JOURNAL OF POPULATION THERAPEUTICS AND CLINICAL PHARMACOLOGY

ANTIMICROBIAL DRUG REPURPOSING:

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Submitted: 13 April 2023; Accepted: 17 May 2023; Published: 29 June 2023

RESEARCH ARTICLE DOI: **10.47750/jptcp.2023.30.17.02**

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ABSTRACT:

Antimicrobial drug repurposing, occasionally referred to as drug repositioning or drug reprofiling, is a strategy used to find novel therapeutic uses for currently available antimicrobial medications. Repurposing currently available medications offers a viable strategy to deal with the rising antimicrobial resistance and the limited supply of innovative antimicrobial medicines that are causing this global health problem. Identifying medications with well-known safety profiles and modes of action that may be useful in treating various microbial targets or diseases . Repurposing avoids many of the early stages of drug development by making use of the substantial information and research already undertaken on existing medications, hastening the discovery of new treatment options. Additionally, by using medications with distinct mechanisms of action, repurposing may be able to overcome drug resistance. Understanding the drug's mechanism of action, conducting high-throughput screening, preclinical investigations, and clinical trials to assess efficacy and safety are often milestones in the process. There are successful cases of repurposing antimicrobial drugs, which shows the promise of this strategy to meet unmet needs in infectious diseases. Antimicrobial medication repurposing, which offers quicker and more affordable options to conventional drug development techniques, is an overall promising strategy to address antimicrobial resistance.

Keywords: Drug-resistance, drug repurposing, drug repositioning, antimicrobial activity, microbial infections, treatment.

INTRODUCTION:

The success of Pfizer in 1998 when Sildenafil (Viagra) was switched from treating angina to erectile dysfunction marked the beginning of the era of repurposed pharmaceuticals. (1). The concept of drug “repurposing” or repositioning “or “reprofiling “or “redirecting” or “rediscovery”, and “redeployment” has been applied in treatment of the patients harboring multidrug resistant pathogens. Several studies have shown that antimicrobial drugs repurposing has emerged as a promising strategy in the battle against infectious diseases. Repurposing existing medications offers a time- and money-efficient way to address these concerns in light of the emergence of microorganisms that are resistant to antimicrobial treatments (AMR) as well as the small number of new antibiotics being developed. 4.95 million people died from drug-resistant illnesses in the world in 2019, and 1.27 million of those fatalities were directly related to AMR (2). A total of 80 medicines (46 antibiotics and 34 unconventional antibacterial agents) were in clinical development as of November 2021, with three of them now in the pre-registration stage. They aim to

-- Targeting priority infections, 28 antibiotics and 21 non-traditional antibacterials

-- 13 conventional antibiotics and 1 unconventional antibiotic targeting M. tuberculosis.

-- 12 non-traditional antibacterials and 5 antibiotics targeting C. difficile (3)

By repurposing approved drugs originally developed for other indications, researchers can potentially bypass the lengthy and costly process of developing entirely new compounds. This approach not only expedites the availability of potential treatments but also leverages existing knowledge of drug safety and pharmacokinetics. Through careful screening and evaluation, these repurposed antimicrobial drugs hold the potential to provide effective solutions to combat a wide range of infectious diseases, improving patient outcomes and reducing the burden on global healthcare systems (4).

Repurposing drugs is not a novel idea. In fact, it makes up roughly thirty percent of all current FDA-approved medications (5). Pharmaceutical firms have access to drug repurposing as a tool to reduce costs, boost productivity, and reduce investment and safety concerns (6). It may be less expensive and take less time to get FDA approval to develop a repurposed medicine as opposed to a newly discovered chemical (7). By using this strategy, it is also possible to bring back a failed drug, frequently under a new indication, adding value to an investment that was wasted. Effective medication repurposing may have three outcomes: new targets and new indications for already-approved drugs, line extensions for previously rejected candidates, and new targets and new indications for currently-approved drugs (5,7).

Drugs that have been put on hold may have been stopped by the sponsor for strategic reasons or because they were ineffective or unsafe. Existing medications are those that have received FDA approval and are currently on the market. The best choices for repurposing are typically drugs for which safety and toxicity data have already been established (i.e., cleared Phase I trials), as doing so considerably reduces the risk of the clinical development stages. Additionally, sponsors can use pre-existing safety and/or efficacy data to speed up the regulatory approval of their medicine using the 505(b)(2) pathway, another expedited route. This method, which was established in 1984, is used when medications that have already received approval have undergone alterations (4). Using the 505(b)(2) method, ceftazidime-avibactam was authorized in 2015. It combines an authorized cephalosporin (ceftazidime) and a brand-new -lactamase inhibitor (avibactam). Additionally, ceftazidime-avibactam was recognized as a Qualified Infectious Disease Product (QIDP), earning it fast-track approval, priority review, and an extra five years of exclusivity (8).

