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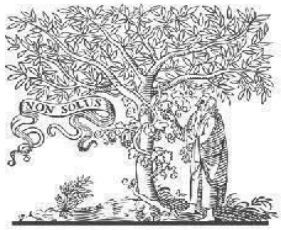

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EXPLORING DRUG REPURPOSING FOR CENTRAL NERVOUS SYSTEM DISORDERS: AN OVERVIEW

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Abstract
Drug repurposing offers a significant opportunity to expand the use of established, safe therapeutics to previously underserved patient populations. Numerous instances exist where existing drugs have found new applications, often discovered incidentally or through targeted investigations that originally focused on the drug's primary mechanism of action. The rise of big data repositories and advanced analytical tools has catalyzed the development of systematic approaches to drug repurposing, garnering increased interest in recent years. Currently, cutting-edge computational methods facilitate both experimental and in silico approaches to systematically screen and repurpose medications. Integration of molecular data with other datasets is crucial for establishing robust drug repurposing pipelines that yield reliable findings. This integration enhances the efficiency of identifying new therapeutic uses for existing drugs, thereby advancing drug research and development.

Key words: Parkinson's disease, Ambroxol, Isradipine, Inosine, Alzheimer's disease, Anti-cancer agents, Paclitaxel, Bexarotene, Carmustine, Anti-hypertensive drugs, Bipolar disorder, Anti-inflammatory drugs, Aspirin, Statins, Allopurinol, Angiotensin agents.

Introduction
Drug repurposing, the practice of identifying new applications for existing molecules, offers potential advantages by reducing the time, cost, and risk associated with traditional drug discovery processes. Compared to de novo drug discovery, which involves seeking novel active ingredients, drug repurposing leverages existing medical knowledge to swiftly identify new therapeutic possibilities, thereby mitigating development risks (Ashburn and Thor, 1). Allarakhia emphasized the use of "potential drug candidates" as a foundation for pharmaceutical repositioning, linking "drug repurposing" to advancements made with previously approved medications (2).
Countries worldwide are actively funding efforts related to drug repurposing. In the United States, for instance, the National Center for Advancing Translational Sciences (NCATS) initiated the Discovering New Therapeutic Uses for Existing Molecules Program, aiming to expedite the development of new treatments by exploring alternative uses for agents that have already progressed through critical developmental milestones (3). In the United Kingdom, researchers can seek funding for clinical trial repurposing through the Medical Research

Council's (MRC) Developmental Pathway Funding Scheme (4). The Netherlands Organization for Health Research and Development (ZonMw) supports a similar initiative termed "stimulation of drug rediscovery," focusing specifically on drug repositioning (5).

DRUG REPURPOSING IN PARKINSON'S DISEASE:

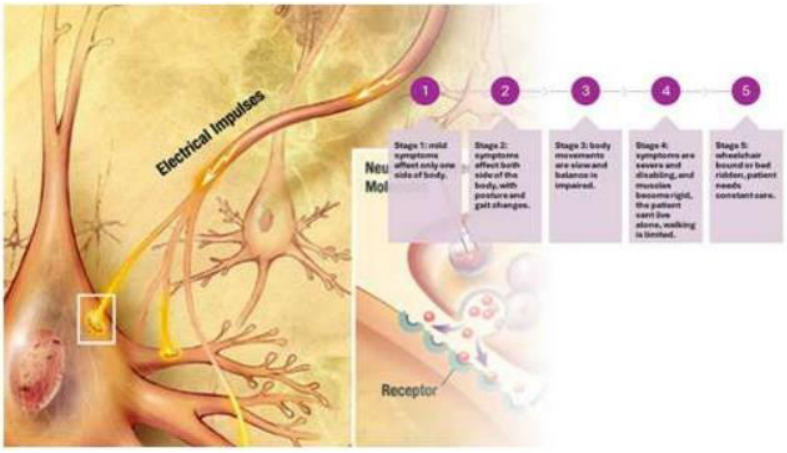

Figure 1: Drug repurposing in Parkinson's Disease

DRUG REPURPOSING IN ALZHEIMER'S DISEASE:

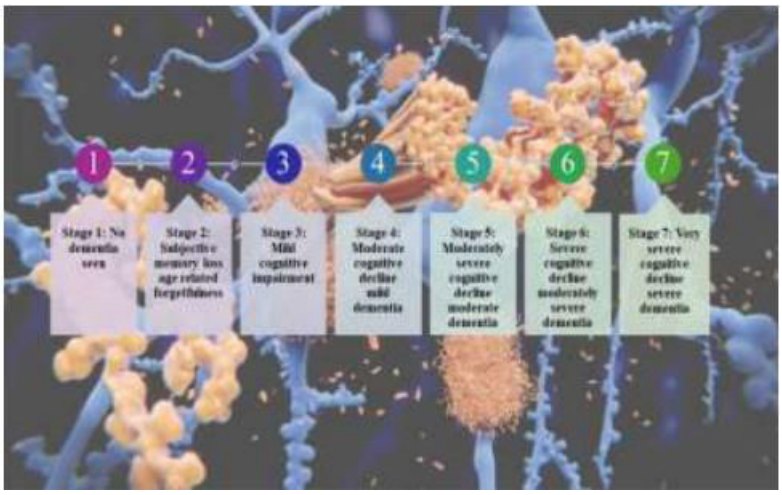

Figure 2: Drug repurposing in Alzheimer's Disease

Anticancer Agents:

The study focused particularly on the inverse relationship between Alzheimer's disease (AD) and cancer. The shared signaling pathways between dementia and cancer, such as oxidative stress, mitochondrial dysfunction, misfolded protein production, and impaired cell metabolism, underlie this association (42). Research has also indicated that older individuals who have survived breast cancer and undergone chemotherapy have a reduced risk of developing AD compared to the control group (43). Conversely, studies among cancer patients have shown a minimal risk of developing Alzheimer's disease, and vice versa (44). Due to this link, several anti-cancer drugs are being repurposed for AD treatment. Notably, bexarotene, carmustine, imatinib, paclitaxel, among others, have garnered recent scientific interest.

