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Development of new drugs to treat central nervous system disorders

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Introduction:

Converting results from fundamental studies into practical medicinal innovations is a key objective of biomedical research. Developing medications for disorders affecting the central nervous system (CNS) is difficult, even with the advancements in drug discovery techniques. New medications targeting major disorders of the central nervous system have a significant failure rate when compared to other areas of drug research. Unfortunately, there are currently no effective treatments for central nervous system illnesses; instead, these treatments aim to alleviate symptoms. Misunderstanding the fundamentals of central nervous system disease, the potential for central nervous system side effects, and the inability of pharmaceuticals to cross the blood-brain barrier (BBB) are the primary causes of failed central nervous system medication development.

It has been known for decades what causes many CNS illnesses. As an example, senile dementia is the most common type of age-related neurodegenerative disease globally, and Alzheimer's disease (AD) is the most common kind of this condition. Aβ peptides were thought to represent potential avenues for treating Alzheimer's disease. A more popular view now holds that Alzheimer's disease (AD) is likely the result of a complex interplay of several factors, some of which include oxidative stress, neuroinflammation, energetic deficit, vascular damage, synaptic failure, axonal injury, tau pathology, and mitochondrial dysfunction. Stroke is a leading killer and a leading source of impairment for those who survive it. The idea of the neurovascular unit (NVU) was put up due to the fact that numerous neuroprotective medications that have been proven in fundamental research have not been effective in clinical settings in preventing ischemic stroke. Parenchymal cells, including astrocytes, neurons, and interneurons, as well as endothelial cells and related blood-brain barrier tight junctions, basal lamina, and pericytes make up the NVU. Not only has the idea of NVU improved and expanded basic research into stroke, but all central nervous system diseases have benefited from it as well.

No matter how much we learn about the causes of central nervous system illnesses, developing effective treatments remains a challenge. So far, there are very few medications that have shown promise in improving outcomes in AD and stroke. The development of drugs to treat AD has been exceptionally

.challenging; between 2002 and 2012, a success rate of 99.6 percent was achieved; and at present, this rate remains low. Crucial phase III efficacy trials for neuroprotective medicines for stroke have all been unsuccessful. Another difficult central nervous system condition is brain metastases. The tragic clinical reality of cancer spread to the central nervous system (CNS) is that, despite extensive treatment, the anticipated survival period is less than one year. Recent research has shown that targeted medicines can sometimes exhibit brain activity and be administered to brain metastasized tumors; furthermore, some original tumors are more responsive to these therapies than others. Many resources are devoted to studying and preventing primary cancer, yet the medical needs of patients with brain metastases remain unfulfilled. When it comes to targeted brain metastases, no medications have been approved as of yet.

- **Blood-brain barrier:**

As continuous, nonfenestrated vessels with extra features that enable them to tightly control the movement of molecules, ions, and cells between the blood and the central nervous system (CNS), the brain's tiny capillaries are distinctive morphological and functional units that perform multiple functions, including supplying oxygen and nutrients like glucose, amino acids, and precursors to neurotransmitters. The BBB protects the central nervous system (CNS) against toxins, infections, inflammation, damage, and disease by tightly regulating homeostasis, an essential component for healthy neuronal function. Endothelial cells translocate nutrients, electrolytes, and metabolic waste via different transporters because there are no vascular fenestrae (Daneman & Prat,2015). Endothelial cells express receptors or carriers on both the luminal and abluminal membranes; these molecules actively move down concentration gradients from the arterial lumen to the brain parenchyma. In order to control the exchange of potassium for sodium, the abluminal membrane of the blood-brain barrier contains sodium pumps (Na+, K+-ATPase). Receptors expressed at the abluminal membrane facilitate the clearance of potentially harmful compounds from the brain parenchyma. One such material is amyloid beta, a peptide that is implicated in the pathogenesis of Alzheimer's disease. Enzymatic metabolism or active efflux from the vascular endothelium into the blood prevent small lipophilic compounds with

