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Drug Repurposing: An Overview on Central Nervous System Disorders

Pradnya swami*, Dr. Rahul Buchade, Shweta Bhagwat
SES'S Indira College of Pharmacy, Tathawade Pune (411033)

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ABSTRACT
Repurposing medications provide an opportunity to reach previously unreached patient populations with proven safe therapeutics. Many examples exist of finding new applications for already-known chemicals; most come from unintentional findings or focused study that was recently limited to the mode of action of a certain medicine. With the advent of big data repositories and related analytical tools, as well as the need for novel approaches to drug research and development, the development of systematic methods for medication repurposing has garnered interest in recent years. Currently, several state-of-the-art computational methods are available that enable both experimental and in silico methods to support the systematic reuse of screens. Integrating molecular data with other data is necessary for an efficient drug repurposing pipeline to guarantee reliable findings.

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.

I. INTRODUCTION

By finding new applications for already-existing molecules and lowering the time, cost, and risk involved in the latter process, drug repurposing has the potential to improve traditional drug discovery. (1) To offer numerous benefits in comparison to de novo drug discovery, the traditional method of medication development that entails searching for a novel active ingredient. Using the current corpus of knowledge in medicine to identify drug repositioning prospects more quickly could mean fewer development risks, according to Ashburn and Thor. (1)whereas Allarakhia utilized "potential drug candidates" as a foundation for repositioning pharmaceuticals, connected "drug repurposing" to advances employing previously approved medicines.(2)

Drug repositioning-related efforts are being funded by several nations worldwide. In the US, for example, the National Centre for Advancing Translational Sciences (NCATS) launched the Discovering New Therapeutic Uses for Existing Molecules Program.The initiative's stated objective is "to improve the difficult and drawn-out process of developing new treatments and cures for disease by finding new uses for agents that have already passed several important development path milestones."(3)Researchers in the UK can apply for funds to repurpose clinical studies through the Medical Research Council's (MRC) Developmental Pathway Funding Scheme.(4)The study, termed "stimulation of drug rediscovery," is supported by the Netherlands Organization for Health Research and Development (ZonMw) and focuses on drug repositioning.(5)

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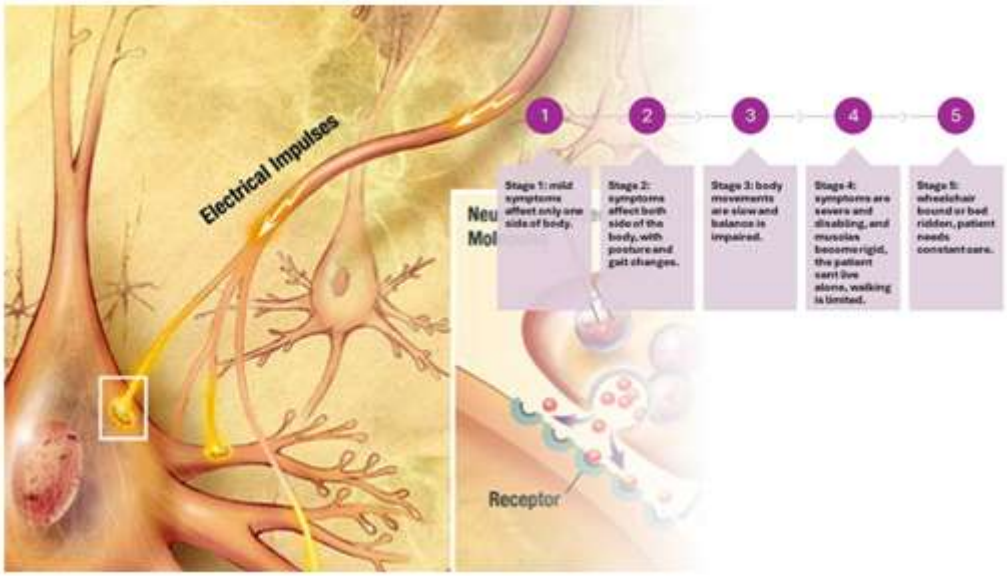
1. DRUG REPURPOSING IN PARKINSON'S DISEASE:



- **Ambroxol:**

The glucosylceramidase beta acid (GBA1) gene, which has been found to be the single largest risk factor for the development of idiopathic Parkinson's disease (PD), is mutated in up to 25% of PD patients. (6)While Gaucher's disease (GD) can be caused by a single mutation, Parkinson's disease (PD) is more likely to result from homozygous or compound heterozygous mutations in this gene. It is thought that the GBA-encoded enzyme glucosecerebrosidase (GCase), which is involved in altering lysosomal function and α-synuclein folding, is responsible for the GBA-mediated loss of function in Parkinson's disease (PD), albeit the precise mechanism underlying this loss of function remains unclear. The substantia nigra (SN) has notably decreased GCase activity in both GBAPD-positive and GBA-negative individuals. (7, 8)

Reduced GCase activity in animal models causes greater α-synuclein accumulation in the neocortical accumulation and related in vivo motor and cognitive impairments. (9)Clinical and behavioral issues can be avoided by using viral gene therapy to induce exogenous GCaseoverexpression. (10),Several studies investigated into the use of tiny molecules to increase GCase activity, despite potential difficulty with transport to affected tissues. These molecules work as chaperones to increase GCase activity by assisting mutant GCase molecules in folding appropriately in the endoplasmic reticulum to enable their passage to lysosomes. (6)Ambroxol, a secretolytic medication licensed to treat respiratory disorders, has been shown to have pharmacological chaperone properties. (11)

- **Isradipine:**

The high energy requirements of the neurons' spontaneous pacemaking properties are thought to be related to the dopaminergic neurons of the SN pars compacta (SNc) in Parkinson's disease (PD) selective vulnerability and degeneration. (12)To accompany this independent pacemaking, mild oscillations of calcium input are brought on by the opening of the Cav1 (Cav1.2, Cav1.3) Ca2+ channels in the plasma membrane. These channels support mitochondrial intermediate metabolism and oxidative phosphorylation to help meet intracellular bioenergetic needs. However, people become more reliant on these outlets as they become older. Combining this continuous generation of free radical species with other stressors associated with Parkinson's disease (PD), such as misfolded α-synuclein or mutations in GBA1, can lead to an increase in mitochondrial oxidative stress, which expedites the aging and death of cells. (13)Although the Cav1 Ca2+ channels are required for the SNcpacemaking function, they are not essential for it. Therefore, SNc dopamine neurons may deteriorate less quickly if these channels are blocked to lower oxidative stress.

Epidemiological data lend support to the theory that people on centrally acting dihydropyridines (DHPs), calcium channel blockers that have been used for many years to treat hypertension and angina, may be less likely

International Journal of Pharmaceutical Research and Applications
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than people on other treatments to develop Parkinson's disease (PD).(14-16)The most likely subtype of Cav1 Ca2+ channels to mediate risk in Parkinson's disease is thought to be Cav1.3 channels rather than the more common Cav1.2 channels.

- **Inosine:**

People with higher serum urate levels, an antioxidant, had a lower risk of developing Parkinson's disease (PD), according to research utilizing Mendelian randomization. (17, 18); however, the correlation is weaker and less reliable in women (19-22). Moreover, a lower rate of disease progression is linked to increased urate levels in PD patients' serum and CSF (23)Moreover, therapy of mice to raise urate levels protected against dopaminergic cell death caused by MPTP, 6-OHDA, and rotenone in toxin-based models of Parkinson's disease. It was thought that these effects resulted from modifications to Akt-GSK-3B signaling and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein, which is a master regulator of the oxidative stress response. (19-22)

- **Ursodeoxycholic Acid (UDCA):**

Considering how crucial mitochondrial function is to the etiology of both familial and sporadic Parkinson's disease (27) In order to find possible compounds for repurposing in Parkinson's disease (PD), researchers screened 2000 compounds from the Microsource Compound library using a unique high-throughput test. They evaluated the compounds' rescue effects on mitochondrial activity in parkin (PARK2)-mutant fibroblasts. (28) Due to the lack of clinical safety data and the fact that neither medication was an approved substance, researchers next assessed the effects of ursodeoxycholic acid (UDCA), which is closely related. UDCA is the first-line treatment for primary biliary cirrhosis and has been used for many years as a treatment for cholestatic liver disease. Later research revealed that UDCA, possibly through elevated Akt phosphorylation, restored mitochondrial activity in both parkin- and LRRK2-mutant cells. In hepatocellular models, UDCA has also shown strong anti-apoptotic, antioxidant, and anti-inflammatory properties. (29, 30)

