass that is easy to swallow[77].

6.4. Mechanism of action



6.5. Dosage

For three days in a row, take 100 mg twice a day (morning and night) to treat roundworm (Ascaris lumbricoides). Three days in a row at 100 mg twice a day (morning and night) for hookworm (Ancylostoma duodenale). For three days in a row, take 100 mg of whipworm (Trichuris trichiura) twice a day in the morning and the evening. Enterobius vermicularis, or pinworm, 100 mg once orally, capillariasis Infection: 200 mg must be taken twice a day by mouth for 20 days [78]. Cestodes Infection: Take 300 mg twice a day for three to six days[79]. Filariasis: Administer 300 mg orally each day for a duration of 28 to 45 days[80] of the medicine taken orally, less than ten percent (10%) is absorbed systemically and is quickly metabolised by liver enzymes. Any CYP450 inducer, such as phenytoin or carbamazepine, can also lower plasma levels.

6.6. Adverse effect

The prevalent side effects associated with mebendazole administration include anorexia, abdominal discomfort, diarrhoea, flatulence, nausea, emesis, cephalalgia, tinnitus, and increased liver enzymes[81]. A minority of patients may develop seizures, while others may exhibit hypersensitivity symptoms, including rash, urticaria, and angioedema. Mebendazole toxicity typically manifests as gastrointestinal irritation; however, there are documented cases of more severe adverse effects, such as neutropenia (including agranulocytosis) and/or thrombocytopenia, especially in patients administered elevated dosages or subjected to extended treatment durations beyond the standard recommendations[82].

6.7. Repurposing

Mebendazole is a newly proposed pharmacological agent in oncology targeting cells resistant to established medicines. Mebendazole demonstrates cytotoxic properties that synergise with ionising radiation and several chemotherapeutic drugs, while also eliciting an antitumoural immune response[83]. Recent studies indicate that mebendazole is a superior alternative to vincristine for the treatment of brain tumours in experimental animals.

7 Amantadine

7.1. Introduction

Amantadine is an antiviral medication that was created for the prophylaxis and management of influenza A [84-87]. Its antiviral action's mechanism is unclear; however, it seems to involve blocking ion channels to interfere with the viral M2 protein's transmembrane domain and preventing the virus from assembling during replication. Amantadine proved successful in treating influenza A, but as viruses become more resistant, it may not be as helpful in subsequent outbreaks. Antipsychotic medication still faces difficulties treating Parkinsonism and other drug-induced extrapyramidal responses, generally known as drug-induced movement disorders (DIMDs)[88]. With the development of newer antipsychotics, the frequency and prevalence of DIMDs have decreased; nonetheless, the danger still exists due to expanding medication indications, extensive marketing, and off-label prescription[89-93].

