DRUGS REPURPOSING: THE HOPE FOR NEW THERAPEUTIC APPLICATIONS

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Abstract:

Background: Pharmacists are essential to designing, synthesizing, and formulating appropriate drug dosage forms to address healthcare needs for specific diseases or health conditions. Drugs are initially developed to treat their intended diseases, known as their initial or primary use. When these drugs are later used to treat different diseases, this process is called drug repurposing. Repurposed drugs can include marketed medications that failed in their initial purpose or those that failed to show sufficient efficacy in later clinical trial stages.

Aim: This review article aims to highlight the concept of drug repurposing and emphasize its important applications in modern drug development.

Methods: This review evaluates research on drug repurposing, concentrating on medications that failed for their intended uses or failed to provide the required results in advanced clinical studies.

Results: Improved drug availability and shorter development and approval times are just two benefits of drug repurposing. It also provides an opportunity to meet unmet medical needs, notably during public health emergencies. Examining medications like erythromycin and hydroxychloroquine for COVID-19 shows the usefulness of this strategy.

Conclusion: Scientists are very interested in drug repurposing because it can provide safe, efficient, and affordable treatment solutions more quickly. This tactic is still a viable and useful approach in modern pharmaceutical research, despite difficulties in expanding the availability of repurposed medications.

Keywords: Clinical trials, In-vitro, In-vivo, Drug Repurposing, Orphan drugs

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Introduction:

In the past few decades of the present century, there has been a remarkable uprising in the field of pharmaceutical research & development to bring out novel medicinal compounds into the market. It has been a great challenge for the researcher to follow a strict empirical as well as rational approach to design a drug and to maintain high standards of safety and therapeutic efficacy, together with tremendous increased investment of capital in the research and development, and to finish all the phases of clinical trials. 'Drug design' or 'tailor-made compound' aims at developing a drug with a high degree of chemotherapeutic index and specific action.

Designing & developing a drug is the practice of presenting a fresh pharmaceutical drug to the drug market for the treatment of a particular disease. To identify the root causes of any disease & accordingly, the invention of a drug moiety is not the simplest process. It is a very complicated or complex process that typically proceeds for more than a decade. It consists of preclinical research on microbes and wildlife, and most importantly, to obtain regulatory status and approval.[2,3,4]

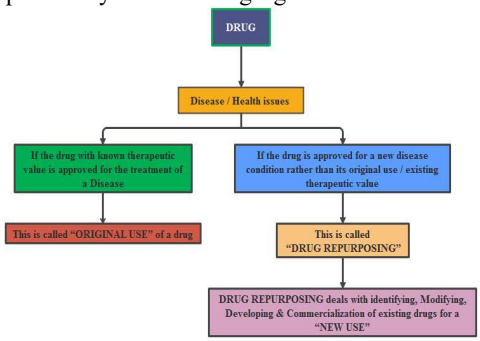
The world is in a growing stage. The idea, innovation, and research are at their peak. It is developing, based on the advancement of science & technology. The human efforts or activities are going to be easier & easier day by day. But in the meantime, there is an imbalance between nature with developing tools of science & technology. It causes several natural hazards to human society as well as other living animals. It may be responsible for the development of unknown diseases, which may cause the death of several people (i.e., COVID-19, Black fungus, White fungus, etc.) in a short fraction of time across the world. In this case,

we need to develop a solution for the prevention of the causes of diseases as much as possible.

Particularly in the situation where a disease arrived, and we need immediate medication, then in this case, drug repurposing is too important because the existing drug or any approved drug can be used for that case. Usually, drugs show their action when they interact with the target/receptor/ protein, resulting in a transduction pathway with a pharmacological response. A can drug bind with multiple proteins to give multiple responses & hence multiple pharmacological activities may result.