When studies on animal models proved fruitless, zidovudine's development as an anticancer drug was put on hold. After a challenging clinical trial, zidovudine was rapidly approved by the FDA in 1987 (9). Years later, zidovudine was found to exhibit potent in vitro HIV activity. This signaled the start of the antiretroviral era and opened the door to the development of more life-saving antiretroviral medications. The story of thalidomide is likely the most illustrative illustration of resuming a discontinued medication. Thalidomide was first offered to pregnant women in 1957 as a cure for morning sickness, but it was later discovered to have terrible teratogenic effects that resulted in more than 10,000 birth abnormalities and was pulled off the market in 1961 (10). Thalidomide resurfaced in the late 1990s due to renewed interest in its use to treat erythema nodosum leprous, a condition for which it got FDA approval in 1998 (pregnant women were omitted from the research cohort). This prompted the sponsor

(Celgene) to actively pursue the creation of analogues devoid of the teratogenic side effects and research into alternative applications (11). In 2003, thalidomide was approved to treat multiple myeloma as well, and it quickly shot to the top of Celgene's bestseller list (12). The thalidomide story shows that repurposing opportunities can materialize even from the most unlikely sources. This is because the drug was previously thought to be terrible. This gives rise to the optimism that antimicrobials will also be capable of successful repurposing. This article's goal is to provide a comprehensive review on studies published on antimicrobial drug repurposing, benefits and drawbacks of repurposing drugs for antimicrobial use, as well as potential future applications.

METHODOLOGY FOR DATA COLLECTION:

The present review article was written by collecting relevant articles from the use of existing databases like Scopus, Web of Science, PubMed, Google Scholar, and Google Search work using the most appropriate keywords have been considered in the case of these studies. A list of keywords that have been employed here has been highlighted below: “Antimicrobial Drug-repurposing”, “Antimicrobial drug repositioning”” Antimicrobial drug resistance”, “antimicrobial activity”, “microbial infections”, and “treatment with repurposed drugs”

Inclusion criteria:

1. Peer-reviewed articles published in last 10 years (2013-2023)
2. Articles published in the English language

Exclusion criteria:

1. Articles before 2013
2. other languages

APPROACHES TO ANTIMICROBIAL REPURPOSING:

There are a number of different approaches to antimicrobial repurposing, including:

A. Screening: This involves testing a large number of drugs to see if they have any antimicrobial activity. This can be done using a variety of methods, including cell culture assays, animal models, and in vitro assays.

B. Target-based: This approach involves identifying drugs that target specific bacterial proteins or pathways. This can be done using a variety of methods, including gene knockout studies, protein-protein interaction studies, and chemical genomics.

C. Mechanism-based: This approach involves identifying drugs that work through a specific mechanism of action. This can be done using a variety of methods, including structural biology, molecular dynamics, and computational chemistry.

Once a drug has been identified as a potential repurposed antimicrobial, it is important to understand its mechanism of action. This will help to determine the best doses and regimens for use, as well as the potential for side effects.

Published articles on "Antimicrobial repurposing"

Table 1- List of Articles published on "Antimicrobial repurposing"

<table>
<tr><th>Paper title</th><th>Key findings</th></tr>
<tr><td>Repurposing inhibitors of phosphoinositide 3-kinase as adjuvant therapeutics for bacterial infections (13)</td><td>•Repurposing host-directed medications, such as phosphoinositide 3-kinase inhibitors, would prevent intracellular survival of bacteria
•The FDA has cleared PI3K inhibitors for treating cancer, but they could also be used as adjuvants to treat bacterial infections effectively.

<table><tr><th>Pathogens</th><th>Repurposed drugs</th></tr><tr><td>Intracellular pathogens like Chlamydia, Fransicella, Bacillus, Burkholderia, Salmonella, M. tuberculosis</td><td>Antibiotics + CAL 101/Idelasib/ Bay80-6946/Copanlisb/ IPI 145/Duvelisib/ BYL 719/Alpelesib</td></tr></table></td></tr>
<tr><td>Drug Repurposing Approaches towards Defeating Multidrug-Resistant Gram-Negative Pathogens: Novel Polymyxin/Non-Antibiotic Combinations (14)</td><td>Combining traditional antibiotics like beta lactams and polymyxins with non-antibiotics (called adjuvants) is an effective way to treat MDR Bacteria

