International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 18, Issue 3, 2026

Review Article

THE COVID-19 CATALYST: A CRITICAL REVIEW OF ACCELERATED DRUG REPURPOSING STRATEGIES, LESSONS LEARNED, AND FUTURE DIRECTIONS

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Received: 24 Oct 2025, Revised and Accepted: 19 Feb 2026

ABSTRACT

To examine the significant effects of the COVID-19 pandemic on medication repurposing as a swift alternative to conventional drug development, highlighting algorithmic, omics-based, and clinical translation methodologies. The COVID-19 pandemic is discussed starting with core concepts, encompassing definitions, classification systems, regulatory perspectives, and notable historical developments. For the reverse matching of drugs to illness profiles, we looked at both advanced computational tools and omics-based methods. The paper discussed flexible clinical trial approaches and how the rules were altered during the epidemic. Drug-candidate identification was shortened from years to months thanks to AI-assisted virtual screening, which enabled the rapid examination of thousands of approved compounds. About forty promising repurposed medications started clinical trials during the first year of the pandemic. Reliable efficacy results were rapidly produced by adaptive, data-driven trials, such as RECOVERY and ACTT. Successful medications like remdesivir, dexamethasone, and baricitinib showed definite benefits in recovery and mortality despite failures like hydroxychloroquine and lopinavir/ritonavir. Toxicity prediction and target matching were further enhanced by integrated chemical and biological databases, enabling quicker and more precise go/no-go determinations.

AI techniques, omics data, and adaptive clinisupervision, significantly reducing drug-development timescales from years to months without compromising regulatory oversight, as demonstrated by the COVID-19 pandemic. In addition to addressing obstacles such as off-target effects, regulatory limitations, intellectual property concerns, and limited model generalizability, the study emphasizes that future advancements will depend on the increased use of real-world evidence, precision-medicine-based repurposing, and open research collaboration.

Keywords: Algorithmic prediction, Drug repurposing, COVID-19, Omics-guided research, In silico approach, Molecular docking, Accelerated clinical development

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DOI: https://dx.doi.org/10.22159/ijap.2026v18i3.57254 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

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INTRODUCTION

The COVID-19 pandemic exposed the shortcomings of conventional drug research, which often takes ten years or longer to go from discovery to clinical usage, and highlighted an urgent global need for effective remedies [1]. Drug repurposing immediately emerged as a viable strategy, enabling researchers to expedite the development of medications into clinical trials by leveraging existing safety, pharmacokinetics (PKs), toxicity, and manufacturing data [of rapid evaluation of certain classes, such as immunomodulators, supportive treatments, and antivirals, which yielded both positive and negative results, underscoring the need for thorough scientific and regulatory review [3]. By increasing computational screening, artificial intelligence(AI)-driven modelling, *in silico* tools, real-world data (RWD) analytics, and quick clinical trial platforms, COVID-19 also expedited contemporary repurposing efforts [4]. To emphasize important lessons, excellent approaches, current challenges, and potential future directions for drug repurposing beyond the pandemic, this review highlights these developments [5].

PubMed, Scopus, Web of Science, Google Scholar, and ClinicalTrials. gov were used in an organized literature search. The following keywords were utilized in various Boolean combinations: "drug repurposing," "COVID-19," "SARS-CoV-2," "machine learning (ML)," "computational drug discovery," "clinical trials," and "emergency regulatory approval." Peer-reviewed studies, clinical trial reports, regulatory documents, and systematic reviews from 2019 to 2025 were all considered. Included were studies on clinical outcomes, computational prediction techniques, regulatory pathways, and repurposing COVID-19 medications. Duplicates, low-quality or unreliable sources, and articles written in languages other than English were not included. This strategy ensured broad and focused coverage of the rapidly evolving landscape of drug repurposing during the pandemic.