Drug repurposing:

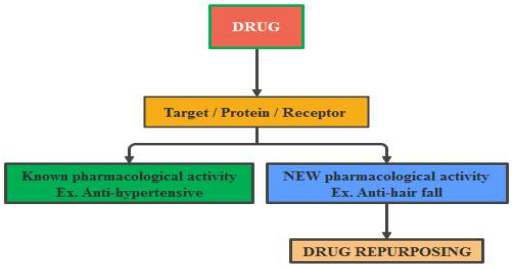
Drug repurposing is one of the modified or innovative methods for the utilization of the application of the approved or existing therapeutic drug to the healing of a new disease condition. Simply, it is the use of already approved drugs (for some disease) for the treatment of any other disease. It is also called drug repositioning. Drug repurposing is possible by modification of any existing drug & being approved once again by the regulatory authority for new uses other than the already existing therapeutic indication of that drug. Drug repurposing explores the hidden pharmacological activity of a drug. The conventional approach of drugs is based on the identification of the known target & accordingly response of the drug. But repurposing drug targets the known, unknown protein/receptor, which may result in a new therapeutic indication. It can be explained by the following figure 1.



(Fig. 1: Drug repurposing)

Strategies of drug repurposing:

Strategies of drug repurposing can be classified into two types. It depends upon the interaction of the drugs with the target/ protein, whether it involves a single protein or multiple protein molecules to elicit one or more pharmacological activities. It can be divided as follows.

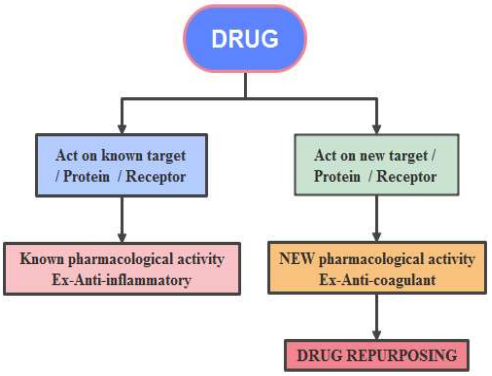


a) **On target:**

(Fig. 2: On-target strategies)

Here, the known mechanism of action of the drug is used. The target or receptor is the same, but it may result in known pharmacological activities with another new pharmacological activity.[5,6]

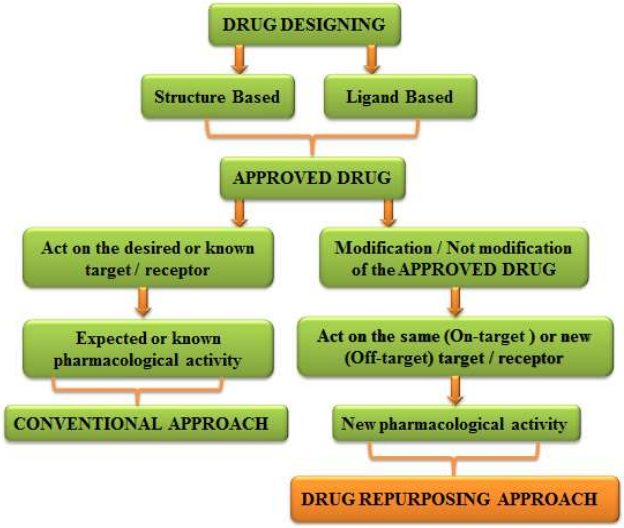
b) **Off target:** Here, new pharmacological activity results from the unknown mechanism of the drug when it interacts with the new target/receptor.[5,6]



(Fig. 3: Off-target strategies)

Drug Repurposing approach:

The conventional approach for drug designing, synthesis & its approval from regulatory bodies is too complex & time-consuming. Whereas repurposing drug approaches start from conventional drugs, which act as their precursor. A schematic presentation of approaches to drug repurposing is as follows.



(Fig. 4: Drug repurpose approach)

Comparison of advantages between Drug Repurposing approaches with Conventional drug discovery approaches:[7,8,9,10]

The advantages of repurposing drugs are quite encouraging compared to traditional drugs or conventional drugs. But without traditional drugs or conventional drugs, there are no repurposing

drugs. Some of the important differentiations of advantages between the above types of drugs are tabulated as follows.