<table><tr><th>Mechanism of action of antibiotics</th><th>Repurposed drugs</th></tr><tr><td>Antibiotic-inactivating enzyme inhibition</td><td>BL+BLI like Avibactam/Vaborbactam/Tazobactam/Clavulanic acid/Sulbactam/Relebactam</td></tr><tr><td>Membrane permeabilization</td><td>Vancomycin /Rifamycin/Erythromycin+Unacetylated tridecaptin</td></tr></table></td></tr>
</table>

	Tetracyclines+Tetracyclines analogues Aminoglycosides+Aminoglycosides analogues
	Fluoroquinolones+Polybasic peptide–levofloxacin conjugates Phenylalanine-arginine β-naphthylamide (PAβN)
	Clarithromycin Doxycycline Clindamycin+Spectinamides
	Ceftazidime+ Catechol
Increased antibiotic intracellular concentration	Tetracycline, Ampicillin, Penicillin, Chloramphenicol, Ceftazidime, Gentamicin, Ciprofloxacin + EDTA
Damage to biofilms	Ciprofloxacin Isothiazolone + Nitroxides

Pathogens	**Drugs repurposed**
K. pneumoniae, *A. baumannii*, *P. aeruginosa*	Polymixin + Tamoxifen/Raloxifene/Torimefene/Mitotane / Thiethylperazine/Chlorpromazine/ Sertraline

	K.pneumoniae	Polymixin+ Zidovudine/ Prochlorperazine/
	K. pneumoniae, P. aeruginosa	Polymixin+ Caspofungin/
	E. coli, P. aeruginosa	Polymixin + Miconazole
	K. pneumoniae, A. baumannii, P. aeruginosa, N. gonorrhoeae, N. meningitidis, M. catarrhalis	Polymixin + Cannabidiol
	A. baumannii, E. coli, P. aeruginosa, S. maltophilia	Polymixin + Curcumin
	P. aeruginosa	Polymixin+ Ivacaftor
	K. pneumoniae, A. baumanii, P. aeruginosa. coli, E. cloacae	Polymixin + Closantel/Rafoxanide/OOxyclozanide/

<table>
<tr><td></td><td>
<table>
<tr><td>K. pneumoniae, A. baumannii, P. aeruginosa, E. coli</td><td>Polymixin+Auranofin</td></tr>
<tr><td>K. pneumoniae, E. coli, E. cloacae</td><td>Polymixin + Zidovudine</td></tr>
<tr><td>Salmonella</td><td>Polymixin + Tetrandrine</td></tr>
<tr><td>E. coli</td><td>Polymixin + Melatonin</td></tr>
<tr><td>A. baumannii</td><td>Polymixin +Curcumin</td></tr>
</table>
</td></tr>
<tr><td>Anthelmintic drugs for repurposing against Gram-negative bacilli infections (15)</td><td>•Repurposing anthelmintic drugs for the treatment of Gram-negative bacilli infections is one potential method to hasten the drug development process and save money and time.
•Colistin resistance in Gram-negative bacteria is reversed by the anthelmintic medication niclosamide.</td></tr>
<tr><td>Drug repurposing for next-generation combination therapies against multidrug-resistant bacteria (16)</td><td>Drug repurposing of non-antibiotic drugs as potential antibiotic adjuvants offers a sustainable and effective strategy to confront multidrug-resistant bacteria.</td></tr>
</table>

	<table><tr><th>Pathogens</th><th>Repurposed drugs</th></tr><tr><td>MRSA</td><td>Antibiotics+Zaragozic acid/ MAC-545496/Hypericin/Ticlopidine/Clomiphene/Auranofin/ Ebselen</td></tr><tr><td>CRE</td><td>Antibiotics+Aspergillomarasmine A/Captopril/ Disulfiram/ Thiorphan/Tiopronin/Benzophenone/Cefaclor /Ebselen/ Pterostilbene/Mitoxantrone</td></tr><tr><td>MRCPC</td><td>Colistin+ Pterostilbene/Osthole/Pentamidine/Melatonin</td></tr><tr><td>TET(X)</td><td>Tigecycline+ Azidothymidine</td></tr></table>
Repurposing of escitalopram oxalate and clonazepam in combination with ciprofloxacin and sulfamethoxazole/trimethoprim for treatment of multidrug-resistant microorganisms and evaluation of the	• When combined with ciprofloxacin and sulfamethoxazole-trimethoprim as well as alone, escitalopram oxalate and clonazepam have demonstrated considerable antibacterial activity against infections that are resistant to multiple antibiotics. •Clonazepam was effective against both Gram-positive and Gram-negative bacteria, but escitalopram oxalate was predominantly effective against Gram-positive bacteria.