Research has shown that similar effects apply to other neurodegenerative disease models, including Parkinson's disease. It has been demonstrated that UDCA can improve behavioral function in rodents by increasing the survival of nigral transplanted tissue and partially rescuing a PD model of Caenorhabditis elegans. (31, 32)

- **Deferiprone:**

An emerging body of research indicates that disturbance of cerebral iron homeostasis is linked to several neurodegenerative diseases, including Parkinson's disease (PD), and may thus be a new target for treatment. While iron builds up in the brain during normal aging, investigations on post-mortem, sporadic Parkinson's disease (sporadic PD) patients' magnetic resonance imaging (MRI), and transcranial ultrasonography imaging have shown significant regional iron accumulation in the SN. (33-35) Subsequent research has verified that hyperiron deposits in certain dopaminergic neurons within the SNc are linked to neuromelanin granules, Lewy bodies, and activated microglia. (36-38)

By producing reactive oxygen species, stimulating microglia and pro-inflammatory pathways, encouraging α-synuclein misfolding and aggregation, and inducing cell death through iron-dependent pathways known as "ferroptosis," this excess labile iron can have an impact on neurodegeneration. (39-41) In contrast to other iron chelators, deferiprone can pass the blood-brain barrier in mouse models and redistribute extracellular excess iron to the extracellular apotransferrin to prevent significant systemic iron losses.(41) Clinical trials of repurposing drugs given in the following table.(Table No 1)

Sr no	Name of drug	Clinical trial gov ID	Phase	Dose	Description
1	Ambroxol	NCT02941822	Phase 2	Day 1-7: 60 mg three times a day Day 8-14: 120 mg three times a day 180 mg three times a day for days 15–21 Day 22–28: Three	Participants with Parkinson's disease will have their safety, tolerability, and pharmacodynamics assessed in this trial. Throughout the duration of the trial,

International Journal of Pharmaceutical Research and Applications
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				times a day, 300 mg Day 29-186: 420 mg three times a day	participants will administer ambroxol at five different dose levels and complete clinical assessments, lumbar punctures, venepunctures, biomarker blood tests, and cognitive assessments.
2	Isradipine	NCT02168842	Phase 3	In this multi-center trial, 336 people will be enrolled at about 56 sites throughout the US and Canada. In this trial, patients with recently diagnosed Parkinson's disease are treated with 10 mg of isradipine vs a placebo.	According to findings from laboratory investigations, isradipine may stop the onset of Parkinson-like symptoms in animal models. In certain PD patients, isradipine has been studied. In the first research, patients with early Parkinson's disease (PD) and normal blood pressure were given isradipine controlled release (CR), which was found to be safe and reasonably well tolerated
3	Inosine	NCT02642393	Phase 3	Capsules containing 500 mg of inosine (active drug) or ~500 mg of lactose (placebo) will be taken orally up to two capsules three times per day (i.e., up to 3 g/day) for 24 months.	Gradually increasing the initial dose to the anticipated goal dose, it will be optimized based on individual parameters such as gender and pretreatment serum urate. The primary outcome variable (MDS-UPDRS) will be measured at every study visit following screening, and secondary outcome variables.
4	Ursodeoxycholic acid (UDCA)	NCT03840005	Phase 2	30 patients will be randomised to UDCA at a dose of 30 mg/kg or matched placebo using a 2:1 split (20 patients on UDCA,	Excellent safety and tolerability of UDCA at a dose of 30 mg/kg were validated by the UP trial. The UDCA treatment group experienced mild