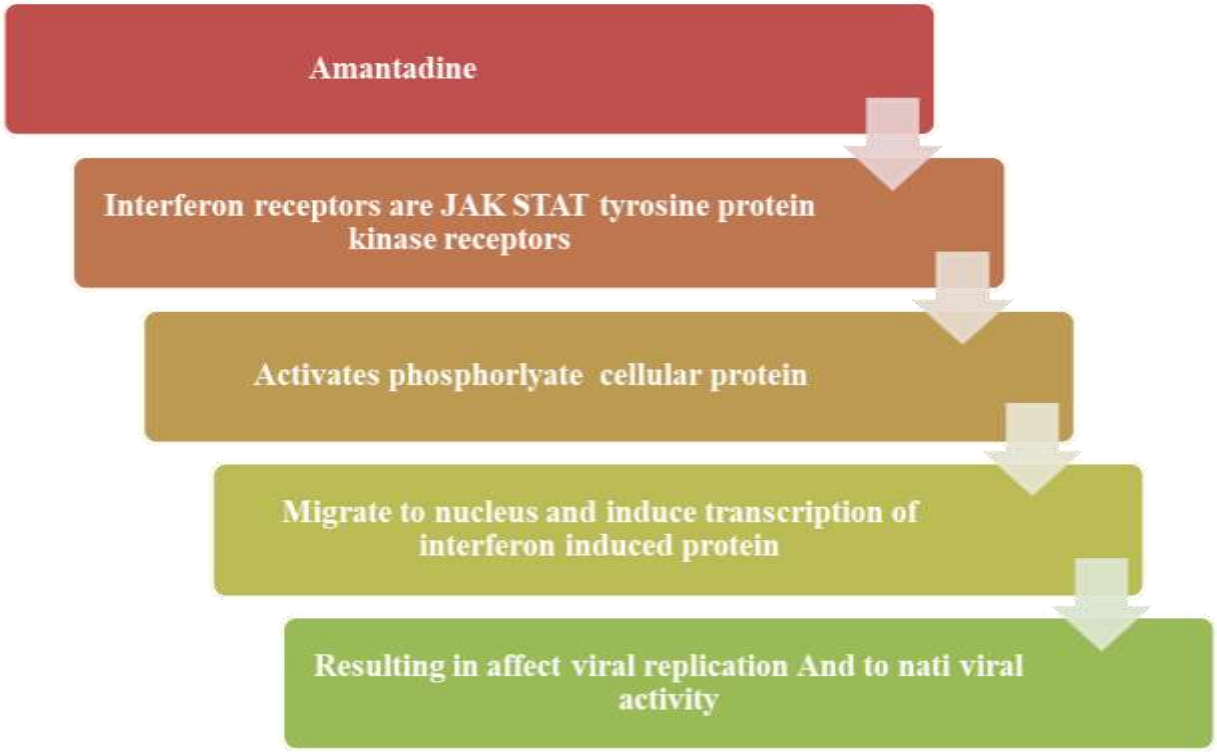
7.2. History

Amantadine was initially licensed in 1966 as a preventative measure against Asian influenza. However, it wasn't until Schwab and colleagues observed that one of their PD patients' cardinal symptoms improved while on amantadine as a flu treatment and worsened when the medication was stopped that the drug's value for treating Parkinson's disease became clear[94]. Due to this, amantadine was tested in a clinical trial for Parkinson's disease (PD) in 1968, and results showed that two thirds of patients had symptomatic relief[95]. Even though it is no longer used as an anti-influenza medication, later research confirmed amantadine's efficacy and safety in treating Parkinson's disease[96,97]. Amantadine was first prescribed for Parkinson's disease (PD) in the 1970s. It was used as a monotherapy as well as an adjuvant with levodopa and anticholinergic medications. The discovery of amantadine's antagonistic properties and experimental evidence pointing to an essential involvement of augmented striatal glutamatergic transmission in the aetiology of levodopa-induced dyskinesias (LIDs) in the 1990s eventually led to human and experimental studies demonstrating amantadine's anti-dyskinetic activity[98-100]. The only medication that has demonstrated efficacy in addressing levodopa-induced dyskinesias in Parkinson's disease is amantadine 5. Furthermore, the medication is utilized off-label and experimentally to treat several movement diseases as Huntington's disease(HD), Multiple System Atrophy (MSA), and Progressive Supranuclear Palsy (PSP). The discovery of amantadine's antagonistic properties and experimental evidence pointing to an essential involvement of augmented striatal glutamatergic signalling in the aetiology of levodopa-induced dyskinesias (LIDs).

7.3. Pharmacokinetics

Oral IR-amantadine absorption varies, with a period to steady state of 4-5 days and an average tmax of 3 hours (1–12 hours). Amantadine's plasma elimination half-life, which increases with age and justifies dose adjustment in cases of renal failure, is typically 16–17 secretion. In the US, two oral ER-amantadine formulations have just gone on sale. With a median tmax of 7.5 hours and a half-life of roughly 16 hours, once-daily ER-formulation (Vertical Pharmaceuticals, Bridgewater, NJ, USA) offers an average plasma concentration over a 24-hour period that is comparable to the identical daily dosage of IR-amantadine administered bis-daily[101,102]. Additionally, amantadine sulfate is offered as an IV infusion solution (PK-Merz infusion, Merz Frankfurt am Main, Germany). With a 15-hour mean elimination half-life, two times longer in senior patient peak plasma concentrations happen roughly two to eight hours after a single dosage administered across three hours[103].

7.4. Mechanism of action



7.5. Dosage

7.5.1. Renal impairment

Since the kidneys are the main organs via which amantadine is eliminated, renal function has a major impact on the drug's clearance. Dosage modifications are essential in those with impaired renal function in order to avoid toxicity. It is suggested that people having a 30-to 50 mL/min creatinine clearance (CrCl) take 100 mg daily. It is recommended to provide patients with CrCl 15–29 mL/min 100 mg every three days. Amantadine use should be limited or done under strict medical supervision in patients receiving hemodialysis or with a CrCl less than 15 mL/min.

