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Review Article

Exploring repurposed drugs in the treatment of various diseases

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ABSTRACT

Drug repurposing is a revolutionary method, as it offers new labels for already licensed and proven drugs. Drug repurposing has the potential to furnish new therapeutic alternatives for patients, deliver relevant clinical improvements while reducing the clinical development time of molecules in contrast to the de novo development of a new chemical entity, offering an economic merit by reducing the development times of medicines, but also by optimizing affordable medicines of high quality such as generic medicine. Owing to high cost and failure rates associated with conventional drug manufacturing methods, many pharmaceutical firms concentrate primarily on drug repurposing strategies. This review addresses the advantageous effects of the available approved medication compounds that can be used as repurposed medications for the treatment of other disease or condition such as cancer, respiratory diseases, tuberculosis, depression, Parkinsonism and schizophrenia.

Key Words: Drug repurposing, Cancer, Respiratory diseases, Tuberculosis, Neurological diseases.

INTRODUCTION

Drug repurposing is a term that has been entrenched for several years and relates to the use of the same pool of potentially re-positioned, re-formulated molecules, or coupled with new technical platforms and services [1]. Drug repurposing has the ability to provide novel therapeutic substitutes for patients, to produce substantial clinical benefits while shortening the time of clinical development of drugs, as compared to the de novo development of a new chemical entity, giving economic merit by reducing the time of development of medications, as well as by enhancing affordable high-quality medications such as generic medicine. The research circle increasingly recognizes the importance of drug repurposing, as seen in the public, non-profit and private sector efforts in this field. The added value of medicinal products represents an opportunity for society to resolve a range of medicinal inefficiencies in healthcare related to the excessive use of medicinal products, the lack of appropriate treatment choices, the scarcity of mature drugs,

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geographical disparity in access to medicinal products and also the potential to improve patient safety, increase the efficiency of the healthcare system [2].

Identifying novel indications of known substances by repurposing drugs has the possibility to supplement conventional drug development by reducing the high monetary and time-related costs and risks associated with the latter. With a safety or toxicity-related failure rate of ~45 percent, reducing the safety risk, in addition to saving up to 5-7 years in average drug development time, gives drug developers and patients alike an enticing prospect. The latter have a major advantage in very quick access to medications, which would not only be inaccessible otherwise, but also have firmly established safety profiles [3].

REVIEW OF LITERATURE

Advantages

This technique provides various benefits over the production of a completely new drug for a specific indication. First, and perhaps most significantly, the probability of failure is lower; because the repurposed drug has already been found to be sufficiently effective in preclinical models and humans when early-stage tests have been completed, it is less likely to fail in subsequent efficacy studies at least from a safety perspective. Second, the timeline for drug production can be that, because much of the preclinical testing, safety evaluation and, in some situations, production of the formulation may have already been completed. Third, less investment is required, but this may differ highly depending on the candidate's stage and development process. For a repurposed drug, the regulatory and Phase III costs may remain mostly the same as for a new drug in the same indication, but notable savings in preclinical and Phase I and Phase II costs could still occur. Together, these benefits have the potential to lead to a less expensive and quicker return on investment in the development of repurposed drugs, with lower overall associated costs after accounting for failures. Finally, repurposed drugs will uncover new targets and pathways which can be manipulated further [4].

Cancer treatment

Increasing costs, a lot of time consumption and a great risk of failure involving with the de novo process of developing new anticancer drugs have induced the pharmaceutical industry to look for alternative strategies that can facilitate and accelerate the entire process. The best repurposable oncological drug candidates are the agents whose original patent protection has formerly expired and for which there is the possibility of developing a formulation that will require new patent protection, along with a different therapeutic indication [5].

Artesunate

Artesunate, a semi-synthetic derivative of artemisinin, historically used as a reactive oxygen species (ROS) inducer in the treatment of malaria; it is used as the first line therapy for both adults and children with severe malaria [6]. With regard to nonmalarial indications, artesunate has been demonstrated to have potent activity against different forms of viruses, such as trypanosoma and schistosoma; it also shows strong cytotoxic activity toward various cancer cells, including colorectal, gastric, hepatocellular, oesophageal and pancreatic [7]. The probable side effects of utilizingartesunate in oncology will limit the scope for its therapeutic use. A downside of artesunate is the short half-life of plasma in the body, and therefore possible rebound if used as monotherapy [5]. Artesunate used at low doses may result in loss of appetite, decreased activity, tremors, and weakness, whereas high doses can cause embryotoxicity, genotoxicity, neurotoxicity, hematotoxicity, immunotoxicity, or allergic reactions both in vivo and in vitro, but may also lead to death. In this context, oral ingestion of artemisinins may reflect a fairly safe route of administration compared to delayed drug release after e.g. intramuscular injection, because significant toxicity was observed in most animal experiments but not in human studies; oral administration of artesunate could be the same as that observed in animals. It is difficult to draw far-reaching conclusions from the animal studies, and the findings of these tests should be quite accurately validated. Nonetheless, artesunate is generally concluded to be safe at clinical therapeutic doses [5].