Necessity for drug repurposing after COVID

Drug repurposing is a frontline strategy for rapid clinical deployment, as the COVID-19 pandemic highlighted the urgent need for faster therapeutic solutions. The COVID-19 pandemic exposed a global lack of preparedness for rapidly spreading diseases,and we mustemphasize rapid treatment. Drug repurposing was highly significant at the outset of the epidemic since it helped find effective treatments faster than starting new drug research. Drug repurposing is particularly crucial for becoming ready for future health risks and pandemics and dealing with the long-term impacts of COVID. Finding new uses for existing drugs, often known as drug repurposing, has many benefits. These include confirmed safety profiles, PKs, lower costs of development, and quicker use in clinical settings. Remdesivir (REM), dexamethasone (DXM), and baricitinib (BARI) are all medications that have been used for other things that make COVID-19 less serious and lethal. Repurposed candidates didn't always work, but the process demonstrating that pharmaceutical innovation could occur quickly. There are still difficulties after COVID, such as protracted COVID, which affects millions of individuals around the world, new zoonotic infections, and antibiotic resistance that is getting worse. These numbers show that we need to improve the processes address problems with the heart, lungs, and mind, targeting issues within biological networks rather than those, addressing issues with the targets and diseases within biological networks, rather than those issues with the targets and diseases within biological networks, rather than using a single-target approach. This enables the revelation of a multi-target approach, specifically valuable for complicated diseases and herbal drug research. The COVID-19 Open Research Dataset and Evidence (CORD-19) and the National Center for Advancing Translational Sciences (NCATS) illustrate approaches for comprehensive repurposing that are beneficial for both short-term emergency

management and long-term therapeutic strategies. Drug repurposing has evolved from a contingency strategy to a core element of current drug development and pharmacology. To meet the goals of global scale perspectives [2,6–9], sustaining this momentum through continuous investments in integrating data systems, robust regulatory frameworks, and collaborative public-private partnerships is essential. This need laid the groundwork for reassessing the difficulties inherent in conventional pathways and traditional drug development timelines.

Issues with conventional drug discovery timelines

When quick responses are needed during global health emergencies, traditional drug discovery is slow, expensive, and high-risk, creating significant barriers to effective action. Brin$2.6 billion to market may take at least 10-15 y, from selecting a target to regulatory approval, and involves roughly a $ 2.6 billion investment[10]. Even though technology has gotten better, the old way of doing things still doesn't work, with a success rate of fewer than 10%. People drop out of clinical studies mostly because they are toxic, have bad PKs, or don't work. The Food and Drug Administration (FDA) only validates 3.4% of cancer drugs inphase I [11].

The protracted timelines of conventional drug development are incompatible with the urgent need for therapeutics during public health emergencies. Discovering and verifying a target (1-2 y), the general processes in drug development and discovery, and optimization of lead compound (2-3 y), preclinical testing (1.5-2 y), clinical research (6-7 y), and regulatory authorisation (1-2 y). Throughout the process, challenges arise in scientific validation, compliance, and logistics. Over 90% of drugs do not succeed during this phase, which makes the journey from discoveryto market remain high-risk and costly.

Conventional development methods have several limitations. Primarily, the timelines are insufficient for addressing global health crises, such asmonkeypox, COVID-19, and Nipah. Rapid response is essential in such scenarios, and traditional frameworks can't keep pace. Additionally, more complex clinical trials and strict government regulations are escalating the expenses of pharmaceuticals. Thirdly, many promising compounds never progress to clinical testing because they never fail to progress due to gaps in translational infrastructure, complex regulatory requirements, and limited economic incentives. This phenomenon is known as the "valley of death." drugs and treatments for emerging diseases, resulting in patients often having to delay access to treatment. The limited leverage of RWD, multi-omics technologies, and AI pose challenges in validating targets and predicting toxicity. The pandemic highlighted the apparent limitations and highlighted adoptable data-driven solutions. Global health systems relied on drug repurposing, adaptive trials, and emergency use authorizations(EUAs) in response to the limited time to develop new drugs. Rapid evaluation and use of DXM, REM, and BARI highlighted the potential of alternative approaches to facilitate the timely administration of effective treatments in real time. Ultimately transformed drug development globally.