Table-1:

S.N	Conventional drug discovery approaches	Drug Repurposing approach
1	Research and development (R&D) costs are high. i.e., Cost to develop a new drug is $ 12 billion.	Considerably cut research and development (R&D) costs. i.e., Cost to develop a new drug is $ 1.6 billion.
3	The development timeline may be longer and require all Phases of clinical trials.	It decreases the drug development time because existing medicines have already demonstrated safety in the human model, it skips phase-1 clinical trials.
4	In the conventional approach, 10-16 years is estimated for the development of a new drug into the market.	Whereas in drug repurposing, it is estimated to be 03-12 years
5	If there is evidence of adverse effects, then utility may decrease.	Capacity for recycling, even with evidence of undesirable effects and failed effectiveness in some indications for specific diseases.
6	In the clinical development process, there is a risk of failure.	In the clinical development process, there is a reduced risk of failure.
7	It focuses on the drug that is basically used to treat chronic & complex diseases.	It focuses on quickly developing & re-developing the disease (infectious), neglected diseases & difficulty to treat diseases
8	Maybe clinical safety & a lower success rate.	Increase clinical safety & high success rate.
9	It explores the predicted mechanism of action of synthetic drugs.	This approach can explore the unknown mechanisms of action of known or existing drugs due to the availability of database resources.

Drawbacks of drug repurposing:

Drug repurposing also has many challenges to overcome in the market. The drug, which already exists in the market for any specific uses, is making it quite difficult to prescribe the same for another use. Some of the important challenges are as follows.

a) Duration of three years (03) is provided by the Food and Drug Administration (FDA) for novel use of the formerly used drug for obtaining a new or fresh indication, and due to this short period, it is quite difficult to recover the capitalized currency and due to which it results financial loss for the medicine company[11].

b) When an approved drug (marketed drug) is brought back to the clinical trial for any other pharmacological activity, it is required to go through all regulatory requirements. i.e., obtaining another patent, filling New Drug Application (NDA), and validation of pharmacokinetic parameters. It makes it a time-consuming, costly, and complicated process, but less than conventionally approached drugs.[12]

c) Not all repurposed drugs are successful.[13]

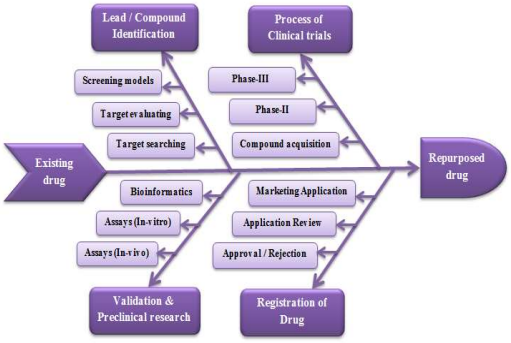
Steps involved in the repurposing of drugs[14]:

It can be explained by the following fish bone diagram[14]

(Fig. 5: Fish bone diagram for the process of Drug repurposing)

Application of drug repurpose:

The research on drug repurposing is being explored. It is still to identify the lead moiety, as it is the more challenging task that may undergo modification or without modification for a new



therapeutic indication. Some of the important repurposing drug with new uses along with their initial use is tabulated below.

Drug Name	Initial use & New use of drug		Explanation/cause for new use	References
MECAMYLAMINE	**Initial use**	Hypertension	Alexandra S et al studied the effects of ultra-low doses of mecamylamine in fifteen (6 female)	E. Vieta[15] T. P. George et al[16], Singh et al[17], Alexandra S
	New use	ADHD Depression		

			non-smokers with ADHD. They performed a double-blind study of mecamylamine and a placebo. They monitored recognition memory, Behavioural inhibition, delay aversion, etc. Mecamylamine did not improve core ADHD cognitive symptoms but significantly improved recognition memory, which may have important clinical implications.	et al[18]
ROPINIROLE	**Initial use**	Hypertension	K.D Sethi et al investigated the effect of Ropinirole in early parkinsonism condition. They performed a six-month (06) extension of a double-blind, placebo-controlled	R. Tomasiuk et al[19] K. D. Sethi[20]
	New use	Parkinson's disease, idiopathic restless leg syndrome		
			evaluation. They found that Ropinirole was effective as well as well-tolerated for monotherapy in the early stages of Parkinson's disease.	
VALSARTAN	**Initial use**	Hypertension	Jun Wang et al studied valsartan in vitro. They found that valsartan ceased AD-type neuropathology of Tg2576 mice. Their preclinical studies suggested that valsartan has AD-modifying activity and has provided protection against progressive Aβ-related memory deficits that occur with Alzheimer's disease or in those at high risk of developing Alzheimer's disease.	A. Corbett et al[21] Jun Wang et al[22]
	New use	Alzheimer's disease		
	Initial	Hypertension	K Asok Kumar et al	Palit P et al[23] K