Aspirin

Aspirin is one of the NSAIDs, widely known for its analgesic and antipyretic properties [8]. The protective function of aspirin also has been widely reported in cardiovascular diseases [5]. This activity was linked to the ability of aspirin to suppress platelet aggregation and to exhibit anticoagulant activity by inhibiting cyclooxygenase 1 (COX-1), associated with the synthesis of thromboxane A2, a key factor in platelet aggregation. Importantly, aspirin anticancer activity was also identified in both the observational and experimental studies [9]. Mechanistically, aspirin's antitumor activity was linked to the possibility of inhibiting the COX-2 enzyme action. It is recognized that COX-2 promotes tumor development, including prostaglandin E2 (PGE 2) synthesis by activating the activated B (NF-μB) nuclear factor, thus recognizing COX-2 as a significant target for anticancer drugs. It should be mentioned here,

however, that aspirin's inhibitory effect on COX-2 activity has usually been observed at very high concentrations, sometimes much higher than is possible physiologically [5]. At the other side, aspirin has decreased the cyclin D1 over expression correlated with cancer progression and has disrupted both the epidermal growth factor (EGF) and its receptor tumor activity [10]. Scientists around the world have widely documented the antitumor effect of aspirin that leads to the prevention of cancer development at various locations, including the colon, endometrium and ovaries. As per all of these results, aspirin is under a series of clinical trials as a repurposable candidate for anticancer drugs [5].

Cimetidine

Cimetidine is a histamine H2 receptor antagonist and it effectively inhibits the development of stomach acid, and is thus primarily used to treat dyspepsia and peptic ulcers [11]. This drug also exhibits an immunomodulatory outcome on cells in the immune system because of its interaction with H2 receptors. Some evidence suggests that these immunomodulatory functions are the cause of cimetidine's antitumor action [12]. Initially, cimetidine was postulated to function by increasing immune function; but, more new studies have also shown that cimetidine works in several other ways (anti-adhesion, anti-angiogenesis, and antiproliferation) to inhibit tumor cell propagation and metastasis [12]. In 38 patients with metastatic renal cell carcinoma, high-dose cimetidine (2, 4 g per day) resulted in an absolute response in 2 of them with minimal toxicity [13]. More promising results were obtained by Marshall et al., who accomplished a response rate of 33 percent for cimetidine/coumarin co-therapy in patients with metastatic cancer. In 16 patients (38 %), however, no response was seen [13]. In a Phase II study of cimetidine and coumarin in patients with metastatic or locally advanced renal cell carcinoma, Dexeus et al. found only a response rate of 6 % [14] that is a few times lower than the previously reported response rate [13].

Doxycycline

Doxycycline is an antibiotic used to treat a broad spectrum of bacterial infections. Doxycycline is widely recommended as a medication for the avoidance of malaria when traveling in endemic areas and its combination with quinine has been described as an effective therapeutic strategy for malaria treatment when combination therapy based on artemisinin is not available or when antimalarial treatment with artesunate is ineffective. In recent years, doxycycline has also been documented to have interesting antiproliferative and cytotoxic activities against various cancers besides its potent antibacterial properties. The mechanism of anticancer action of doxycycline includes numerous signalling pathways. It alters cytokine expression and the secretion of miscellaneous proteins, involving inhibition of matrix metalloproteinases (MMPs), especially matrix metalloproteinase 2 (MMP-2) and MMP-9, suppression of the focal adhesion kinase (FAK) phosphorylation, lowering of VEGF and tissue inhibitor MMP-2 (TIMP-2) secretion, inhibition of protease activated receptor 1 (PAR-1) signalling, reduction of B-cell lymphoma-extra-large (Bcl-XL) antiapoptotic protein expression, lowering the expression of interleukin 8 (IL-8), and selective suppression of the expression of cancer stem cells (CSCs). All of the above mechanisms of doxycycline activity towards cancer cells have driven to the inhibition of the disease's development, which has become the basis of a series of clinical trials [5].

Ivermectin

Ivermectin, an antibiotic and a potent antiparasitic agent that was first discovered and isolated from Streptomyces avermitilis in Japan in 1967 [16]. It exhibits antitumor activity in distinct types of cancer, it includes breast cancer, bowel cancer, glioma, neck and head cancer, leukemia, melanoma, pancreatic cancer, and prostate cancer [17]. There are multiple mechanism of action of ivermectin, it involves inhibition of the AKT/mTOR signalling pathway, inhibition of the activity of multidrug-resistant proteins, inhibition of the Wnt/T-cell factor (TCF) signalling pathway, reduction of the expression of p21-activated kinase 1 (PAK1), specific inhibition of the viability of the CSCs population (CD44+/CD24–), reduction of the expression of markers related to the self renewal of CSCs, like NANOG, OCT-4 and SOX-2, at the protein and mRNA level, inhibition of the nuclear expression of yes-associated protein 1 (YAP1), and selective inhibition of SIN3 which regulates key functions in breast cancer [5]. The aspect of the multidrug resistance (MDR) is accountable for inefficient treatment of cancer with cytostatic agents. According to a vast body of evidence, ivermectin exerts an antitumor effect through the degradation of PAK1 [18], [17], whose activity is a growth factor in more than 70% of human tumors, including breast and colon cancer [5]. Ivermectin has been shown to be effective blocking the oncogenic PAK1 kinase in ovarian cancer with the IC50 values 6 between 5–20 μM, depending on cell lines used[18].