Bexarotene:

Bexarotene, an antineoplastic agent primarily approved for cutaneous cancers, received FDA approval in late 1999. Recent preclinical and clinical studies suggest potential use for treating Alzheimer's disease by enhancing brain function through reduction of amyloid β levels in the brain. Encouraging evidence from preclinical and clinical trials supports the repositioning of anticancer drugs for AD treatment (45,46). For instance, Cramer et al., 2012 (47), applied bexarotene in a repositioning approach to treat AD, demonstrating that oral administration in an animal model increased amyloid β clearance by over 50% in less than 72 hours. Similarly, Bachmeier et al., 2013 (48), found that Retinoid X receptor (RXR) stimulation via bexarotene promoted metabolic clearance of amyloid β in an apoE-dependent manner, rapidly improving behavioral impairments. Clinical studies further support bexarotene's repositioning potential for Alzheimer's disease treatment.

Anti-Hypertensive Drugs:

The incidence of AD correlates with hypertension, prompting numerous studies on potential therapeutic effects of various antihypertensive drug classes in AD. Hypertension can damage hippocampal tissue through ischemia caused by atherosclerosis and cerebral amyloid angiopathy.

Nilvadipine:

Nilvadipine, a calcium channel blocker used for hypertension, is also being repurposed for Alzheimer's treatment (49). Research in 2013 found that older adults with hypertension showed greater signs of AD in their spinal fluid. High blood pressure can damage brain blood vessels, impairing critical brain functions like thinking and memory (50). Clinical research has shown that nilvadipine stabilizes cognitive decline and reduces AD incidence in patients. In vitro studies suggest nilvadipine reduces amyloid β buildup, primarily through effects on L-type calcium channels (51,52). Phase 3 clinical trials have already demonstrated positive outcomes for AD treatment.

Carvedilol:

Carvedilol, a non-selective vasodilator and α/β-adrenergic receptor antagonist used for hypertension, significantly reduces brain oligomeric amyloid β levels. It enhances neuronal transmission and preserves certain cognitive functions in AD patients (53,54). Carvedilol's unique 3D pharmacophore conformation allows it to bind amyloid β and prevent aggregation into oligomeric fibrils. In mouse models of AD, carvedilol improves synaptic transmission and cognitive outcomes related to amyloid β (55,56). Ongoing phase IV clinical trials provide promising support for carvedilol's potential use in AD treatment.

This ongoing clinical trial of repurposed drugs is detailed in the following table (Table No. 2).

DRUG REPURPOSING ON BIPOLAR DISORDER

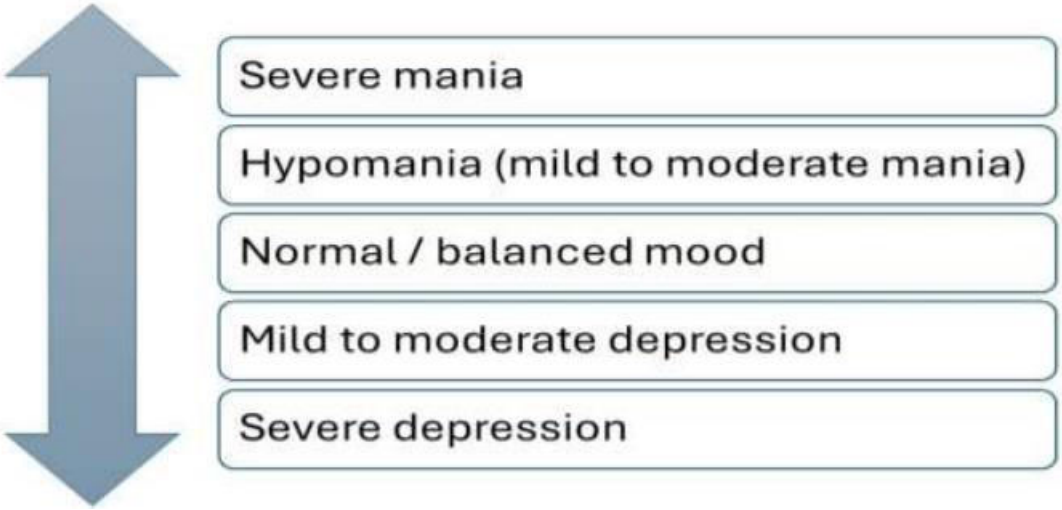

Fig 3: Signs and Symptoms of bipolar disorder

Conclusion:

Optimizing research efficiency requires significant investments of time, energy, and expertise in integrating technical solutions. Furthermore, increased financial support for clinical trials in drug repurposing, coupled with technical guidance, is strongly recommended. Adequate funding for preclinical research in drug repurposing is essential for gathering data necessary for subsequent clinical trials. This approach enhances the likelihood of applying drugs with potential to treat rare diseases in therapeutic strategies for clinical neurological disorders.

Drug repurposing represents an innovative strategy to expedite drug development for neurological diseases. These repurposed medications offer a promising avenue for improving various pathological conditions, particularly neurological disorders. Moving forward, it is crucial to delve into the molecular mechanisms underlying drug repurposing. This is essential because the targets of repurposed drugs for neurological diseases may differ from their original indications. Such insights can enhance the effectiveness and safety profile of these drugs.

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