The pharmaceutical industry uses faster, more accurate technologies to produce drugs, overcoming the challenges associated with the current approach. AI and ML identify targets and rapidly evaluate virtual compound libraries. In silico models forecast drug efficacy and toxicity before clinical trials. Network pharmacology and chemical database data mining are making it easier to find new therapeutic uses for drugs already used for other purposes. Real-world evidence (RWE), wearable devices, and multi-omics data all help make clinical trials easier to plan and conduct. These techniques could help accelerate drug research, reducing costs, and increase the likelihood of success. But there are still issues. Still, bright prospects are stuck in the translational bottleneck due to funding, rules, or data issues. To fill this gap, we need to use biomarker-driven methods, personalized medicine frameworks, and partnerships in open science. As the world prepares for future health disasters, agile, data-driven solutions in mainstream pharmaceutical research and development are crucial [1, 12-14]. The shift toward accelerated and technology-assisted approaches, such as AI-driven discovery and large-scale repurposing initiatives, was prompted by these limitations.

Purpose and focus of the review

This review focuses on analyzing how drug repurposing changed after COVID-19 and the clinical, technological, and regulatory frameworks that allowed its growth. The COVID-19 pandemic has spurred research into unconventional pharmaceuticals, rendering medication repurposing a primary strategy for expedited therapeutic intervention. The emergence of new diseases, long-term post-COVID-19 conditions, and antimicrobial resistance, combined with limited healthcare systems and resource constraints, highlights the critical necessity for repurposing strategies. The primary intention of this review is to discuss and emphasize strategies for drug repurposing. This underscores the importance of a pharmacotherapy approach and therapeutic interventions in strengthening the public health readiness following a pandemic. The pandemic revealed constraints for conventional drug research and demonstrated the potential for adaptable repurposing strategies. Secondly, the review focuses on repurposing the existing medications, including computational screening, AI-based predictive models, network pharmacology, phenotypic assays, and RWD analysis from practical instances of pandemics and various disease conditions.

This review also examineswhether the repurposing of drugs for COVID-19 has worked. REM and DXM demonstrate examples; the case of hydroxychloroquine (HCQ) highlights the challenges in transforming technological achievements in optimising repurposing pipelines. Additional digital health innovations, omics data, virtual screening, and bioinformatics strategies have collectively accelerated rapid identification of drugs for repurposing. Ethical and legal aspects are essential in repurposing drugs. The critical aspects related to intellectual property rights, drug labeling, post-market surveillance, and expedited procedures for the FDA and European Medicines Agency (EMA). A clear understanding of these factors is necessary for appreciating the approval of repurposed drugs and treating patients in a real-time setting. Lastly, the review concludes byexamining medication repurposing and standard development pipelines, enabling the precision of medication, supporting pandemic readiness, promoting open science, and facilitating public-private partnership advancing strategies to promote resilience for future health emergencies and strongly reinforcing the international drug development framework.

This article addresses multiple critical aspects, including the historical background and conceptual framework of pharmacological repurposing. It further explores the differences between standard and repurposed drug development approaches. Illustrating their relevance toboth non-infectious and infectious diseases, such as COVID-19. Technologies such as AI, ML, multi-omics, and RWD. Recent work (2019–2025) examines successful and unsuccessfulcase studies of reuse. Regulatory procedures and policy structures in significant pharmaceutical markets arecharacterized by ongoing scientific, economic, legal, and clinical obstacles. The review suggests future pharmaceutical repurposing techniques for ecosystems of healthcare innovation. This in-depth, evidence-based overview of drug repurposing is based on contemporary scientific papers, regulatory documents, and technological platforms. It proposes refining this methodology to address urgent therapeutic needs, decrease drug development costs, and confront clinical issues emerging in the post-pandemic context [15-18]. This establishes the framework for comprehending the definitions, categorizations, and techniques that form contemporary drug repurposing strategies.