Metformin

Metformin is a biguanidine derivative; it has been employed in standard treatment for type 2 diabetes (diabetes mellitus type 2, DMT2) for more than

half a century, especially in relation to overweight diabetes sufferers [19]. Epidemiological studies of diabetes patients have demonstrated growing morbidity and mortality from malignant cancer, including breast and colon cancer, as well as pancreatic and endometrial cancer [5]. Review of electronic medical records containing data on more than 21,000 diabetic patients showed that the application of metformin could be associated with a reduction in cancer incidence and related mortality rates compared to those in patients treated with other antidiabetic agents [20]; a reduction in the occurrence of cancers and related mortality rates; Another meta-analysis of 65,540 diagnosed cancers in patients with diabetes indicated that the use of metformin could reduce the risk of developing cancers by 31% and the mortality by 34% [21]. The main mechanism of metformin anticancer activity is the activation of serine-threonine kinase via liver kinase B1; it leads to tuberous sclerosis complex 2 (TSC-2) phosphorylation, which further inhibits the mTOR signaling pathway that regulates cell growth and division processes, but also protein synthesis and angiogenesis [5]. The PI3K / AKT signaling pathway is one of the crucial pathways with increased activity in many cancers, which regulates cell growth , cell proliferation and cell survival, and metformin is capable of inhibiting this signaling pathway. Furthermore, metformin has decreased the expression of inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), which can be triggered by NF-κB. Recently it has been realized that metformin's antitumor potential is linked to the suppressive effect on CSCs associated with cancer recurrence, radiation / chemotherapy resistance, and metastasis [5].

Metronidazole

While MBZ possesses many attractive features for drug repurposing, some potential drawbacks still need to be clarified. Many trials that examined target-therapies inhibiting a single pathway led to disappointing results, possibly due to the over-activation of multiple survival mechanisms that characterize these cells [22]. MBZ's ability to inhibit various pathways and processes involved in tumor survival and progression may resolve this cap, and describes the effects on CSCs in part. Contrastingly, its large range of activity may also influence the factors common between CSCs and normal stem cells that are associated with stemness. In addition, this compound induces DNA damage, and in vivo studies have disclosed it's teratogenic and genotoxiceffect, resulting in skeletal malformations and abnormalities in mice and rats [23] and retinal layer malformation in a zebrafish model [24]; for these reasons, MBZ is contraindicated during pregnancy. Mebendazole tolerability is impressive in the usual low-dose regimens and serious side effects have also seldom been recorded during extended high-dose protocols, but the safety of its administration for a prolonged period of time in conjunction with permitted antineoplastic therapies and in the oncology setting has yet to be verified. In conclusion, the evidence outlined in this analysis supports mebendazole as an ideal candidate for drug repurposition, warranting more study in clinical trials to validate its safety in the oncology setting and efficacy as an anticancer therapy [25].

Itraconazole

Itraconazole is used for the treatment of fungal infections. It can be used for advanced or recurrent non-squamous non-small-cell lung cancer; (NSCLC). Improved overall survival vs. pemetrexed monotherapy, trial discontinued owing to increased use of pemetrexed in the first-line setting, which impeded further recruitment [26].

Clarithromycin

Clarithromycin is usually used for bacterial infections. In a study, single drug tested in a Japanese population, Clarithromycin found to be effective for advanced or recurrent small-cell lung cancer (SCLC) or NSCLC [27]. Clarithromycin for indolent non-Hodgkin lymphoma n = 60 [28], 2 year progression-free survival data only available as an abstract; data from more than 30 non-randomized trials support effectiveness of clarithromycin in other hematological malignancies (especially MM), but no other randomized trial to date [29].

Nitroglycerine

Nitroglycerine is normally indicated for Angina. Nitroglycerine found effective for advanced-stage NSCLC in a study [30], (289 days vs. 413 days, HR = 2.5, 95% CI 1.6–3.9, P <0.001). However, a similar phase II study was terminated early owing to inclusion issues, but suggested higher response rate (RR) but no difference in OS [31].In contrast to these results, failure in two other trials was noticed when combined with a different regimen[32, 33].

Verapamil

Verapamil is normally used for the treatment of Hypertension. A study revealed effects of Verapamil for metastatic breast cancer [34]. OS benefit (median of 209 days vs. 323 days, *P* = 0.036, HR not reported); associated to now unusual chemotherapy regimen (vindesine and 5-fluorouracil) was found [35].

Disulfiram

Disulfiram (dithiocarb) usually indicated for the treatment of Alcohol dependence. Trend towards metastatic Breast cancer OS benefit (5-year survival rate of 55% vs. 81%, P = 0.07) was found [36]. Development of dithiocarb discontinued by

company after failure in trials for HIV treatment, dithiocarb is the first metabolite of disulfiram. Disulfiram for metastatic NSCLC, median of 7.1 months vs. 10.0 months, P = 0.041, HR not reported); tested in combination with a common first-line regimen (cisplatin/vinorelbine) [37].

Chloroquine

Chloroquine normally used for the treatment of Malaria, rheumatoid arthritis. Chloroquine for glioblastoma n = 30 [38], trend towards OS benefit (median of 11 months vs. 24 months, HR = 0.52, 95% CI 0.21–1.26, P = 0.14). Additional patients treated afterwards, updated analysis supports OS benefit [39].

Low molecular heparin

Low molecular heparin is usually indicated for prevention of clotting, treatment of venous thromboembolic events. In an open labeled study it was found that Low molecular weight heparin was effective for SCLC (limited and extensive stages), n = 84 [40], OS benefit with dalteparin (median of 8.0 months vs. 13.0 months, P = 0.01, HR not reported). Dalteparin was administered in addition to chemotherapy or radiotherapy [40].