7.5.2. Elderly patients

Amantadine adverse effects, such as disorientation, hallucinations, and orthostatic hypotension, are more common among the elderly. The usual beginning dose for this population is 100 mg per day, with gradual titration as necessary. Elderly patients on amantadine must be regularly monitored for side effects, especially cognitive abnormalities

7.5.3. *Paediatric use*

Amantadine is less frequently used in children; however, it has been used to treat influenza A. For kids ages one to nine, the recommended dosage is 4.4–8.8 mg/kg/day (maximum 150 mg/day), split into two doses. The recommended dosage for youngsters between the ages of 9 and 12 is 100 mg twice a day[104].

7.6. Adverse effect

In the context of clinical practice, amantadine discontinuation is typically caused by two types of adverse events: mental status changes, such as uncertainty, hallucinations of vision, and agitated moods are particularly prevalent among older and cognitively impaired individuals, and they may be brought on by the drug's anticholinergic, anti-glutamatergic, and dopaminergic effects. Amantadine should not be used in those who have previously experienced drug-induced psychosis necessitates robust reasons before to using it in individuals with cognitive impairments who cannot benefit from close patient monitoring. Livingdon reticularis, with or without limb oedema, is another common cause of amantadine withdrawal. It's unknown what mechanisms underlie this unappealing cosmetic reaction. Its look is distinct from both the uncommon erythromelalgia that is mostly seen with the earlier ergolinic agonists and the leg oedema that is frequently seen with dopamine agonists[105].

7.7. Repurposing

7.7.1. Acute dystonias

A class of movement disorders known as dystonias is defined by short-lived, sporadic, or chronic spasms or contractions that cause involuntary twisting as well as repetitive postures or movements[106-108]. An acute movement problem known as drug-induced dystonia can be painful and upsetting, and it can adversely affect the patient. compliance with treatment[109]. When antipsychotics are administered parenterally, dystonia is usually seen only a few hours of contact and appears in 95% of patients during the initial five days of treatment. Although dystonia brought on by drugs can affect any muscle group, it often only affects one or a small number of them. Typically, the head, jaw, mouth, eyes, and neck are impacted[110].

7.7.2. Parkinson disease

Parkinsonism brought on by drugs is characterized by bradykinesia, stiffness, and shake. The syndrome is subacute that might be clinically confused with idiopathic Parkinson's disease. Parkinsonism is more frequent, more challenging to treat, and can result in severe disability even though it is less acute than dystonia. While the development of parkinsonism may take days or weeks to manifest, it may happen rather soon after antipsychotic medication begins. 90% of instances happen within three months, while between 50% and 75% happen within one month[111].

8 Conclusion

As we approach the onset of a new era in medicine, drug repurposing emerges as a pivotal strategy that can transform the landscape of healthcare. This innovative approach not only expedites the development of new therapies but also maximizes the potential of existing medications to address urgent health challenges. The incorporation of cutting-edge technology like big data analytics and artificial intelligence, is streamlining the identification of new indications, making it possible to respond swiftly to emerging diseases and unmet medical needs.

The strategic advantages of drug repurposing extend beyond cost-effectiveness and speed; they also hold the promise of personalized medicine, tailoring treatments to individual patient profiles. By tapping into established safety data and clinical insights, researchers can repurpose drugs for conditions that previously had limited therapeutic options, providing hope for patients with rare or complex diseases.

In summary, the future of medicine lies in embracing the promise of medication repurposing as a viable pathway to enhance treatment options and improve health outcomes. By harnessing existing knowledge and advancing technological capabilities, we can unlock new therapeutic possibilities that not only advance medical science but also bring tangible benefits to patients around the world.

Drug repurposing stands at the forefront of the future of medicine, offering strategic insights into the efficient development of new therapies. With its potential to reduce costs, expedite the drug development timeline, and address unmet medical needs, this approach is not only a testament to the ingenuity of the healthcare sector but also a beacon of hope for patients worldwide. As we continue to explore the untapped potential of existing medications, the promise of drug repurposing will undoubtedly shape the landscape of modern medicine for years to come. Through innovative collaborations and the leveraging of cutting-edge technologies, we can unlock new horizons in therapeutic development, ultimately enhancing the quality of care and improving health outcomes globally.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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