International Journal of Pharmaceutical Research and Applications
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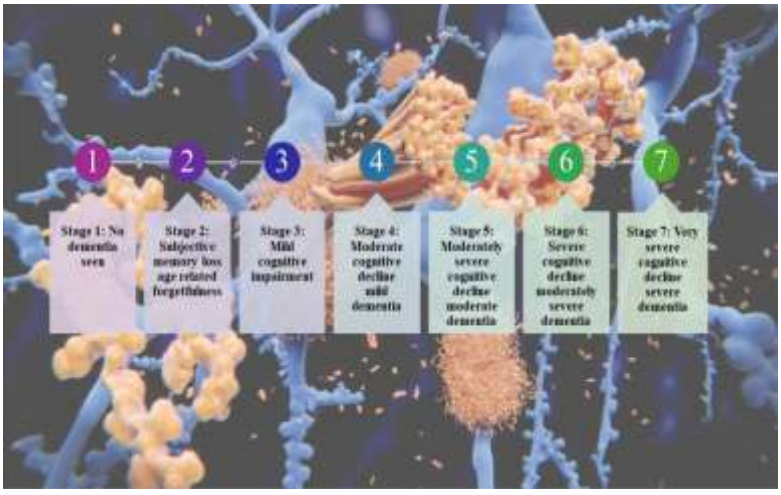
				10 on placebo). This will include 48-week exposure period & a subsequent 8-week washout period. Every patient will receive a thorough evaluation at Screening, Baseline, 12, 24, 36, 48, and 56 weeks. The trial medication will be taken orally three times a day in equal amounts with meals. The dose will be increased gradually by 250 mg (1 capsule) every 3 days until patient reaches a dose of 30 mg/kg.	diarrhea and nausea more frequently than any other treatment-related adverse event. Only one patient experienced serious adverse effects while on a placebo.
5	Deferiprone	NCT02655315	Phase 2	Half of participants will receive the deferiprone to 15 mg / kg twice daily morning and evening (30mg / kg per day), while the other half will receive a placeboThe treatment lasts nine months.	This study assesses the efficacy of ironchelation as a treatment approach to impede Parkinson's disease progression.

Table No 1: Clinical trials for drug repurposed in parkinson's disease.

DRUG REPURPOSING IN ALZHEIMER'S DISEASE:



International Journal of Pharmaceutical Research and Applications
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Anticancer agents:

The study concentrated especially on the inverse link between Alzheimer's and cancer. The idea that dementia and malignant neoplastic disease share signaling pathways—such as oxidative stress, mitochondrial dysfunction, misfolded protein production, and impaired cell metabolism—explains the association (42). Studies have also demonstrated that, in comparison to the control group, older individuals who have survived breast cancer and had chemotherapy have a decreased risk of developing AD (43). Research on cancer patients has indicated that their risk of Alzheimer's disease is minimal, and vice versa (44). Research has previously shown a link between Alzheimer's disease and cancer, and as a result, several anti-cancer medications are being repurposed to treat AD. A select few of them, including bexarotene, carmustine, imatinib, paclitaxel, etc., have recently attracted scientific interest.

- **Bexarotene:**

Antineoplastic bexarotene is essentially authorized for the management of cutaneous cancer. The US FDA approved it in late 1999 for the treatment of neoplastic disorders; however, more recent preclinical and clinical research suggests that it may also be used to treat Alzheimer's disease. It enhances brain function by lowering the amount of amyloid β produced in the brain. A small number of preclinical and clinical trials provided encouraging evidence for the use of anticancer drugs in the treatment of AD (45,46). Cramer et al. 2012 (47). Apply bexarotene in the Repositioning method to treat AD. According to the study, bexarotene given orally to an animal model of AD boosted the amount of amyloid β cleared in less than 72 hours—by more than 50%. Once more in 2013 Bachmeier et al (48). Established that, in an apoE-dependent manner, Retinoid X receptor (RXR) stimulation causes metabolic clearance of Amyloid β and rapidly recovers behavioral impairments. One clinical study even backs up the repositioning of bexarotene for the treatment of Alzheimer's disease.

Anti-Hypertensive drugs:

The incidence of AD is correlated with hypertension, and numerous research have examined the possible therapeutic effects of numerous antihypertensive drug types in AD. Through ischemia brought on by atherosclerosis and cerebral amyloid angiopathy, hypertension can damage the hippocampal tissue.

- **Nilvadipine:**

One calcium channel blocker used to treat hypertension is nilvadipine. However, it is being utilized for Alzheimer's Reuse (49). Researchers found in 2013 that spinal fluid from older adults with high blood pressure or hypertension showed greater signs of Alzheimer's disease. High blood pressure can damage blood arteries in the brain, impairing two of the brain's most vital functions: thinking and memory (50). When used in Alzheimer's patients, nilvadipine is quite safe and well tolerated. It has been demonstrated in clinical research that this medication stabilizes cognitive decline and reduces the incidence of AD. In vitro research indicates that nilvadipine reduces the buildup of amyloid β; nevertheless, the effects are observed at significantly larger levels than those shown on L-type calcium channels (51,52). Nivaldipine is a potential treatment for AD since it has been shown to potentially improve the removal of amyloid β from the brain. Phase 3 clinical trial already demonstrating a positive outcome for the treatment of AD.