Auranofin (Ridaura)

Auranofin (Ridaura) Gold thiolate compounds are active nanomolar-acting TrxR inhibitors. Auranofin is an orally available, lipophilic, organogold thiolate compound approved for anti-inflammatory and possible antineoplastic treatment of rheumatoid arthritis. It has also been found that Auranofin crosses the blood – brain barrier through the central nervous system to exceed 0.2 to 5μM, so as to be safe and effective as an anticancer agent against brain tumours [41].

Celecoxib

Celecoxib is another licensed medication well adapted for redesigning and repurposing as an anticancer drug because of its strong pro-oxidant activity in promoting and potentiating the development of ROS in cancer cells to induce cell death [42, 43].Celecoxib also targets the production of ROS in the mitochondrial cancer to overwhelm cancer cells, triggering intrinsic apoptosis. Celecoxib has also been developed as a drug that kills CSCs (approximately 20-30μM IC50 for human breast cancer or rat hepatoma CSCs), suppresses self-renewal of CSCs, sensitizes against chemo resistance, inhibits mesenchymal transformation epithelial, and mitigates metastasis and tumorigenesis [44, 45].

Glucocorticoids in AML

So far, glucocorticoids in AML have no therapeutic role in antileukemia, and their use is actually discouraged due to an immunosuppressive effect. Two reports, however, recommend that glucucorticoids possibly beneficial in subsets of AML. Cytarabine-resistant and wild-type patients with FLT3 possibly respond to glucocorticoids [46]. More precisely, it is suggested that an individual of AML patients with loss-of - function mutations in the RUNX1 gene have a particular advantage of glucocorticoids in a dose-dependent manner, evidently [47]. A glucocorticoid biomarker may be quickly implemented in routine AML therapy, particularly because glucocorticoids are already usually used in the treatment of ALL [46].

Statins, HMg-CoA Reductase inhibitors

Statins, HMG-CoA reductase inhibitors, were investigated as antileukemic agents in AML. Statins tested as monotherapy have shown no convincing results in clinical trials. Statins may demonstrate the restricted potential of a repurposed drug monotherapy in an aggressive cancer of the blood such as AML. Present understanding of statin dose is not complete, and is likely to require careful modeling to optimize statin effects in AML. Two reports imply that pravastatin in combination with idarubicin and cytarabine in relapsed AML may be beneficial, whereas de novo AML did not aid from this combination [48, 49].

The Benzimidazole Family

The antihelmintic drug family benzimidazole was tested for antileukemic effects. It is proposed that benzimidazoles inhibit amino glutamate catabolism andpeptidase activity, minimize glucose absorption, increase intracellular calcium rates and inhibit the formation of microtubules. Mebendazole's antileukemic activity was discovered in Mixed Lineage Leukaemia on an in vitro drug test of AML cells with genetic changes. NCI-60 panel leukaemia cell lines including HL-60, K562, and CEM were prone to in vitro mebendazol [46].

Valproic Acid

Valproic acid from an anticonvulsant to an antileukemic drug. This branched short-chain fatty acid is used today in mood stabilizing and epilepsy drug for bipolar disorder as a long-term treatment of anticonvulsant [50]. Valproic acid was rediscovered as a histone deacetylase (HDAC) inhibitor in 2001 for its anticancer activity and was also found to induce differentiation and/or apoptosis of transformed hematopoietic stem cells and patient AML cells. Hypoacetylation of histone-associated proteins by DNA leads to tight packaging of chromatin resulting in gene repression involving differentiation, proliferation and apoptosis. HDACs are frequently over-expressed in cancer cells, even in AML cells [46]. Recently, valproic acid has been linked with standard induction therapy in elderly AML

patients, and even though not contributing in an overall enhanced clinical outcome, the 5-year relapse-free survival for patients furthermore treated with valproic acid has raised significantly [51].

Quinacrine (Mepacrine, Atabrine)

Quinacrine is an acridine dye generated in the US at the beginning of the Second World War as an antimalarial drug and used by millions of military personnel. Quinacrine is presently used off-label as a therapy enhancer in systemic lupus erythematosus [52]. Early works also indicated that quinacrine, aggregates in tumor tissue, including leukemic spleen in mouse and rat models. Action mechanisms involve inhibition of the NF-πB signal transduction pathway and activation of the protein tumor suppressor p53 [46]. Quinacrine was lately selected as the major hit in a drug screen, searching for compounds with low toxicity and high antileukemic activity toward healthy peripheral mononuclear cells in which ribosome biogenesis was found to be the target of quinacrine [53].

Antidepressants

Tricyclic antidepressants are a class of drugs in their structure that contain three fused rings and are used to treat clinical depression and other mood disorders. Of particular note, several studies reported antidepressants having antineoplastic effects. Mechanistically, tricyclic agents like clomipramine have been demonstrated to exert their antineoplastic effect by inhibiting the mitochondrial complex III, then leading to reduced oxygen consumption and ultimately to induction of apoptosis via caspase activation. Another tricyclic drug, amitriptyline, is recommended for use as an oxidation therapy agent, i.e. a medication that has the ability to both raise levels of reactive oxygen species and lower levels of antioxidants. [54].