Definitions and groups

Drug repurposing, also known as drug repositioning, is the process of finding new therapeutic applications for pharmaceuticals that have already been approved or commercialized. This approach offers a quicker and safer development pathway than developing brand-new treatments. Repurposing uses pharmacological, PKs, and toxicological data instead of new drugs and unproven mechanisms. This makes it safer, faster, and cheaper to make medications in the early phases. Repurposing speeds up the processof getting pharmaceuticals into clinical usage by skipping the

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preclinical and early clinical phases. This is particularly significant for public health and the treatment of rare diseases. Mechanistic reasoning sorts different types of pharmaceutical repurposing efforts into various groups. When a medication is utilized for a different ailment but still acts on the same biological target, this is called on-target repurposing. Sildenafil, which opens up blood vessels, was first made to treat angina but is now used to treat ED. Drug off-target repurposing happens when a drug targets a biological target that it wasn't meant to. Thalidomide has stopped being used for morning sickness. It can cause congenital disabilities, although it was used to treat multiple myeloma because it can change the immune system. This includes repurposing that focuses on diseases and targets. Disease-centric repurposing uses antivirals to treat viral infections. Target-centric repurposing employs kinase inhibitors from one cancer type in other tumors with similar molecular etiology, based on the premise that the same biological target is relevant across several disease situations. Modern classification includes methods based on a specific technique. Computational repurposing leverages AI, ML, and data mining to identify new drug-disease correlations. Experimental repurposing identifies novel therapeutic effects using phenotypic screening and cell-based assays. High-throughput drug library screening and other systematic screening approaches have sped up the process of repurposing medications in the pipeline. Pushpakom *et al.* (2019) characterize "drug repurposing" as the exploration of innovative therapeutic applications for pre-existing drugs. This accelerates the process of putting the drug into clinical use by skipping a lot of the early-stage development work. Modern pharmacotherapy employs this pragmatic and efficacious approach to address urgent therapeutic needs. Building on these definitions, historical examples demonstrate how repurposing has helped achieve successful therapeutic outcomes in a variety of disease areas.

Table 1: Different ways to repurpose drugs [2, 19-23]

Type	Description	Example	Reference
On-target	Same objective, new disease	Sildenafil for high blood pressure in the lungs	[19]
Off-target	New objective, new disease	Thalidomide for multiple myeloma	[20]
Disease-centric	Similar disease mechanisms	Drugs that fight the flu for COVID-19	[2]
Target-centric	Target pertinent to many diseases	Kinase inhibitors in different types of cancer	[21]
Computational	Reusing AI, ML, or bioinformatics	BARI was found via AI	[22]
Experimental	Testing in the lab for new disease models	Phenotypic tests for cancer medicines	[23]

AI: Artificial intelligence, ML: Machine learning, BARI: Baricitinib

Lessons learned and historical successes

As demonstrated by successful instances such as sildenafil, dexamethasone, and thalidomide, drug repurposing has continuously produced notable clinical improvements, indicating its high therapeutic and strategic significance. Thalidomide is an immunomodulatory drug that was first marketed as a sedative in the 1950s. It was subsequently utilized to treat multiple myeloma and erythema nodosumleprosum. Sildenafil (viagra®) was created to treat angina, but it worked best for erectile dysfunction and pulmonary arterial hypertension because it makes blood vessels wider. Patients reported growing back hair they didn't expect; therefore,minoxidil was reintroduced as a treatment for hair loss. Drug repurposing played a crucial role in helping meet the urgent demand for effective treatments during the COVID-19 outbreak. REM was first utilized to treat Ebola; however, it was then used to treat COVID-19 and receivedan EUAbased on early clinical benefits. One of the most effective early pandemic treatments was DXM, a corticosteroid that was easy to procure. It reduced the number of deaths among COVID-19 patients in the hospital and who needed help breathing.

These examples teach us different things about how to use drugs in new ways. The ailment's biology, the medicine's method, and the intervention's time all play a role in how effectively it works. Second, HCQ was effective against SARS-CoV-2 in a lab but didn't work in big clinical trials. Third, regulatory flexibility, including the FDA's EUAs process, facilitated the swift employment of repurposed medications. For these paths to be secure and valuable in the real world, they need strong proof and regular checks once they are available to the public. As we move into a discussion of the regulatory systems governing repurposed drugs, these outcomes also highlight the significance of robust clinical evidence and regulatory flexibility.