- **Carvedilol:**

Carvedilol is a non-selective vasodilator and antagonist of α/β-adrenergic receptors. The medication used to treat high blood pressure. It considerably lowers the amount of brain oligomeric Amyloid β material. Neuronal transmission was significantly enhanced by carvingilol therapy, and this enhancement was associated with the preservation of certain learnings in Alzheimer's patients' brains (53,54). According to a recent study, the medication helps AD patients' memory. Carvedilol possesses a specific conformation of the 3D pharmacophore, which is linked to its capacity to bind Amyloid β and prevent it from aggregating into oligomeric fibrils. In mice models of AD, carvedilol improves synaptic transmission and amyloid β related and cognitive outcomes (55,56). A hopeful argument in favour of using the medication for AD is the ongoing phase IV clinical trial. Clinical trials of repurposing drugs given in the following table. (Table No 2)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1382-1393 www.ijprajournal.com ISSN: 2456-4494

Sr no	Drug	Clinical trial gov ID	Phase	Dose	Description
1	Bexarotene	NCT01782742	Phase 2	300 mg of bexarotene administered for one month compared to placebo.	The purpose of this research is to ascertain the safety and impact on aberrant proteins identified in the brain.
2	Nilvadipine	NCT02017340	Phase 3	8 mg of nilvadipine taken once a day for 78 weeks	Clinical trials using nilvadipine have demonstrated stability of cognitive decline and decreased incidence of AD, demonstrating to both symptomatic and disease-modifying advantages. For AD patients, nilvadipine is safe and well tolerated.
3	Carvedilol	NCT03775096	Phase 2	Dose for oral formulations is 3.125 mg, 6.25 mg, 12.5 mg, 25 mg	Carvedilol is associated with greater reduction of sympathetic activity, as measured by 123I-MIBG myocardial uptake, than metoprolol and other selective beta-blockers.

Table No 2: Clinical trials of drug repurposed in Alzheimer's disease.

DRUG REPURPOSING ON BIPOLAR DISORDER:

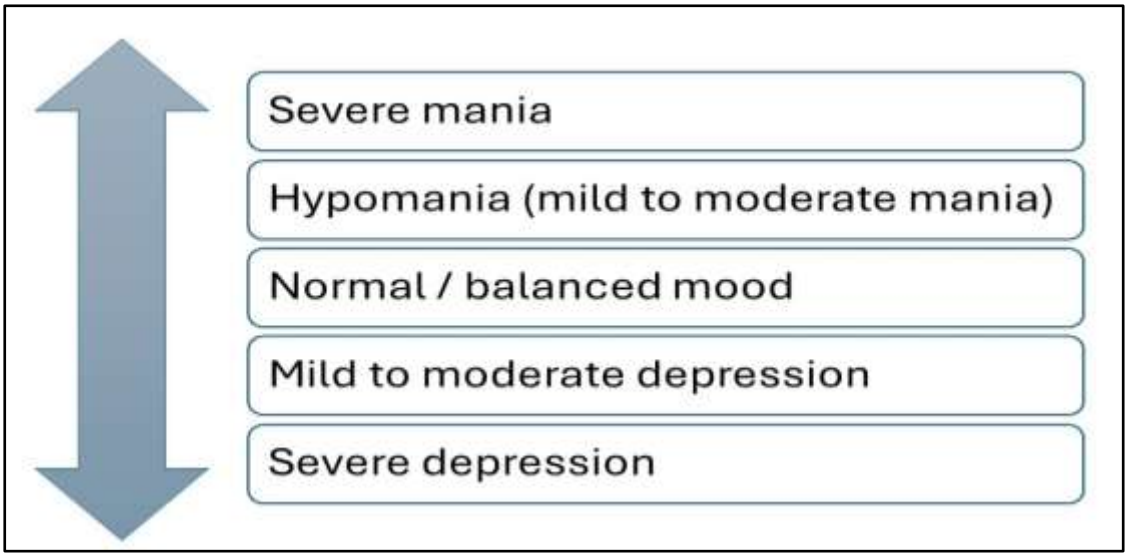

Fig 3: Signs and Symptoms of bipolar disorder

- **Aspirin:**

Aspirin acetylates COX-2 and selectively inhibits COX-1 over COX-2, preventing arachidonic acid from being converted to prostaglandins and thromboxane A2. Preclinical data suggests that inhibiting COX-1 is neuroprotective but inhibiting COX-2 promotes the influx of leukocytes into the brain, worsening tissue damage (57). According to a preliminary randomized study, aspirin may influence bipolar depression (58).