Ritonavir

Ritonavir is widely used to boost the potency of other protease inhibitors in HIV treatment. An amble body of data acquired from different types of cancer displays that ritonavir can be able to inhibit the progression of the cell cycle, induce apoptosis and alter metabolism by multiple mechanisms. Additional to up-regulation of p53, the down-regulation of Rb, cycline-dependent kinases, furthermore anti-apoptotic proteins results in inhibition of cell cycle progression and increased apoptosis in breast, ovarian and pancreatic cancer cells [54].

Nelfinavir

Nelfinavir is a further effective protease inhibitor against both HIV-1 and HIV-2. Ritonavir has anti-cancer activities, with the suggested key mechanisms being inhibition of Akt-signaling and activation of ER stress. Treatment with nelfinavir can reduce both Akt and STAT3 phosphorylation, and nelfinavir treatment has seen relapse of prostate xenograft tumors. In multiple myeloma, treatment results in decreased signalling by inhibition of the 26S proteasome via Akt, STAT3 and Erk1/2. In ovarian, breast cancer , liposarcoma, and in non-small cell lung cancer cells, nelfinavir is a potent inducer of endoplasmatic reticulum stress and consecutive inducer of an unfolded protein response[54].

Niclosamide

Niclosamide is an old anthelmintic drug, which has been widely used for more than 50 years to treat tapeworm infestations. In recent years, the interest in its novel role in anticancer therapy has been growing. Niclosamide can by inhibiting the STAT3 pathway reverse CRC resistance to molecular targeted therapy. Constitutive activation of the STAT3 pathway, which prevents apoptosis and causes proliferation and invasion of cells, promotes acquired anti-EGFR therapy resistance in CRC. Other forms of cancer including bladder cancer, neck and head squamous cell carcinoma, on-small cell lung cancer and has reported niclosamide-mediated reversal of the resistance. Another mechanism proposed is to inhibit signalling for Wnt/βcatenin. Cetuximab resistance is associated with the activation of Wnt / β-catenin signalling. Thus inhibition of this pathway will restore CRC sensitivity to the treatment of cetuximab. Niclosamide as anticancer agent is limited in clinical trials [55].

Respiratory Diseases

Ibrutinib

Patients in a pilot study, already on ibrutinib for underlying lymphoid malignancy, ibrutinib was found to induce sustained removal of reactivity to ragweed or cat allergens via skin and basophil activation tests, through a mechanism that was thought to be mediated by inhibiting IgE-dependent basophil and mast cell activation. The promising outcomes require more clinical research [56].

Rapamycin

It is recognized that the mechanistic purpose of rapamycin (mTOR) pathway is modulating the signalling of both adaptive and innate immune cells [56]. Rapamycin, the namesake mTOR inhibitor, is approved for immunosuppression during organ transplantation. While beneficial for general immunosuppression, rapamycin can be harnessed at lower doses or administered locally to treat allergic diseases. Researchers find rapamycin would relieve allergic airways. Inflammation in a mouse model by inhibiting the distinction between eosinophils [57]. Nonetheless, a separate study found that rapamycin was less potent than steroid

treatment compared to dexamethasone treatment in an existing allergic asthma model, indicating that it needs to be dosed before full onset of symptoms [56].

Imatinib

Imatinib has been established to reduce the proliferation and activation of T cells by inhibiting dose-dependent signalling of T-cell receptors, an additional mechanism that is useful for the treatment of allergies [56]. Studies have already found effectiveness in treating allergy and asthma with Approved Article imatinib. Imatinib has been shown to reverse the production of aberrant C4 leukotriene in neutrophils in CML patients [58]. Powerful bronchoconstrictors and inflammatory agents are essential mediators of asthma pathogenesis thus fostering myelogenesis and thus cancer in CML. Combining this information, in two patients with both CML and asthma-like lower airway symptoms, patients treated with imatinib to treat their cancer exhibited impressive resolution of airway symptoms, suggesting targeted effects for asthma [56].

Statins

Statins are a commonly used class of medication that inhibits HMG-CoA reductase in reducing cholesterol levels. Some statins have also been established to have some anti-inflammatory properties. Fluvastatin had been shown be an effective suppressor of activation of the mouse mast cell, partly by inhibiting degranulation. A retrospective cohort study has found effects of statins on inhaled corticosteroids in asthma patients, reducing chances of emergency room visits or hospitalization by nearly half [56]. A double-blind, randomized control trial, however, found that atorvastatin was not effective in reducing persistent mild to moderate asthma symptoms [59]. Further work is needed to clarify these discrepancies.

Metformin

Metformin is a drug widely prescribed for patients with type II diabetes. It works to suppress hepatic gluconeogenesis but it's unclear the exact molecular mechanism of action [56]. One supposed mechanism is the activation of adenosine monophosphate AMP, activated protein kinase (AMPK), and metformin via AMPK activation has been shown to decrease airway remodelling and inflammation in a chronic mouse asthma model. In the same research, metformin also helped protect mice from bleomycin-induced lung injury, reducing eosinophilic inflammation, peribronchial fibrosis and smooth muscle secretion. Metformin reversed insulin resistance in mice, and moreover reduced eosinophilia in bronchoalveolar lavages due to the challenge of ovalbumin, which showed a decline in asthmatic symptoms. Despite these positive preclinical results, a retrospective study was conducted to determine whether metformin users were safe against asthma in patients with diabetes and asthma. Of 1,332 patients with both conditions, one-third were metformin patients with a reduced risk of asthma exacerbation and hospitalization associated with asthma, indicating that this may be an appropriate therapy for this patient population [56].