<table>
<tr><td>cleavage capacity of plasmid DNA. (17)</td><td>When administered in conjunction, they showed a notable synergistic effect.</td></tr>
<tr><td>Repositioning of non-antibiotic drugs as an alternative to microbial resistance: a systematic review. (18)</td><td>•Several types of non-antibiotic medications exhibit strong in vitro and in vivo antibacterial action against both Gram-positive and Gram-negative clinical isolates as well as fungi.
• The majority of these drugs demonstrated improved antibacterial action when combined with antibiotics.
• The presence of the aromatic rings in the structure supports the antibacterial activity.

<table>
<tr><th>Pathogens</th><th>Repurposed drugs</th></tr>
<tr><td>KPC,
CONS</td><td>Ciprofloxacin/ Sulfan trimethoprim+Amitriptylin</td></tr>
<tr><td>KPC</td><td>Colistin
+Amitriptyline</td></tr>
<tr><td>A. baumannii, S. epidermidis, E. faecalis , MRSA, VRE</td><td>Clomipramine</td></tr>
<tr><td>Candida spp</td><td>Doxepin
Imipramine
Nortriptyline</td></tr>
<tr><td>S. aureus NCIM 2079, P. aeruginosa NCIM 2036 , K. pneumonie NCIM 2719, E. cloacae NCIM 2164, P. mirabilis</td><td>Ciprofloxacin/Gentamicin</td></tr>
<tr><td>E. coli, K. pneumoniae ATCC 700603, P. aeruginosa ATCC 27853, S. aureus , E. faecalis, S. epidermidis ATCC12228,</td><td>Ciprofloxacin+Fluoxetine</td></tr>
</table>
</td></tr>
</table>

	M. luteus ATCC 7468 and *B. cereus* ATCC 14579, MDR clinical isolates		
	C. albicans ATCC 10231	Flucanoazole+Fluoxetine	
	S. aureus, A. baumannii, S. epidermidis, E. faecalis , MRSA, VRE	Fluvoxamine	
	E. coli, K. pneumoniae ATCC 700603, *P. aeruginosa* ATCC 27853, *S. aureus* , *E. faecalis, S. epidermidis* ATCC12228, *M. luteus* ATCC 7468 and *B. cereus* ATCC 14579, MDR clinical isolates	Paroxetine	
	E. coli	Levofloxacin/Tetracycline/Chloramphen Rifampicin/Oxacillin/Linezolid/ Clarithromycin+Sertraline	
	Corynebacterium group D2	Tetracycline/Ciprofloxacin+Sertraline	
	9 ATCC standard strains and 9 MDR clinical isolates	Disulfiram/ Sulfamethoxazole trimethoprim/ Ciprofloxacin +Sertraline	
	E. coli ATCC 8739	Venlafaxine	
Can Drug Repurposing be Effective Against Carbapenem-Resistant Acinetobacter baumannii? (19)	•The rapid and inexpensive method of treating carbapenem-resistant A. baumannii may be drug repurposing. •The most likely options are fusidic acid and colistin for repurposing, possibly in combination with a third drug. •Some medications may be less useful in clinical practice due to high toxicity and low plasma concentrations. •Apramycin, Mitomycin, 5- Fluorouracil, Fusidic acid +Colistin, Niclosamide+Colistin, Polymixin B -Mitotane are effective for treatment of carbapenem-resistant A. baumannii		

Repurposing of existing drugs for the bacterial infections: An In silico and In vitro study. (20)	• According to in silico research, gram positive and gram-negative bacteria had a variety of targets on which metformin, propranolol, and amitriptyline interacted. • The Microtiter assay, Minimum Inhibitory Concentration (MIC), Post-Antibiotic Assay, and Biofilm Formation were used to evaluate the antibacterial potential of metformin, propranolol, and amitriptyline. •Metformin, propranolol, and amitriptyline have all been shown to have antibacterial action against bacteria such as Bacillus pumilus, Pseudomonas aeruginosa, and Staphylococcus aureus in tests conducted in vitro.
Repurposing of Drugs for Antibacterial Activities on Selected ESKAPE Bacteria Staphylococcus aureus and Pseudomonas aeruginosa (21)	•Ten non-antimicrobial substances were tested for antibacterial activity against the ESKAPE pathogens Pseudomonas aeruginosa and Staphylococcus aureus. • Curcumin had MICs of 50 g/ml and 100 g/ml for P. aeruginosa and S. aureus, respectively, and demonstrated the strongest antibacterial action against both species. •It was discovered that ciprofloxacin's antibacterial properties were enhanced when curcumin was added for P. aeruginosa and S. aureus
A Macromolecule Reversing Antibiotic Resistance Phenotype and Repurposing Drugs as Potent Antibiotics (22)	•A unique strategy has been developed to improve antibiotic efficacy and combat drug resistance by combining traditional antibiotics with the translocation mechanism of an antimicrobial polycarbonate with guanidinium functionalization. •The rifampicin resistance phenotype in Acinetobacter baumannii is reversed by this approach, which results in a 2.5 x 105-fold drop in the minimum inhibitory concentration (MIC) and a 4096-fold reduction in the minimum bactericidal concentration (MBC). • This technique also enables the repurposing of auranofin as an antibiotic against multidrug-resistant (MDR) Gram-negative bacteria, with a 512-fold MIC and 128-fold MBC reduction, respectively.