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Volume 9, Issue 3 May-June 2024, pp: 1382-1393 www.ijprajournal.com ISSN: 2456-4494

- **Minocycline:**

Minocycline, a second-generation tetracycline derivative produced synthetically, exhibits properties that include anti-inflammatory, anti-apoptotic, and antioxidant effects. (59) Minocycline influences the transmission of glutamate and monoamine neurotransmitters. (60) Minocycline plays a role in safeguarding the brain by suppressing activated microglia. (61) A meta-analysis of randomized controlled trials (RCTs) was undertaken to comprehensively assess the efficacy and safety of adjunctive minocycline in the treatment of schizophrenia, bipolar disorder, and major depressive disorder (MDD), aiming to better understand its clinical effects on these conditions.

- **Allopurinol:**

Kraepelin, who initially described the connection between manic symptoms, uric acid excretion, hyperuricemia, and gout, suggested the potential involvement of purines and uric acid in mania quite some time ago. (62,63) Observers noted that there was a temporary increase in uric acid excretion during remission from manic episodes. (64) Genetic data indicate a potential involvement of purinergic dysfunction in the underlying mechanisms of bipolar disorder and recurrent major depression. (65,66) In recent times, the growing body of evidence supporting the efficacy of allopurinol has sparked increased interest in investigating the role of the purinergic system in bipolar mood disorder. Clinical trials of repurposing drugs given in the following table. (Table No 3)

Sr no	Drug	Clinical trial gov id	Phase	Dose	Description
1	Aspirin	NCT05035316	Phase 2	acetylsalicylic acid,150 mg, 1 tablet/day	This randomized, double-blinded, placebo-controlled trial aims to explore whether adding low-dose aspirin to standard drug treatment enhances mood stabilization in patients with BD. The study will investigate whether this augmentation primarily affects antimanic, antidepressant, or relapse prophylactic outcomes.
2	Minocycline	NCT01514422	Phase 4	100 to 300mg per day for 8 weeks	This study aims to assess whether administering minocycline to individuals with bipolar depression over an 8-week period will lead to improvements in their depressive symptoms. Additionally, participants will have the option to undergo proton magnetic resonance spectroscopy (1H-MRS) to measure N-Acetylaspartate (NAA) levels in the brain, which are believed to be reduced in bipolar disorder.
3	Allopurinol	NCT00732251	Phase 4	300-600 mg/day over a 24-month	A recent study demonstrated the

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1382-1393 www.ijprajournal.com ISSN: 2456-4494

				period	effectiveness of allopurinol in treating bipolar mania. hypothesis posits that incorporating allopurinol alongside standard medications for bipolar disorder will lead to a reduction in the recurrence of manic episodes compared to standard medication alone.

Table No 3: Clinical trials of drug repurposed in bipolar disorder.

II. CONCLUSION:

To optimize research efficiency, significant investments of time, energy, and expertise are essential for integrating technical solutions. Additionally, increased financial backing for clinical trials on drug repurposing, along with technical assistance, is strongly recommended. Adequate financial support for preclinical research on drug repurposing is crucial for gathering the necessary data for subsequent clinical trials. Consequently, drugs that have the potential to treat rare diseases are more likely to be applicable in the therapeutic treatment of clinical neurological diseases.

Drug repurposing represents an innovative strategy aimed at accelerating the drug development process for neurological diseases. These repurposed medications offer a promising pathway for enhancing various pathological conditions, particularly neurological disorders. Moving forward, it's imperative to delve into the molecular mechanisms underlying drug repurposing. This is crucial because the targets of repurposed drugs for neurological diseases may differ from their original targets in treating other ailments. By doing so, we can enhance the effectiveness and safety of these drugs.

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