Azithromycin

Azithromycin, an antibiotic has been studied extensively as an asthma treatment, with the concept that bacterial infection may aggravate asthmatic symptoms and that azithromycin also has anti-inflammatory activities. In paediatric patients in a clinical trial involving children 13 years old, azithromycin reduced the period of asthma-like symptoms. Nonetheless, no clinically significant advantage was observed in a broad randomized clinical trial involving an adult population comparing azithromycin to placebo for treating acute asthma exacerbations. Nonetheless, a separate randomized clinical study of 420 adults with chronic symptomatic asthma observed a greater quality of life in patients treated with oral azithromycin with fewer exacerbations. Finally, a recent postulated pathogenesis mechanism for asthma has opened up a common class of drugs, antifungals, to treat a disease traditionally treated with immunomodulatory drugs. Several-allergens contain proteases, which have been shown to break fibrinogen and produce proteins that function as TLR4 agonists that cause inflammation. In particular, fungi can colonize the airways, secreting proteases that can play a major role in treatment-resistant patients with asthma. This indicates that, in addition to immunomodulating agents, the use of specific antifungal agents such as oral triazoles and inhaled amphotericin B may be an effective strategy in treating asthma [56].

Tuberculosis

Sulfadiazine

Sulfadiazine, an anti-leprosy drug has been repurposed for the treatment of MDR-TB and XDR-TB. Sulfadiazine was effective and safe against treatment with MDR-TB and TDR-TB [60].

Clofazimine (CZM)

Clofazimine (CZM) has been utilized as an anti-leprosy drug since half the century. Recently, therapy for MDRTB has been repurposed. CZM is favoured as a second-line anti-TB drug and utilized in combination with other anti-TB medications to treat drug-resistant tuberculosis. CZM appears to be a prodrug in M. tuberculosis, reduced by type 2-NADH dehydrogenase, which releases reactive oxygen species (ROS) after oxygen reoxidation.

CZM displays notable anti-mycobacterial and anti-inflammatory activity by inhibition of phospholipase and effects on potassium carriers, respectively [60].

Linezolid

Linezolid, an antibiotic used to treat gram-positive bacterial infections with oxazolidinone, has also been repurposed to treat drug-resistant TB (MDR-TB and XDR-TB). Linezolid is an effective anti-TB medication used for treating MDR-TB and XDR-TB with numerous side effects such as neurotoxicity and hematological toxicity suggested that linezolid has low rate of discontinuation, well tolerated and good efficacy in MDR-TB therapy [60]. Most recently, in a case study reported that bedaquiline and linezolid drug combinations may be safe for XDR-TB in the late third trimester of pregnancy or in pregnant women. Pregnant woman delivered a child without follow-up fetal abnormalities showed no fetal toxicity up to 2 years after delivery [61].

Minocycline

Minocycline is also one of the repurposed medications, used in the treatment of leprosy since the 1980s. It was repurposed in Japan in 2008 for monitoring XDR-TB patient treatment. Combinatorial amoxicillin / clavulanic acid therapy with other second-line drugs was used in the treatment of MDR-TB. It's cheaper, and less risk has made the WHO group five drugs the drug of choice [60]. The M tuberculosis has recently been lowered by combinatorial therapy with amoxicillin / clavulanic acid and carbapenems [62].

Neurological Diseases

The detection of successful neurological disease-modifying therapies remains a major obstacle for drug research and development. Drug repurposing aims to develop new applications for pre-existing drugs and is a significant opportunity to meet a need that is currently unmet. This is significantly more time-efficient and cost-effective than the production of drugs de novo and has created significant neurological condition successes. However, only 30 per cent of repurposed drugs and 10 per cent of novel candidate molecules gain market approval across all medical disciplines [63].

Depression

Valproic acid

Valproic acid, an acknowledged anti-epileptic drug that improves neurotransmission of c-amino butyric acid, has enhanced the efficacy of antidepressant medications in patients with resistant depression. In addition, valproic acid has attenuated low-dose depression-like activity in mice by stimulating the 3-kinase phosphatidyl inositol pathway, Akt phosphorylation, and mammalian rapamycin signalling target [64].

Ketamine

Ketamine, a phencyclidine analog that has been clinically used as an intravenous non-dissociative anaesthetic drug since 1970, has recently been used as an off-label antidepressant and as a pain reliever. Low-dose ketamine has been shown to act rapidly and is therefore particularly useful in the treatment of resistant depression. Ketamine demonstrates its anaesthetic actions by non-competitive blocking of N-methyl - D-aspartate glutamate receptors. Otherwise, ketamine metabolites hydroxynorketaminesperse were found to mediate its antidepressant effects by activating a-amino-3-hydroxy-5-methyl-4-isoxazole propionicacid (AMPA) receptors [64].

Scopolamine

It has been stated that scopolamine, an anticholinergic drug used for motion sickness. Clinical studies have also showed rapid antidepressant effects of scopolamine [65]. It seems crucial to signify that a prior clinical study disclosed that N-acetyl cysteine was ineffective as add-on therapy in improving patients' response to antidepressant drugs compared to placebo, suggesting that N-acetyl cysteine could enhance patient's resilience to stress, and indirectly, this may probably result in overall therapeutic outcome in depressed patients [64].