molecular weights less than 400 Da from passing across the BBB through passive diffusion through the lipid bilayer membranes of endothelial cells (ECs). In most cases, ATP-binding cassette transporters (ABC) like P-glycoprotein (P-gp), BCRPs, and MRPs (multidrug resistance-associated proteins) are responsible for active efflux. Proteins known as ABC transporters cross membranes and facilitate substrate translocation against a concentration gradient by means of the breakdown of adenosine triphosphate (ATP) (Wong et al.,2013). Multiple cell types come together to produce the intricate structures that are the brain's capillaries. Endothelial cells, which surround pericytes, make up the capillary wall and act as the actual barrier. Pericytes cover an estimated 30–70% of the arterial surface, yet this number fluctuates widely (anything from 22–70% according to various studies). The endothelial cells and pericytes are encased in the basement membrane, and astrocyte endfeet cover approximately 99% of the capillaries. When it comes to the development and features of the BBB as well as the distinct endothelial phenotype, both pericytes and astrocytes play a role. Because of their close proximity to ECs, they are able to express and release soluble factors, which modulate these tasks. It is clear that these cells play a significant role in maintaining the BBB's integrity and restricted permeability since the astrocytes and pericytes that communicate with ECs improve tight junctions (TJ) and decrease the gap junctional area . The NVU incorporates the distinct and specialized cellular architecture and function of the brain microvasculature and includes brain capillary endothelial cells along with adjacent cells such as astrocytes, pericytes, microglia, neurons, mast cells, and circulating immune cells (Keaney & Campbell,2015).

- **Medicine repositioning :**

The creation of central nervous system medications remains a significant hurdle, despite the decades of effort spent on creating in vitro BBB models, the quality of which is improving. Research into potential novel treatments for central nervous system (CNS) illnesses is a time-consuming and expensive endeavor that often yields unsatisfactory and expensive results. Alternatively, a time- and money-saving option is to repurpose safe existing medications for new applications. Repositioning or repurposing

pharmaceuticals involves finding new uses for already-approved medications by taking use of their adaptability. More and more people are opting for this other method that makes use of medication discovery fast-tracking. Because of the availability of high-throughput in vitro screening for the interaction of off-patent medicines with known molecular targets, drug repositioning is especially well-suited to the public sector. As a synonym for "drug repositioning," the terms "drug repurposing" and "drug reprofiling" have been used interchangeably in the literature. There is yet no agreed-upon definition of drug repositioning or related concepts. As a structural template for the synthesis of derivatives active against another disease, medications approved for one condition are referred to as drug repositioning, whereas old drugs that can be utilized for new uses without modification are referred to as drug repurposing (Talevi,2018).

It is completely possible that medications now available for central nervous system (CNS) conditions could also act on other CNS ailments, given that these drugs have been shown to have some impact on the CNS. Another plus for medication development is the fact that side effects are no longer an issue.As a result of pharmacological repositioning, most central nervous system (CNS) medications that were licensed originally for various CNS conditions have now found a new home. The share of central nervous system (CNS) medications in the pipeline, however, was lower. Additional research is necessary to confirm these findings; nonetheless, the issue of BBB penetration could be a contributing factor. While the blood-brain barrier (BBB) prevents the vast majority of pharmaceuticals and drug candidates from reaching the brain, existing central nervous system (CNS) medications have a better chance of penetrating the barrier. Actually, certain central nervous system (CNS) medications have been repurposed as other CNS therapies at least twice. Figure 6A and B show that in vitro BBB models are useful for validating potential medication repositioning options. From this vantage point, we list a few typical CNS disorders that have been the target of medication repositioning initiatives(Tiriveedhi,2018)

- **Alzheimer's Disease:**

Amyloid beta (Aβ) plaque depositions, neurofibrillary tangles, brain shrinkage and neurodegeneration, neuroinflammation, poor neurogenesis, vascular and BBB disturbances, and other complicated pathologies make up the underlying cause of Alzheimer's disease. The discovery of effective treatments for Alzheimer's disease is impeded by the poor pathophysiological characterization, even if research into the disease has advanced recently. Indeed, no pharmacological therapies for AD have been found to be successful thus far. Here, a new approach focused on the redistribution of already-approved medications for other diseases seems like a good bet. Through the use of in silico experiments, Kumar et al. investigated the molecular interactions between the several protein targets implicated in AD and the already-known antipsychotic medications. They used molecular docking to assess around 150 antipsychotic medications against five key protein targets: NMDA, monoamine oxidase (MAO), acetylcholinesterase (AchE), butyrylcholinesterase (BuChE), and beta secretase cleavage enzyme 1 (BACE 1) (Scheltens et al.,2016). Their research has shown promise in targeting various AD-related targets with top antipsychotic medications like pimozide, bromperidol, melperone, anisoperidone, benperidol, and anisopirol. According to their research, benperidol is the most promising candidate for the NMDA, MAO A, cholinergic (AchE and BuChE), and beta secretase cleavage enzyme (BACE 1) systems. Around forty percent of the Alzheimer's disease clinical trials that are underway right now are utilizing medication repositioning. Insulin, pioglitazone, leukotriene, and candesartan are among the other potential possibilities being investigated in these AD clinical studies, along with other unique CNS medicines including rasagiline, levetiracetam, and riluzole. The recent announcement that Alzheimer's disease (AD) is a complex multifactorial disorder with numerous significant pathologic components and not just one dominant biological element (like beta-amyloid) is probably the catalyst for this change. Potentially revolutionary changes in the care of Alzheimer's disease patients might result from drug repositioning strategies (Scheltens et al.,2021).