AMLODIPINE	**use**		investigated	Asok et al[24]
	New use	Anti-bacterial, Antileishmanial & Antitrypanosomial	Amlodipine for antimicrobial activity against 15-gram +ve and gram–negative bacteria. They concluded the sensitivity toward amlodipine is as as follows. Staphylococcus aureus, Vibrio cholerae, Vibrio parahaemolyticus, Shigella spp., Salmonella spp., Bacillus spp., while microorganisms like E coli, Klebsiella spp., and P aeruginosa were found to be resistant to the lower concentrations of the drug. They finally concluded that the drug amlodipine possesses bactericidal action, they confirmed it through in-vivo taking to Swiss strain of white mice.	
SILDENAFIL	**Initial use**	Hypertension	They studied a dose-response study in 532 men for a period of 24 weeks. They were treated with oral sildenafil at different concentrations. They found that an increased dose of Sildenafil causes enhanced erectile function. Final 28 days of dose-escalation study in men, those who are taking sildenafil were found that about 69 % of all sexual intercourse were effective whereas men taking placebo (P<0.001) have 22 % attempt at intercourse were effective.	Goldstein I et al[25]
	New use	Erectile dysfunction		
ISRADIPINE	**Initial use**	Hypertension	They studied 336 participants comparing Isradipine to Placebo for the treatment	Hema Sree et al[26] [27]
	New use	Parkinson Disease (Phase-3		

		Clinical trial)	of Parkinson's disease. In the first, they used isradipine controlled release (CR) for early Parkinson's disease and normal blood pressure patients & they concluded that Isradipine was well tolerated and safe. The controlled-release formulation of isradipine was not available for use, and therefore, they studied the immediate-release formulation. They consider various parameters in their study i.e. neuropsychiatric testing, cognitive testing, collection of blood and urine samples and testing, clinical assessment of motor, etc.	
	In	Hyperte	They	Bidab

PROPRANOLOL	**initial use**	nsion	compare the anti-migraine activity of propranolol and sodium valproate, taking two groups of volunteers (Total-63) with migraine without aura. They divided them into two groups, Where Group-A (32) was treated with propranolol and Group B (31) was treated with sodium valproate. The reduction of frequency of headache per month was 13.86 +/- 2.11 to 4.23 +/- 3.24 in group A whereas from 13.23 +/- 2.43 to 5.83 +/- 4.04 in group B. They found a decrease of baseline headache occurrence per month was healthier in group A (p = 0.044)	adi E et al[28]
	New use	Migraine prophylaxis		

			where propranolol was used.	
CHLOROQUINE	**Initial use**	Malaria	Tomonori Kimura et al explored chloroquine, which is an autophagy inhibitor, by confirming its antitumor activity. They are doubtful that chloroquine in combination with anticancer drugs may aggravate kidney damage. They investigated the functions of autophagy in cancer and kidney injury. Their research was particularly concentrated on the use of chloroquine for the treatment of cancer,	Kimura T et al[29]
	New use	Suppress growth of tumour cells		
	New use	Inhibits SARS-CoV-2 infection tested against a clinical isolate of 2019-nCoV	They searched the clinicaltrials.gov database in March 2020. They identified 24 clinical trials, involving	Rosa SGV et al[30], Vanden Eynde et al[31], Sanders JM et al[32]
			in vitro (Clinical trial)	more than 20 medicines, where Chloroquine was repositioned against COVID-19.	
HYDROXY-CHLOROQUINE	**Initial use**	Malaria	Gautret et al. investigated the outcome of hydroxychloroquine on viral loads. Its treatment caused a viral load decrease/fading in COVID-19 patients, and its effect is reinforced by azithromycin. It was found that hydroxychloroquine was efficient on SARS-CoV-2 and was reported to be effective in patients with Chinese COVID-19.	Rosa SGV et al[30], Vanden Eynde et al[31], Sanders JM et al[32] Gautret P et al[33]
	New use	Shown to reduce viral load in COVID 19 patients (Phase-3, Clinical trial)		
AMPHOTERICIN-B	**Initial use**	Anti-fungal	McLaren et al reported in their review regarding psychotropic treatment that the drugs recommen	K. D. McLaren et al[34]
	New use	Bipolar disorder		