Repurposed drug candidates for antituberculosis therapy (23)	•Anti-TB properties have been discovered in a number of medications that have been approved for clinical usage or clinical trials. •Several repurposed medications, such as linezolid, clofazimine, amikacin, and meropenem, have been found to be effective against TB.
Repurposing Screen Identifies Unconventional Drugs with Activity Against Multidrug Resistant Acinetobacter baumannii (24)	• 43 active compounds were discovered using a drug repurposing screen to combat a multidrug resistant strain of Acinetobacter baumannii. •Three of these drugs, 5-fluorouracil, fluspirilene, and Bay 11-7082, made the MDR-AB strain more susceptible to the two-drug combination of azithromycin and colistin.
Drug Repurposing to Fight Colistin and Carbapenem-Resistant Bacteria (25)	•Multi-drug resistant bacteria can be successfully treated via drug repurposing, which can be accomplished using phenotypic, computational, and serendipitous methods. •The use of repurposed medications to treat colistin- and carbapenem-resistant bacteria has been effective. Relevant repurposing reports for carbapenem and colistin resistant bacteria. • Zidovudine • Niclosamide • Pentamidine • Ciclopirox • 5-fluorouracil • Mitotane • Gallium • Tamoxifen /Raloxifene/Toremifene • Sertraline • Citalopram • Bay 11-7082 • Spironolactone • Resveratrol • Pterostilbene • Eugenol

Repurposing of Existing Statin drugs for treatment of Microbial Infections: How much Promising? (26)	•Studies on the antibacterial properties of statin medications have produced encouraging results. •Clinical investigations have demonstrated the preventive role of statin medications in lowering morbidity and mortality associated with a variety of viral illnesses.
Repurposing of nucleoside- and nucleobase-derivative drugs as antibiotics and biofilm inhibitors (27)	• Drugs which are analogues of nucleosides and nucleobases are an appealing class to repurpose as antibacterial agents. • By extending the therapeutic range of currently existing antibiotics, these medications can work in synergy with antibiotics. • By inhibiting bacterial pathogenicity and biofilm development, nucleoside and nucleobase analogue medications can make pathogens more sensitive to antibiotic therapy and host immune defenses.
Repurposing and Revival of the Drugs: A New Approach to Combat the Drug Resistant Tuberculosis (28)	•The emergence of drug-resistant tuberculosis, including MDR-TB, XDR-TB, and TDR-TB, has increased the difficulty of combating these harmful Mycobacterium tuberculosis organisms. • The newer medications bedaquiline and delamanid used in the treatment of MDR-TB, XDR-TB, and TDR-TB may be the choice for a potential combination chemotherapy against these harmful pathogens due to their bactericidal and synergistic effects. Some of the repurposed medicines for TB are • Sulfadiazine • Clofazimine • Linezolid • Minocycline • Metformin • Verapamil Combinatorial therapy of • amoxicillin/clavulanic acid along with other second-line drugs • amoxicillin/clavulanic acid and carbapenems,

	• Clofazimine in combination with ethambutol and moxifloxacin • Sulfamethoxazole with rifampicin • Clofazimine with bedaquiline and pyrazinamide • bedaquiline and linezolid • carbapenems with rifampicin
Repurposing Ivacaftor for treatment of Staphylococcus aureus infections. (29)	• Strong antibacterial activity exists for ivacaftor against vancomycin- and other multidrug-resistant strains of Staphylococcus aureus. • Ivacaftor has potential as an antimicrobial agent to treat staphylococcal infections .
Drug repurposing: a new front in the war against Staphylococcus aureus. (30)	•The potential of Staphylococcus aureus to develop and sustain antibiotic resistance means that it still poses a serious threat to public health. • This review offers a summary of the currently authorized drugs with the repurposing potential against Staphylococcus aureus
Drug repurposing for the treatment of staphylococcal infections.(31)	It has been demonstrated that a number of therapeutic compounds and approved medications have antibacterial action against Staphylococcus aureus. Approved drugs with activity against S. aureus • 5-fluoro-2'-deoxyuridine • Auranofin • 5-fluorouracil • Levocabastine • Celecoxib • Fluvastatin • Disulfiram • Dicyclomine