Table 2: Examples of successful drug repurposing [3, 19, 20, 24-27]

Drug	Original use	Repurposed use	How it works	Reference
Thalidomide	Sedative	Multiple myeloma	Blocking tumor necrosis factor (TNF)-α	[20]
Sildenafil	Angina	Erectile dysfunction, PAH	Blocker of PDE5	[19]
Minoxidil	Hypertension	Losing hair	Vasodilation helps hair follicles develop	[24]
REM	Ebola	COVID-19	Inhibition of RNA-dependent RNA polymerase	[25]
DXM		Severe COVID-19	Corticosteroid lessens cytokine storm	[3]
Methotrexate	Cancer	Rheumatoid arthritis	Immunosuppressive effect	[26]
Colchicine	Gout	COVID-19 (in the testing stage)	NLRP3 suppression helps reduce inflammation	[27]

TNF: Tumor necrosis factor, PAH: pulmonary arterial hypertension, PDE5:Phosphodiesterase Type 5, REM: Remdesivir, RNA: Ribonucleic Acid, DXM: dexamethasone, NLRP3: NOD-like receptor family pyrin domaincontaining 3.

Regulatory perspectives on repurposed pharmaceuticals

The speedy approval of repurposed treatments has been made possible by regulatory frameworks like the FDA's 505(b)(2) pathway and international emergency authorization regimes. Depending on their initial clearance status, the new usage, and the requirements of the regulatory body, repurposed pharmaceuticals have distinct challenges and measures to follow. The FDA's 505(b)(2) new drug application (NDA) process makes it easier for drugs that have been used for a different purpose to get approved in the US. By adapting this method, sponsors utilise existing research or earlier FDA regulations to adjust and prove the therapy is safe and beneficial for a newalternative purpose. During a crisis where no approved or suitable treatments exist during emergencies, the FDA has the authority to issue EUAs to permit unapproved or approved drugs for alternative use. Despite issues such asintellectual property constraints, limited commercial profits, and inadequate incentives, these often limit pharmaceutical companies from investing in drug repurposing. As Article 10 of Directive 2001/83/EC outlines, the EMA is responsible for managing the repurposing of drugs in the EU. It promotes flexible and adaptive pathways, improving review processes and access to repurposed therapies,

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especially when effective options persist. Under the New Drugs and Clinical Trial Rules, 2019, the rules empower CDSCO to monitor repurposing of drugs in India. These guidelines permit approved drugs to receive exemptions from data requirements for new therapeutic uses when scientific or clinical data support them. During the COVID-19 pandemic, global organisations such as the World Health Organisation (WHO) and the NCATS promoted the benefits of drug repurposing globally. People are building open-access databases and platforms to collaborate and accelerate research by repurposing existing data. The epidemic has caused regulatory harmonization and data-driven, evidence-based repurposing efforts in several areas. To ensure timely repurposing of medicines, new rules and better communication between agencies are critically necessary [28-33]. To make repurposing a dependable, long-lasting strategy for future public health emergencies, regulatory harmonization and transparency must be strengthened.

Table 3: Alook at regulatory pathways around the world

Region	Pathway	Key feature	Regulatory support
USA	505(b)(2) NDA	Allows the use of published data or existing data	FDA guidance; EUAs in case of emergencies
EU	Article 10 (Mixed/Hybrid Dossier)	Needs some data and evidence from the literature	EMA adaptive pathways are available
India	NDCT Rules in 2019	Data waiver possible if literature supports new use	In some situations, CDSCO will accept data from throughout the world
Japan	System for Re-examination	New indications can be added via an abbreviated process	PMDA encourages post-marketing studies
China	New Chemical Pathway for NCE	Similar to de novo, unless strong evidence is presented	Needs bridging studies
WHO	Prequalification and Solidarity Trials	A global platform for quick evaluation	Used for COVID-19 repurposing efforts