			ded for bipolar disorder patients with medical comorbidity. They reported several drugs like olanzapine, valproate, and lamotrigine, with some adjunct drugs with restricted efficacy data.	
CICLOPIROX	**Initial use**	Anti-fungal	Kimberly M et al investigated ciclopirox potency against A *baumannii*, *E coli*, and *K pneumoniae.* They found that ciclopirox, at a concentration of 5 to 15 µg/ml, reduces the growth of bacteria.	Rangel-Vega A et al[35], Carlson-Banning et al[36]
	New use	Bacteriostatic and bactericidal activity		
AMANTADINE	**Initial use**	Anti-viral	It was used in the case of Influenza-A, but it also has a slight anti-Parkinsonian action. Clinical trials have shown that it has the capacity to decline indications of rigidity, bradykinesia, and tremor, which basically occurs in parkinsonism disease. It showed a synergistic effect with another anti-Parkinsonian drug levodopa.	Lee HM et al[37], Chang C et al[38]
	New use	Parkinson's Disease		
REMDESIVIR	**Initial use**	Anti-viral	Wang M et al studied in-vitro-nCoV & they reported that remdesivir is quite effective for its control. They recommend that it should be used in humans infected with coronavirus as it has a safety profile, records & it is effectively used for various other illnesses.	Rosa SGV et al[30], Wang M et al[39], Dong L et al[40], Deng L et al[41]
	New use	Shown to reduce viral load in vitro and improved clinical symptoms in some COVID-19-infected hospitalized Patients (Phase-3)		
LOPINAVIR & RITONAVIR	**Initial use**	Anti-viral	Jaegyun Lim et al investigated by administering lopinavir/ritonavir, where they found viral loads of β-coronaviru	Rosa SGV et al[30], Deng L et al[41], Lim J et al[42], Cao B et al[43]
	New use	Reduce viral loads and improved clinical		

		symptoms COVID-19 patients. Another controlled A clinical trial showed no effect of lopinavir-ritonavir on COVID 19 (Phase-4)	s significantly reduced and reported no or slight titers of coronavirus. Bin Cao et al reported that hospitalized patients severely infected with COVID-19 had no benefit from lopinavir-ritonavir treatment, compared to standard care.	
ZIDOVUDINE	**Initial use**	Anti-viral	Namba, T et al reported the anti-cancer activity of zidovudine. Upon treatment, along with gemcitabine found to inhibit the growth of gemcitabine-resistant pancreatic cancer cells in nude mice. Even the target of cancer is unknown.	Clouser CL et al[44], Namba, T et al [45]
	New use	Cancer		
AMANTADINE	**Initial use**	Influenza	Riederer P et al reported that Amantadine was found to influence rigor and akinesia. It also has a slight effect on rest tremors as well. They reported an improvement of parkinsonian patients during therapy with amantadine. Verhagen Metman et al reported a recent study or investigation on the treatment of Parkinson's disease, by treatment with amantadine, they confirmed that it can reduce dyskinesias without varying the L-DOPA antiparkinsonian effects.	R. S. Schwab et al[46], Riederer P et al[47], Verhagen Metman[48]
	New use	Parkinson's disease, ADHD		
AURANOFIN	**Initial use**	Anti-rheumatic	Thangamani S et al investigated the antibacterial activity of auranofin. They reported it involves the suppression of bacterial DNA, protein & cell wall synthesis. They	Thangamani S et al[49]
	New use	Anti-bacterial agents		

			confirmed auranofin has a negligible effect against Gram-negative bacteria. The suppression of protein synthesis of bacteria, it results in cessation of the generation of methicillin-resistant Staphylococcus aureus toxins.	
CYCLOSPORINE	**Initial use**	Anti-rheumatic	Dena Westphalen et al reported that cyclosporine is used to treat Rheumatoid Arthritis and psoriasis. It can also be recommended to prevent rejection after solid organ transplants.	Ann MT et al[50], Dena et al [51]
	New use	Transplant rejection		
HYDROXY-CHLOROQUINE	**Initial use**	Anti-rheumatic	Dawit Zewdu et al reported for diabetic patients where Hydroxychloroquine provides improvements in	Antre RV et al[52], Dawit Zewdu et al[53]
	New use	Anti-diabetic		
			results in glycaemic control. They suggested further preclinical and clinical studies to validate the usefulness of Hydroxychloroquine for the treatment of Diabetes Mellitus (DM)	
COLCHICINE	**Initial use**	Gout	Massimo Imazio et al evaluated colchicine for recurrent pericarditis. They also reported its safety & efficacy for the secondary avoidance of recurrent pericarditis. They performed it by double-blind, randomized, placebo-controlled multi-center trials.	Massimo Imazio et al[54]
	New use	Recurrent pericarditis		
ASPIRIN	**Initial use**	Inflammation, Pain	John W et al reported that the most extensively studied antiplatelet drug is Aspirin. Based on a	John W et al[55]
	New use	Anti-platelet		