	Additionally, host immunomodulators and staphylococcal pathogenesis can be interfered with using approved medications.
Is repositioning of drugs a viable alternative in the treatment of tuberculosis? (32)	The treatment of tuberculosis faces a severe problem with antimicrobial resistance. Drug repurposing has been used to treat TB and has resulted in unexpected results in other medical fields. Main drugs proposed as repurposed antibiotics in TB • Fluoroquinolones • Linezolid • Trimethoprim/sulfamethoxazole • Clofazimine • Mefloquine • Thioridazine
Repurposing screens identify rifamycin as potential broad-spectrum therapy for multidrug-resistant Acinetobacter baumannii and select agent microorganisms. (33)	• 17 medicines with promising antibacterial action were found after screening 450 FDA-approved medications from the NIH National Clinical Collection against 12 clinical MDR A. baumannii (MDRAb) isolates from US soldiers and Marines. • It was discovered that three of these substances, all rifamycin's, were efficient at stopping MDRAb and select agent surrogate bacteria's growth and cellular respiration. • When tested in growth prevention assays, all rifamycin's were found to be successful at stopping MDRAb and specific agent surrogate bacteria like Yersinia pestis, Franscicella tularensis, Bacillus anthracis, Yersinia pestis from multiplying and respiring, highlighting the possibility of repurposing.

Antiviral Activity of Approved Antibacterial, Antifungal, Antiprotozoal and Anthelmintic Drugs: Chances for Drug Repurposing for Antiviral Drug Discovery (34)	This study evaluated the antiviral activity of drugs approved for antibacterial, antifungal, antiprotozoal, and anthelmintic uses.

Pathogens	**Repurposed drugs**
Influenza A	Azithromycin
RSV	Clarithromycin
Rhinovirus	Erythromycin Levofloxacin
Zika virus, SARS-CoV-2	Fidaxomicin
SARS-CoV-2	Moxifloxacin Rifampicin
Simian virus 40	Ofloxacin Ciprofloxacin
BK virus, Ciprofloxacin	Ciprofloxacin
Dengue virus, CCHFV,CHIKV	Doxycycline
SARS-CoV	Lymecycline Oxytetracycline Tigecycline Chloramphenicol
HIV and SIV	Minocycline
HIV-1	Cycloserine Fusidic acid
effective against	Antifungal drugs
Enterovirus 71	Amphotericin B Itraconazole
Dengue virus	Posaconazole Itraconazole
SARS-CoV and SARS-CoV-2	Caspofungin

	HSV-1 *HIV-1* — Quinine *HIV-1* — Hydroxychloroquine *SARS-CoV-2* — Atovaquone *SARS-CoV-2* — Mebendazole
Repurposing Molnupiravir as a new opportunity to treat COVID-19 (35)	The drug Molnupiravir, which was originally designed to treat influenza, has been repurposed for the treatment of Covid-19 patients who are mildly to moderately unwell but are at a high risk of progressing to a more serious illness.
Repurposing of antibiotics for clinical management of COVID-19: a narrative review (36)	•The most prevalent antibiotic used in the clinical management of COVID-19 is macrolide, specifically azithromycin. •Teicoplanin, clarithromycin, doxycycline, tetracyclines, levofloxacin, moxifloxacin, ciprofloxacin, and cefuroxime are additional antibiotics used to treat COVID-19.
Antibiotics in Combination with Antifungals to Combat Drug Resistant Candida – A Concept on Drug Repurposing (37)	•Drug-resistant Hospital-acquired infections and mortality are largely caused by Candida spp. • It has been demonstrated that the combination therapy of antibiotics and antifungals described below has synergistic effects against drug-resistant strains, but not drug-susceptible strains. • Gentamicin and Azoles • Aspirin and Amphotericin • Tacrolimus and Azoles • Minocycline and Fluconazole • Aminoglycoside K20 and Azoles.