Anti-inflammatory drugs

The utilization of drugs possessing anti-inflammatory properties for depression shows a turning point in treating depression. Activated inflammatory pathways have been stated to add to the pathogenesis of major depressive disorder MDD, and cytokines such as tumour necrosis factor alpha was found to underlie cognitive impairment in MDD, indicating a possible role of inflammation suppression in the treatment and remission of MDD. One-third of patients with MDD demonstrated a significant improvement when they were treated with potent anti-inflammatory glucocorticoid dexamethasone for 4 days [64]. Other anti-inflammatory drugs including non-steroidal anti-inflammatory drugs and anticytokines drugs have been shown to relieve depressive symptoms and to enhance therapeutic effects of clinically used antidepressant drugs such as selective serotonin reuptake inhibitors [66]. For instance, selective cyclooxygenase II inhibitor celecoxib was reported to improve patients' response to sertraline, a 5HT reuptake inhibitor, apparently via decreasing IL-6 levels. Also, patients who were treated with infliximab, tumour necrosis factor alpha inhibitor, showed an association between improved depressive

symptoms and pre-treatment increased high sensitivity C-reactive protein levels (in particular > 5 mg/l), an inflammatory biomarker which has been reported to elevate in patients with resistant depression [64].

Pioglitazone

There has been controversy, over the possibility that other medications used for metabolic disorders such as diabetes could enhance depressed mood or cognitive impairments associated with diabetes [64]. Clinical research, on the other hand, found that insulin sensitizer antidiabetic drugs stimulating the peroxisome proliferator-activated gamma receptor significantly decreased patients' depressive symptoms. Pioglitazone, for instance, has been demonstrated to improve remission in patients with MDD or bipolar disorders. Pioglitazone has been reported to mediate improvement in depressed patients, possibly by suppressing proinflammatory cytokines such as IL-6. In addition, neuroprotective effects of these antidiabetic drugs have been suggested [64].

Nimodipine

The repurposing of vasodilators for depression treatment has been encouraged by the treatment of vascular depression by improving cerebral blood supply. In the presence of cerebrovascular complications or vascular insufficiency in elderly patients diagnosed with vascular depression, it may be proposed that improving cerebral blood flow by anti-ischaemic and vasodilator medications may have the potential to eliminate the underlying causes of late-life depression or may improve the efficacy of standard treatment with antidepressants. For example, the FDA-approved calcium channel blocker nimodipine for neurological complications of cerebrovascular diseases improved the therapeutic effects of antidepressants in elderly patients with vascular depression and enhanced the depression remission rate in patients diagnosed with vascular depression treated with fluoxetine [64].

Parkinsonism

Ambroxol

Mutations in the glucosylceramidase beta acid (GBA1) gene have been identified as the single largest risk factor for the development of idiopathic Parkinson's disease PD and as being present in up to 25% of patients with PD. Ambroxol, a secretolytic agent licensed for use in the management of respiratory diseases and has been found to act as a pharmacological chaperone to enhance the activity of GCase in PD fibroblast lines, dopaminergic neurons from patients with PD and GBA1 mutations, Drosophilia expressing GBA mutations, transgenic mice over expressing α-synuclein, and non-human primates. Encouragingly, the in vivo data indicated ambroxol could cross the blood–brain barrier and decrease the levels of α-synuclein and phosphorylated α-synuclein [67]. A pilot initial study including 12 patients with GD treated with ambroxol 150 mg/day for 6 months showed good safety and tolerability. A second open-label study involved administration of ambroxol in doses ranging from 375 to 1300 mg/day in five patients with GD for 48 months to assess safety and tolerability. All doses demonstrated increased lymphocyte GCase activity, achieved a mean cerebrospinal fluid (CSF): serum ratio of 15.6% at the highest doses, and improvements in neurological deficits were observed across all patients. These two pilot trials in GD have provided tentative support for repurposing ambroxol in PD, and two trials are presently underway [67].

Isradipine

The selective vulnerability and degeneration of dopaminergic neurons of the SN pars compacta (SNc) in PD is thought to be related to the high energy demands of the spontaneous pacemaking properties of the neurons themselves [68]. This autonomous pacemaking is accompanied by slow oscillations of calcium influx caused by the opening of plasma membrane Cav1 (Cav1.2, Cav1.3) Ca2+ channels, which help meet intracellular bioenergetic demands by stimulating mitochondrial intermediary metabolism and oxidative phosphorylation.

However, reliance on these channels increases with age. This continued production of free radical species in association with other stressors that occur in PD, isradipine, licensed for the management of hypertension, has nearly similar affinity for Cav1.2 and Cav1.3 channels in membrane-binding assays, which, together with good brain bioavailability, has made it the most attractive candidate for repurposing. In view of the promising data, an initial open-label, dose-escalation study of isradipine controlled-release 5–20 mg/day was conducted in patients (n = 31) with early PD to assess safety (STEADY-PD). It demonstrated acceptable tolerability at doses of ≤ 10 mg/day, with leg edema and dizziness causing intolerance at higher doses. Subsequently, STEADY-PD-II, a randomized, double-blind, parallel-group trial, was attempted in 99 subjects with early PD not needing dopaminergic therapy to chiefly assess a tolerable dosage of isradipine (at doses of 5, 10, and 20 mg), with secondary outcomes to detect any preliminary efficacy between the different doses after 52 weeks. The primary outcome again confirmed tolerability was dose dependent, with isradipine 10 mg being the highest tolerated dose [67].