			randomized trial (> 100) in high-risk patients, aspirin decreases □15% vascular death and □30%. nonfatal vascular events.	
DIFLUNISAL	**Initial use**	Inflammation, Pain	Khodaverdian V et al explored the anti-virulence agent (Biaryl compound) Diflunisal, which is one of the FDA-approved NSAIDs. They reported a new use that it may be useful for prophylaxis & adjuvants for methicillin-resistant Staphylococcus aureus (MRSA) in antibiotic therapy.	Khodaverdian V et al[56]
	New use	Anti-bacterial agents		
EBSELEN	**Initial use**	Inflammation, Pain	Shankar Thangamani et al reported that Ebselen showed bactericidal activity. They demonstrated that it showed action by protein synthesis inhibition. They evaluated its therapeutic activity by taking a mouse model with bacterial infection (staphylococcal). Their investigation reported that it has great effectiveness for topical treatment of skin infections, such as MRSA.	Thangamani S et al[57]
	New use	Anti-microbial activity		
IBUPROFEN	**Initial use**	Inflammation, Pain	Ogundeji AO et al investigated that ibuprofen also has anti-microbial activity. They reported in vitro anti-Cryptococcus efficacy of ibuprofen. They also found that it acted synergistically with other anti-fungal drugs, i.e., Amphotericin-B. & fluconazole. They also concluded that the membrane is the	Ogundeji AO et al[58]
	New use	Anti-microbial activity		

			target of the action of ibuprofen.	
ROPINIROLE	**Initial use**	Parkinson's disease	Clete A Kushida reported that ropinirole can be used for the treatment of symptoms of restless leg syndrome and the major significance related to restless leg syndrome. Its symptom decreases, or improvement occurs after 2 nights of ropinirole treatment for restless leg syndrome patients.	Dusek P et al[59], A Kushida et al[60]
	New use	Restless leg syndrome		
BROMOCRIPTINE	**Initial use**	Parkinson's disease	It reported that it can be used as an adjunct to nutrition for the improvement of glycaemic balance in the body with type 2 diabetes mellitus (DM)	[61]
	New use	Diabetes mellitus		
ATOMOXETINE	**Initial use**	Parkinson's disease	Garnock-Jones et al reported that atomoxetine is effective & tolerated, and it is used successfully for attention-deficit hyperactivity disorder (ADHD). They also informed that it was more effective than placebo & current standard therapy. They suggested that atomoxetine is convenient for the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents.	M. R. Mohammadi et al[62], Garnock-Jones et al [63]
	New use	ADHD		
METHOTREXATE	**Initial use**	Cancer	It reported that methotrexate can be used not only in life-threatening neoplastic diseases but also in psoriasis or rheumatoid arthritis patients, which is not effectively responsive to other forms of treatment. It also	[64]
	New use	Psoriasis, Rheumatoid arthritis		

			warned of deaths that may occur by methotrexate treatment for malignancy, rheumatoid arthritis & psoriasis.	
MILTEFOSINE	**Initial use**	Cancer	Ashburn TT et al reported that Miltefosine is more effective for the treatment of leishmaniasis & also has a more significant cure rate in various countries (i.e., India, Bangladesh, Nepal) in visceral leishmaniasis. They also reported that Miltefosine has more clinical failures in recent periods.	Ashburn TT et al[65]
	New use	Visceral leishmaniasis		
5-FLUOROURACIL	**Initial use**	Cancer	Walz JM et al reported that 5-fluorouracil (5-FU) prevents the growth of micro-organisms. They investigated that the outside coating of 5-fluorouracil in central venous catheters diminishes the risk of infection in the catheter. They found no bloodstream infection due to 5-fluorouracil-coated central venous catheters	Walz JM et al[66]
	New use	Anti-bacterial agents		
TAMOXIFEN	**Initial use**	Breast cancer / tumor	A. Yildiz et al reported that tamoxifen can cure mania episodes. They identified the effectiveness of randomized controlled trials in the cure rate of bipolar disorder using tamoxifen. Their result showed that the use of tamoxifen over placebo favoured based on the change in scale of the score for mania.	A. Yildiz et al[67]
	New use	Bipolar disorder Mania		
PHENOTHIAZINE /	**Initial use**	Schizophrenia	Kristiansen JE et al investigated phenothiaz	Kristiansen JE et al[68]