USA: United states of America, NDA: New drug application, FDA: Food and drug administration, EUAs: Emergency use authorization, EU: European Union, EMA: European medicines agency, NDCT: New drugs and clinical trials (Rules), India, CDSCO: Central drugs standard control organization (India), PMDA: Pharmaceuticals and medical devices agency (Japan), WHO: World health organization, NCE: New chemical entities

Systematic methodologies for drug repurposing

In silico screening and data mining

By utilizing structural, chemical, and bioactivity datasets, *in silico* screening and large-scale data mining enable the rapid identification of repurposing candidates. Ultra-large-scale docking systems molecular docking and structure-based design. A structure-based technique called "molecular docking" is used to forecast how medication molecules will interact with targets relevant to disease. It utilizes scoring functions to determine binding affinity and places ligands in the active site of proteins. It was commonly used to quickly screen FDA-approved medications during the COVID-19 pandemic. Although it is quick and target-specific, experimental validation is still necessary because its accuracy depends on the quality of protein structures and scoring algorithms. Tools like AlphaFold2 generate high-confidence protein models that these platforms typically use. These upgrades now enable us to virtually screen billions of molecules against projected targets in only a few days. Compared to traditional experimental methods, this makes finding hits easier. Structure-based virtual screening is beneficial for drug repurposing, especially when no experimental 3D structures are available. This is especially true when it is used with computational binding-site identification. In addition to this strategy, ligand-based methods, suchas quantitative structure–activity correlations and pharmacophore modelling, assist scientists in finding new ways to use pharmaceuticals by looking at how similar chemicals are and how they work in living things. These approaches seek to identify for off-target effects or new linkages between diseases in big chemical and bioactivity datasets from ZINC, ChEMBL, and DrugBank. DrugBank, ReFRAME, COVID-19 Open Research Dataset and Evidence (CORDITE), SMPDB, and the LINCS/CMap resource are all examples of centralized databases and knowledge repositories. Together, they give you entire, annotated datasets that contain medications, targets, pathways, and transcriptome responses. These technologies aid in candidate triage, hypothesis formulation, and cross-referencing, which makes the drug repurposing process work better on a wide scale. Deeper AI-driven learning modthat further improve prediction accuracy are made possible by these computational discoveries.

Table 4: Key databases and initiatives

Database	Purpose	Managed by
Cordite	COVID-19 drug repurposing database	Charité Berlin
ReFRAME	12,000-compound repurposing library	Scripps Research Institute
DrugBank COVID-19	Drug and interaction database	DrugBank. ca
NCATS OpenData Portal	Preclinical repurposing data	NCATS
WHO solidarity trials	Global clinical trial registry	World Health Organization
COVID-19 data portal (EU)	Genomics and compound data	European Bioinformatics Institute (EMBL-EBI)

CORDITE: COVID-19 Open Research Dataset and Evidence, ReFRAME: Repurposing, focused rescue, and accelerated medchem, NCATS: National Center for Advancing Translational Sciences, World Health Organization, EU-European Union, EMBL-European Molecular Biology Laboratory.

AI and ML

By utilizing extensive scientific datasets to forecast medication-disease associations, treatment outcomes, and toxicity, AI and ML improve drug repurposing. By identifying intricate patterns in chemical, biological, and clinical data, sophisticated models like deep learning and graph neural networks (GNNs) enhance drug-target and drug-disease predictions. SMILES, protein characteristics, and omics data are utilized by tools like DeepDrug and GNN-based models to rapidly screen vast chemical spaces and identify COVID-19 candidates. But issues, including unbalanced data, poor interpretability, and overfitting hazards, still exist [34]. Network-based models and deep learning algorithms are vital for current medication repurposing because they help us understand how drugs and diseases are connected by providing us with much data that we can use to scale up our