- **Metastatic Brain Tumor/Glioma:**

Few publications on drug repositioning trials exist, and even fewer on breast cancer drug repositioning, due to the paucity of research on metastatic brain tumors. Time and money are two of the biggest obstacles in the development of anticancer drugs. The success rate of finding new anticancer medications is decreasing since it is becoming more and more difficult to do so. The promise of this method has been proven by numerous examples of successful repurposing in the field of oncology. Metformin, an anti-diabetes medicine, has been repurposed to treat breast cancer, prostate cancer, etc., while aspirin, an antipyretic treatment, has been repurposed to treat colon cancer. Few people with psychosis acquire cancer, according to previous epidemiologic studies. During a nine-year follow-up, researchers found that the cancer incidence was 1.93% in the group of schizophrenia patients without a history of cancer and 2.97% in the control group. This finding provides more evidence that people with schizophrenia have a lower risk of developing cancer compared to the non-schizophrenic group. Some research suggests that neuroleptic medications may have anticancer effects, since they have been associated with a reduced cancer incidence in people with schizophrenia. Furthermore, preclinical investigations have demonstrated anticancer efficacies in some anti-schizophrenia medications, including trifluoperazine and chlorpromazine. Another antipsychotic medication that is often used is fluphenazine hydrochloride. A small number of trials have shown that it can be effective in treating breast cancer. One medication that can cross the blood-brain barrier and reach a relatively high concentration in the brain is fluphenazine hydrochloride, which is used to treat schizophrenia. In a mouse brain metastasis model, fluphenazine hydrochloride showed promising anti-metastatic potential with an inhibition rate of 85%, according to Xu et al.'s evaluation of its activity in the treatment of triple negative breast cancer (TNBC) and brain metastases. Additionally, the medicine significantly reduced the rate of spontaneous lung metastasis. As an added bonus, the mice showed no significant adverse effects from fluphenazine hydrochloride. Because of these findings, researchers have been looking into repurposing fluphenazine hydrochloride for the treatment of metastatic TNBC, a disease that desperately needs new therapeutic choices. The specific ways in which fluphenazine hydrochloride inhibits cancer growth remain a mystery. Research has indicated that antipsychotic drugs can potentially combat cancer

through their diverse methods, such as lysosomal homeostasis disturbance, dysregulation of cholesterol homeostasis, and autophagy induction. Additional research is required to confirm this, however it appears that certain antipsychotic medications may inhibit the progression of cancer (Das et al.,2019).

- **Brain attack :**

It is often believed, but not proven, that neuroprotection treatments only work in animals and have no effect on humans. Reports of studies of putative neuroprotectants in acute stroke patients having unsuccessful or mixed outcomes have consistently reinforced this notion. If it turns out that animal tests can't help doctors make decisions, then the value of stroke models in animals and the ethics of using them in the future are both called into question. Nothing out of 1,026 treatments for stroke therapy has worked in scientific trials, and this could be due to inherent species differences. Repositioning the medication is a viable option here. Critical brain tissue is quickly destroyed in a stroke when a cerebral artery is blocked, setting off a fast-moving chain reaction. Neurons, glial cells, vascular cells, and the matrix between them are all part of this. Stroke survivors have discovered some promising targets for vascular protection, such as nitric oxide, angiopoietin-1, vascular endothelial growth factor, matrix metalloproteases, cytokines, and caspases, which are endogenous mediators of vascular damage. It is possible to target some of these targets with repurposed medications, such as statins, minocycline, angiotensin II receptor blockers, and growth factors like erythropoietin. Experimental models of cerebral ischemia have also shown that statins, melatonin, minocycline, and fasudil—a Rho-kinase inhibitor—are effective vascular protection techniques (Kumar et al.,2012).