CHLORPROMAZINE	**New use**	Anti-bacterial agents	ines in-vitro using 61 bacterial strains (Gram-positive and Gram -ve). They reported it showed antibacterial effect & also concluded that phenothiazines are more effective in gram-positive bacteria. Antibacterial potency of the chlorpromazine was measured as IC50: chlorpromazine (29 micrograms/ml) 92 microM.	
TRIFLUOPERAZINE	**Initial use**	Schizophrenia	Mazumder R et al investigated Trifluoperazine against the various strains of the bacterium (293) and found effective antimicrobial properties of Trifluoperazine. They used the agar dilution method for MIC (Minimum inhibitory concentrations). During an in vivo study in Swiss albino mice, effective protection.	Mazumder R et al[69]
	New use	Anti-bacterial agents		
RETINOIC ACID	**Initial use**	Acne	Avvisati G et al reported that all-trans retinoic acid has the capacity to cause a total decrease of acute promyelocytic leukaemia (alone or with combined all-trans-retinoic acid). But the complication is that it may have retinoic acid syndrome, and it can be treated by dexamethasone administration early.	Avvisati G et al[70]
	New use	Acute promyelocytic leukemia		
GABAPENTIN	**Initial use**	Epilepsy	It is reported that Gabapentin may be indicated for the treatment or control of postherpetic neuralgia, basically	[71]
	New use	Neuropathic pain		

			in the case of adults. It can also be used in case of partial-onset seizures in patients (adults, paediatric)	
MIFEPRISTONE	**Initial use**	Pregnancy termination	Peter Gallagher et al reported that Mifepristone was used broadly for Pregnancy termination, which was the initial target of research for scientists. But it was also found that it possesses ant glucocorticoid activity (Hazra and Pore 2001), & this property is the utmost attention for their application for severe mood disorders and psychosis treatment.	J. K. Belanoff et al[72], Peter Gallagher et al[73]
	New use	Psychotic major depression, Cushing's syndrome		
GALANTAMINE	**Initial use**	Polio, paralysis	Razay G et al studied Galantamine for Alzheimer's disease. They performed a placebo-controlled, double-blind investigation that showed treatment of Alzheimer's disease by galantamine produces enhancements on intellectual tests. According to them, a dose of 16-24 mg/day is most effective.	A. Corbett et al[74] Razay G et al[75]
	New use	Alzheimer's disease		
ARBACLOFEN	**Initial use**	Cerebral palsy	Veenstra-Vander Weele et al reported that GABA-B agonists in animal models of fragile X syndrome and of autism spectrum disorder enhanced brain and social behaviour. They conducted a placebo-controlled, phase-two, randomized, crossover trial and found that there were enhanced social avoidance symptoms with the drug.	C. A. Erickson et al[76], Veenstra-Vander Weele et al[77]
	New use	Fragile X syndrome		
OXYFEDRINE HYDROC	**Initial**	Angina pectoris	Kaushiki Mazumdar et al	Kaushiki mazu