Repurposing approach identifies new treatment options for invasive fungal disease. (38)	• Through drug repositioning using ligand-based and structure-based computational approaches, compounds with promising antifungal efficacy against the species Paracoccidioides were found. •Raltegravir, an antiviral medication, showed positive antifungal efficacy against an experimental strain of mouse paracoccidioidomycosis. • For the treatment of paracoccidioidomycosis, an antiviral medication with promising antifungal action was chosen by combining two in silico approaches for drug repositioning.
Drug Repurposing of the Alcohol Abuse Medication Disulfiram as an Anti-Parasitic Agent (39)	• Disulfiram has been studied as an anti-parasitic agent, with promising results against the parasite Entamoeba histolytica, the leading cause of gastroenteritis. • Drug repurposing of disulfiram as an anti-parasitic agent may offer a novel treatment option for parasitic infections.
Repurposing FDA-approved drug disulfiram plus zinc supplement for treatment of parasitic infections (40)	• A potential strategy for the treatment of parasitic infections involves repurposing the FDA-approved medication disulfiram along with zinc supplementation.
Repurposing of drugs is a viable approach to develop therapeutic strategies against central nervous system-related pathogenic amoebae.(41)	• Almost always, fatal infections of the central nervous system brought on by brain-eating amoebae such Acanthamoeba species, Naegleria fowleri, and Balamuthia mandrillaris arise from these illnesses. • A worrisome problem can be seen by the high death rate, the pharmaceutical industry's lack of interest in drug discovery, and the lack of efficient treatments. • The current treatments for these crippling diseases include amphotericin B, miltefosine, chlorhexidine, pentamidine, and voriconazole, and they are frequently used in combination. • However, clinical evidence shows that these drugs are ineffective and excessively toxic to host cells.

<table>
<tr>
<td>Repositioning of Anthelmintic Drugs for the Treatment of Cancers of the Digestive System (42)</td>
<td>
• Anthelminthics have been proposed as novel anticancer drugs due to their activity against a wide variety of cancers.

• These anthelminthics were administered orally for the treatment of nematode infections and showed mostly poor resorption.

• The host of different targets described seems to be linked to the capability of the benzimidazoles, salicylanilides and cyanine dye derivatives to interact with DNA directly.

<table>
<tr><th>Antimicrobial drug</th><th>Repurposed use</th></tr>
<tr><td>Mebendazole</td><td>Gastric cancer
CRC
HCC</td></tr>
<tr><td>Albendazole</td><td>CRC
HCC
Pancreatic cancer</td></tr>
<tr><td>Flubendazole</td><td>CRC</td></tr>
<tr><td>Niclosamide</td><td>CRC
Esophageal cancer
HCC</td></tr>
<tr><td>Rafoxanide</td><td>CRC
Gastric cancer</td></tr>
<tr><td>Closantel</td><td>Liver cancer, pancreatic cancer</td></tr>
<tr><td>Nitazoxanide</td><td>CRC</td></tr>
<tr><td>Ivermectin</td><td>CRC
Gastric cancer</td></tr>
<tr><td>Praziquantel</td><td>CRC</td></tr>
<tr><td>Pyrvinium pamoate</td><td>Pancreatic cancer
CRC</td></tr>
<tr><td>Piperazine</td><td>CRC
HCC</td></tr>
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Alternatives to antibiotics-a pipeline portfolio review. (43)	• In phase 2 and phase 3 trials, antibodies, probiotics, and vaccines are being evaluated as alternatives to antibiotics. • These alternatives are most effective as adjunctive or preventative treatments, indicating that conventional antibiotics are still necessary.

* MRSA: methicillin-resistant *Staphylococcus aureus*; CRE: carbapenem-resistant Enterobacterales; MCRPE: MCR-producing Enterobacterales, Tet (x)-Tigecycline resistant,KPC-Carbapenamase producing Klebsiella pneumoniae, CONS- Coagulase Negative Staphylococcus aureus , VRE- Vancomycin resistant enterococci-AB- Multi drug resistant Acinetobacter baumanii, TB-Tuberculosis , XDR-Extremely drug resistant, TDR- Total drug resistant- Respiratory syncticial virus, HIV- Human Immunodeficiency virus, SIV- Simian Immunodefiency virus, CCHFV-Crimean Congo Hemorrhagic fever virus,CHIKV-Chikungunya virus, CRC-Colorectal cancer, HCC- Hepatocellular carcinoma

ADVANTAGES OF DRUG REPURPOSING:

- Repurposing existing pharmaceuticals is a more cost-effective method than traditional drug discovery for developing new antibiotics. Due to the fact that the drug's safety and efficacy have already been established through clinical trials, there is less risk of failure.(4)
- Existing drugs can be repurposed quicker than new antibiotics can be created from scratch. This is because the drug does not require the same extensive clinical testing as new drugs. (4)
- Repurposing existing medications is generally safer than creating new antibiotics. Because the drug's safety profile is already known, there is a lower risk of unexpected adverse effects.(5)
- Repurposing existing drugs can result in the discovery of novel applications for the drug. This can be advantageous if the drug is effective against a new target or can be administered in a new manner.(5)
- Repurposing existing medications can aid in reducing the emergence of antimicrobial resistance. This is because the substance is already in use, reducing the need for new applications.(6)

CHALLENGES ASSOCIATED WITH DRUG REPURPOSING

Repurposing antimicrobials is a promising approach to developing new antibiotics, but it is not without its challenges. Here are some of the challenges that need to be addressed in order to make antibiotic repurposing more successful:

- Limited efficacy: Repurposed antimicrobials may not be as effective as new antimicrobials, as they may have been optimized for bacterial infections. (19)

- Increased antimicrobial resistance: The use of any antimicrobial can select for resistant bacteria, and repurposed antimicrobials may be no different. This could lead to the development of resistance to the repurposed antimicrobial, as well as to other antimicrobials.(4)
- Lack of funding: There is less funding available for antibiotic repurposing than for traditional drug discovery. This is because repurposed antimicrobials are seen as less risky, so there is less of a financial incentive to develop them. (4)
- Difficult to find new uses: It can be difficult to find new uses for antimicrobials that are already used to treat bacterial infections. This is because the drug's mechanism of action may be well-understood, so there may be fewer opportunities to find new uses for it. (4)
- The safety profile of the drug may not be fully understood: Even if a drug has been used for a long time, there may still be unknown risks associated with its use. This is especially true for drugs that are being repurposed for new uses.(4)
- The drug may not be as well-tolerated as new antimicrobials: Repurposed antimicrobials may have more side effects than new antimicrobials. This is because the drug has not been specifically designed for the new use, so it may not be as well-suited for it.(5)
- The drug may not be as available as new antimicrobials: Repurposed antimicrobials may not be available in all countries or in all forms. This is because the drug may not be as profitable as new antimicrobials, so there may be less incentive to make it available.(5)
- The need for better screening techniques: To find medications with repurposing potential, better screening techniques are required. Current screening techniques frequently lack the sensitivity needed to detect medications with insufficient antibacterial activity.(6)
- The need for a deeper comprehension of the mechanisms behind the effects of repurposed medications Understanding the mechanisms of action of repurposed medications is essential for optimizing their use. The most effective dosages and treatment plans can then be determined.(6)
- Better preclinical models are required: Better preclinical models are required to evaluate the safety and efficacy of repurposed medications. Predicting how the medications will work in humans can be challenging because the human gut flora is frequently not reflected in the preclinical models used today.(6)
- Better clinical studies are required: Better clinical trials are required to evaluate the effectiveness and safety of repurposed medications. Because current clinical trials are frequently tiny and underpowered, it is challenging to make certain judgments about the efficacy of the medications. (6)

Despite these challenges, antibiotic repurposing is a promising approach to developing new antimicrobials. It is a more cost-effective, faster, and safer way to develop new antimicrobials than traditional drug discovery. It can also lead to the discovery of new uses for existing drugs and help to reduce the development of antimicrobial resistance.

FUTURE PROSPECTIVES:

Repurposing antimicrobial drugs has a variety of potential future applications. These consist of:

- the creation of novel computational and bioinformatics instruments to find possible drug-drug interactions. Large libraries of licensed medications could be screened using these technologies for possible antibacterial activity.
- the process of finding new antimicrobial medication targets using microbiome data collected from patients. With the help of this information, it may be possible to find medications with good safety profiles for usage in humans or that are effective against particular bacterial strains.
- the creation of fresh AMR animal models to evaluate the efficiency and security of drug repurposing. These models could be applied to discover possible drug-drug interactions and speed up drug development.

Antimicrobial medication repurposing has a bright future. This strategy is probably going to become more crucial in the fight against AMR as new technologies continue to be developed and vast datasets become available.

CONCLUSION:

Antimicrobial drugs repurposing is a practical method for preventing the spread of infectious diseases. By examining the potential of already-approved drugs, researchers can benefit from known safety profiles and pharmacokinetic data. This strategy expedites the release of new medications while enhancing the usefulness of therapeutic treatments that are already on the market. As the international healthcare community struggles to address the urgent problem of antimicrobial resistance, repurposing existing drugs is an essential tool in the fight against infectious diseases.

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