As vascular function is fundamental to both cardiovascular disorders and ischemic cerebrovascular diseases, vascular protection appears to be a viable approach to improving stroke prognosis. It is possible that the biological processes and pathways pertaining to vascular function are the connecting factors between ischemic cerebrovascular disorders and cardiovascular diseases. In this study, Zhao et al. utilized an integrated approach that leverages several databases, in silico target selection, gene function enrichment, and network pharmacology analysis. They looked into the possibility of

repurposing 119 pharmaceuticals approved by the FDA for cardiovascular illness to treat ischemic cerebrovascular conditions. Carvedilol, a pleiotropic medication with several targets, was studied for its possible use in treating ischemic cerebrovascular illness. With its α1-blocking efficacy and pleiotropic effects on 17 targets, carvedilol is a nonselective β-adrenergic blocking drug. Their findings suggested that carvedilol's impact in treating ischemic cerebrovascular illness may be associated with the regulation of vascular function, and that this mechanism is related to several targets and signaling pathways. The use of biomolecular profile-based computational drug discovery and repositioning is likely to grow in the years to come (Teasell et al.,2014).

- **Parkinson's Disease:**

We still don't know much about the specific pathophysiological processes that cause neurodegeneration in PD. Just as with other central nervous system (CNS) diseases, developing new drugs for PD is a lengthy, costly, and potentially dangerous procedure. Consequently, it is understandable that the pharmaceutical industry is seeing a sea change in the way PD medications are researched and developed. medication repositioning is being investigated more and more by pharmaceutical corporations as a means to combat the high attrition rate in medication development. Actually, amantadine, which was first created in the 1960s to prevent several types of influenza, has now been authorized for the treatment of PD. In 1968, a case observation was made of a 58-year-old woman with moderately severe Parkinson's disease, which led to the shifting of the drug's focus from anti-flu to anti-Parkinson. The patient reported a dramatic improvement in her symptoms of stiffness, tremor, and akinesia while using amantadine hydrochloride 100 mg tablets for flu prevention, according to the treating neurologist. This chemical is hydrophilic, but it crosses the blood-brain barrier with relative ease because of active transport, most likely through a proton-coupled organic cation antiporter. Curiously, new evidence suggests that amantadine has a wide range of effects in different indications, including MS, traumatic brain injury, and cancer pain (Bloem et al.,2021). The various indications for amantadine will have completely different mechanisms of action. One further example of a medicine

that has been repositioned is Zonisamide. In the 1980s, it was created with the intention of treating epilepsy. Surprisingly, when Murata et al. utilized zonisamide to treat a patient's epilepsy, they also saw an improvement in the patient's PD symptoms. Research suggests that zonisamide's ability to prevent seizures may be due to its influence on T-type calcium channels and voltage-dependent sodium channels. While zonisamide's anti-PD action could be associated with its ability to inhibit monoamine oxidase-B, stimulate dopamine release from the striatum, and block T-type calcium channels, among other mechanisms. Japan approved zonisamide as an anti-PD medicine in 2009 based on these data and further clinical trials (Kalia & Lang,2015).

Existing PD treatments mostly aim at increasing dopaminergic signaling, which might temporarily alleviate motor symptoms but has minimal impact on nonmotor ones. Furthermore, there is no evidence that any of the medications can halt the deterioration in both pathology and clinical status. Even while the clinical relevance of the numerous risk loci identified by genome-wide association studies (GWASs) for PD is still up in the air, it is similar to other complex hereditary diseases. Uenaka et al. provide a strategy that uses GWAS data and in silico databases to find potential PD medications. They found 57 medication families that have been approved by the FDA as potential neuroprotective medicines for PD. Among these, dabrafenib shown exceptional cytoprotective properties; it is a B-Raf kinase inhibitor that has received approval for the treatment of malignant melanoma. According to their findings, dabrafenib protects against PD-related neurotoxicity. Using an animal model, they further demonstrated that this in silico screening strategy was effective. Since there is already data on the medications' safety in human patients, drug repurposing is an encouraging approach to medication development. The sheer volume of medications that have been approved by the FDA makes it impractical to review each one individually. Potentially saving time and money, in silico drug screening may reduce the number of potential treatments for many polygenic disorders by combining GWAS data with databases of medicines and protein-protein interactions (Lees et al.,2009).

- **Conclusion**

Minimizing the time and money spent on developing drugs for the central nervous system is possible through medication repositioning. Currently, treating physicians' meticulous observations have led to the serendipitous discovery of two-thirds of repositioned medications. Furthermore, fundamental researchers, medical professionals, and pharmacists should all pay close attention to patients' day-to-day observations, the proper execution of clinical trials, and the drug's unexpected impacts on patients. In addition, it is anticipated that in silico drug repositioning—a process including data mining, machine learning, and network analysis—will be essential in the advancement of future treatments.

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