HLORIDE	**use**		investigated oxyfedrine HCl for anti-microbial activity (Against Gm +ve & Gm -ve). They found that it possesses significant activity from the MIC by agar dilution technique. They also confirmed it by in vivo (Swiss strain of white mice). They got highly significant in vivo results from the chi-square test.	mdar et al[78]
	New use	Anti-bacterial agents		
DICYCLOMINE	**Initial use**	Spasm inhibitory agent	Karak P et al studied dicyclomine for antibacterial activity both in vivo and in vitro. They used the broth & agar technique and determined the minimum inhibitory concentration. It inhibited most of the bacteria at a concentration of 10µg/ml. Even at low concentration, it was effective for a few bacteria. It showed both bacteriostatic and bactericidal activity.	Karak P et al[79]
	New use	Bacteria-inhibitory agents		
METHDILAZINE	**Initial use**	Skin allergy	Chattopadhyay D et al investigated methdilazine for antimicrobial activity. They reported it has significant anti-bacterial activity (Screened against 367 strains, Gram +ve & Gram -ve). They also concluded that Methdilazine, when administered along with aminoglycosides & specific chemotherapeutic agents, results in a synergistic effect (Anti-bacterial).	Chattopadhyay D et al[80]
	New use	Anti-bacterial agents		
STATINS	**Initial**	Plasma cholesterol-	Tavakkoli A et al reported	Tavakkoli A et al[81]

	use	reducing agent	that statins have antifungal activity. They confirm against the various strains of fungus, i.e., Zygomycetes, Dermatophytes, Aspergillus spp., Candida spp., Saccharomyces cerevisiae, etc.	
	New use	Anti-fungal		
EDARAVONE	**Initial use**	Ischemia of the brain and the myocardium of the heart	Takumida M et al suggested that Edaravone can be useful for cochlear damage, which is usually caused by Exotoxin A and is produced by Pseudomonas aeruginosa (Gram–negative) bacterium. They reported that it can be overcome by the injection of Edaravone.	Takumida M et al[82]
	New use	Anti-bacterial agent		
THALIDOMIDE	**Initial use**	Morning sickness in pregnant women	Latif, T et al reported that thalidomide (an immunomodulatory drug) and its analogues have increased antitumor activity. They also gave the information that thalidomide has a positive effect on multiple myeloma. This immunomodulatory drug is an encouraging class of drugs against multiple myeloma.	Latif, T et al[83]
	New use	Multiple myelomas		
MIFEPRISTONE	**Initial use**	Abortion	Morgan FH et al reviewed that Mifepristone was permitted by the United States Food and Drug Administration (USFDA) for controlling hyperglycaemia in non-surgical patients diagnosed with Cushing's syndrome. It was accepted for oral administration (once daily). According to the 60%	Morgan FH et al[84]
	New use	Cushing's Syndrome		

			of patients had a positive influence on glycaemic control.	
EVEROLIMUS	**Initial use**	To prevent solid organ transplant rejection, To prevent neo-vascularisation of artificial cardiac stents, Regimen of anticancer treatment.	Sharon Samueli et al investigated Everolimus for the treatment of TSC-related epilepsies. They observed that at low concentration it was effective. They found some side effects, but well tolerated by most of the patients. Their research intended to assess the safety & efficacy of everolimus in kids and youths with TSC-related epilepsies.	Franz, D et al[85], Sharon Samueli et al[86]
	New use	Autosomal Dominant genetic disease-Tuberous Sclerosis Complex (TSC)		
CRIZOTINIB	**Initial use**	Anaplastic large-cell lymphoma (ALCL)	Gadgeel SM et al reported that from the available clinical data of tumour patients, they have activated anaplastic lymphoma kinase (ALK) and Crizotinib have found to be effective against these types of patients.	Gadgeel SM et al[87]
	New use	Non-small-cell lung cancer (NSCLC)		
DULOXETINE	**Initial use**	Major depressive disorder	Wolfgang H et al reported that treatment of duloxetine in stress urinary incontinence (SUI) is dependent on the inhibition of the presynaptic reuptake of 5-HT and NE in the spinal cord. It was studied in an acid-induced bladder irritation of a cat model. They found the dose-dependent effects of the drug. The clinical trial in women showed a decrease in incontinence episodes.	Wolfgang H et al[88], Ashburn, Tet al[89]
	New use	Stress Urinary Incontinence		

Conclusion:

Yet more lead compounds exist and need to be identified for modification and exploration to convert them into repurposing drugs. This field of therapeutics is slowly emerging. It tries to find out the hidden or alternative activity of drugs. There are so many drugs that are used initially for a particular disease, but simultaneously, they can

also be used for other new diseases. Repurposing drugs has no doubt advantages over conventional drugs, but these also have a few challenges or barriers. Discovery of more & more repurposing drugs is going to be fruitful & providing extra support & strength to the health care system.

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