Inosine

Increasing data from prospective studies and Mendelian randomization studies indicate individuals with raised levels of serum urate, an antioxidant, have a low risk of developing PD, though the association appears weaker and less consistent in women. Furthermore, raisedurate levels in serum and CSF from patients with PD are related with a decreased rate of disease progression. These effects were thought to occur via modulation of Akt-GSK-3B signalling and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein, a master regulator of the oxidative stress response [67]. In SURE-PD, a randomized, placebo controlled, double-blind, dose-ranging trial of inosine, 75 patients with early PD not yet needing any medication were randomized 1:1:1 to receive either placebo or inosine titrated to produce mild serum urate elevation (6.1–7.0 mg/dl) or moderate urate elevation (7.1–8.0 mg/dl) for 25 months, with the primary endpoint being safety, tolerability, and ability to elevate urate levels in CSF and serum [69]. Inosine was well-tolerated, though three patients developed symptomatic nephrolithiasis. Although the number of patients with PD treated with inosine thus far is limited, these side effects are conceivably problematic for older patients with PD, potentially confining its utility. However, a recently reported trial of ten patients of Asian origin with PD treated with inosine to elevate urate levels to 6.0–8.0 mg/dl reported no adverse effects after 1 year of treatment [67].

Ursodeoxycholic Acid (UDCA)

Given the importance of mitochondrial function in the pathogenesis of familial and sporadic PD. UDCA has been used as treatment for cholestatic liver disease for a number of years and is a first-line treatment for primary biliary cirrhosis. UDCA has also shown potent anti-inflammatory, antioxidant, and anti-apoptotic effects in hepatocellular models and has also showed that these effects broaden to several neurodegenerative models of disease, including PD. In terms of potential repurposing for PD, data from a clinical trial of UDCA in 18 patients with amyotrophic lateral sclerosis (ALS) treated for 4 weeks at doses varying from 15 to 50 mg/kg/day indicated a CSF:serum ratio of approximately 0.6% at the highest dose of 50 mg/kg/day. Although the trial reported good tolerability, the current licensed dose of UDCA is 10–15 mg/kg/day, with an expanded risk of liver toxicity and hepatocellular carcinoma reported at doses of 28 mg/kg/day, so further long-term PD specific data regarding safety, tolerability, and CSF studies are needed [67].

Deferiprone

Growing evidence suggests dysregulation of cerebral iron homeostasis occurs in various neurodegenerative disorders, including PD, and thus represents a novel therapeutic target. Thus, removal of excess cerebral iron in PD may be a helpful strategy. Deferiprone, licenced as a treatment for thalassemia syndromes and cardiac iron-overload diseases at doses of 75–100 mg / kg / day, has been the focus of current studies on iron chelation in PD. Unlike other iron chelators, to avoid serious systemic iron losses, deferiprone can redistribute excess intracellular iron to extracellular apotransferrin and can cross the blood-brain-barrier in rodent models. In addition, deferiprone has been shown in MPTP mouse models to remove excess labile iron and attenuate dopaminergic neuronal loss and inhibit dopaminergic neuron necrosis, ferric ion accumulation, and microglial proliferation and in 6-OHDA rodent models to decrease the hyperechogenic area of the SN. There have been three clinical trials of deferiprone in PD. An initial pilot double-blind, randomized controlled trial (FAIRPARK) with a delayed-start design evaluated 40 patients with early-stage PD randomly assigned to receive oral deferiprone 30 mg/kg/day or placebo for 12 months, using the change in iron overload in the SN (as measured by the T2* MRI sequences) as the primary outcome. The results indicated a 12-month course of deferiprone significantly decreased foci of accumulated iron in the SN of patients with PD without detectable changes in other brain areas or systemic levels [67].

Exenatide

Exenatide is a synthetic glucagon-like peptide-1 (GLP-1) agonist licensed for the management of T2DM as an agent that promotes insulin secretion. Neurotrophic properties of GLP-1 receptor agonists were first identified in 2002. Since then, there have been multiple reports of beneficial effects from GLP-1 receptor agonists in a broad range of toxin-based models of PD, including the MPTP, 6-OHDA, and lipopolysaccharide (LPS) models, and two α-synuclein animal models. These have allowed investigations into the potential mechanisms of action of GLP-1 agonists, which appear to have multiple effects relevant to the neurodegenerative processes of PD. Neurorestorative and neuroprotective effects have been seen in combination with beneficial effects on mitochondrial function, synaptic, plasticity, and stimulation of neurogenesis, and through enhancing the actions of brain-derived neurotrophic factor (BDNF). It is probable that all of these actions are inter-related, conceivably through an effect of GLP-1 receptor stimulation on insulin resistance and downstream Akt signalling [67].

CONCLUSION

This review comprises the beneficial effects of the available licensed medication compounds that can

be used as repurposed medications for the treatment of other disease or condition such as cancer, respiratory diseases, tuberculosis, depression, Parkinsonism and schizophrenia. In conclusion, the data on various repurposed drugs summarized in this review demonstrate new treatment alternatives for various diseases. This is significantly more time-efficient and cost-effective than the production of drugs de novo. These data imply a new alternative treatment of the above mentioned diseases, in which some of drugs may be worth being established in further studies.

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