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research. Network proximity, diffusion, random walks, and knowledge graph embedding are all graph-based methodologies that reveal the relationships between medications, targets, and diseases. SAveRUNNER, NetTAG, and deepDTnet are technologies that use protein-protein interaction networks and drug-target associations to uncover potential candidates for drug combinations and repurposing. The Heterogeneous Graph Transformer architecture enhancesand improves scalability and the capacity to combine data from different sources, improving the drug-disease score using a large knowledge graph. Deep learning models, such as GNNs, autoencoders, convolutional neural networks, recurrent neural networks, and multilayer perceptrons, are utilized to forecast drug-target interactions, efficacy, and toxicity from complex biomedical data. DeepDR, AI DrugNet, and deepDTnet are well-known technologies demonstrating how structural, phenotypic, and network data may help find the best candidates. AI-driven predictive toxicity and efficacy modeling technologies such asDeepCE and GAN-based algorithms, assist in determining ADMET profiles and therapeutic potential by examining transcriptome signatures, chemical properties, and clinical notes. These methods have accelerated and the repurposing of medications for COVID-19 and other complicated diseases by getting rid of candidates that aren't suitable before *in vivo* testing. This builds a bridge toward omics-based approaches, where molecular biological signatures are incorporated into repurposing decisions.

Table 5: Key AI platforms

Platform/Tool	Function	Notable output
BenevolentAI	Knowledge graph-based ML for drug-target prediction	Predicted BARI for COVID-19
Deep drug	Deep learning model for drug-protein interactions	Predicted antivirals and JAK inhibitors
Alpha fold (Deep mind)	Protein structure prediction	Provided 3D models of SARS-CoV-2 proteins
CANDO	Shotgun multitarget repurposing platform	Ranked candidate antivirals
AI4COVID-19	NLP-based literature screening	Identified high-value clinical trial data

AI: Artificial intelligence, ML: Machine learning, BARI: Baricitinib, JAK: Janus kinase, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CANDO: Computational analysis of novel drug opportunities, NLP: Natural language processing.

Omics-driven strategies

Proteomics, metabolomics, and transcriptomics are omics platforms that connect disease markers with drug-induced molecular alterations. They provide excellent mechanistic insights into host-virus interactions and immunological dysfunction in COVID-19 by matching disorders with medications that can modify dysregulated pathways found in genomic and molecular data. However, for accurate predictions, omics datasets often exhibit substantial variability and call for sophisticated computational integration. Transcriptomic reversal studies utilizing L1000/CMap and LINCS datasets identify discernible treatments exhibiting gene expression profiles distinct from pathological states. Using tools like LINCS and the Connectivity Map (CMap), transcriptomic reversal identifies medications that can reverse alterations in gene expression associated with illness. Strong negative correlations between drug transcription patterns and illness signatures indicate therapeutic potential. Although constraints, including cell-line variability and discrepancies between in vitro and in vivo transcriptomes, can affect accuracy, this strategy helped prioritize host-targeted therapeutics for SARS-CoV-2. These multi-omics methods demonstrate the connection between treatment activity and disease biology when combined with proteomics and metabolomics. This helps scientists organize molecules in order based on their biological levels. We can utilize SMPDB to map metabolite changes and routes to better understand how drugs work. Computational techniques are also used in disease signature and reversal analysis frameworks to compare gene expression profiles from diseases (such as RNA sequencing or patient omics data) with changes in transcription caused by drugs. DeepCE and other advanced platforms that utilize generative adversarial networks and graph convolutional networks found options for repurposing SARS-CoV-2, such as faldaprevir and alisporivir. This omics-based approach has effectively enabled substantial medication repurposing by connecting biological pathways with therapeutic concepts [35-40]. These biological shifts from theoretical computation to practical experimental validation required for real-world clinical advancement are supported by these biological insights.

From bench to bedside: pathways and protocols

Structured regulatory pathways backed by *in vitro*, *in vivo*, and early clinical evidence are necessary for the transition from computational prediction to clinical use. Getting repurposed pharmaceuticals from the preclinical stage to clinical use is not easy. Many rules and protocols need to be followed. The first step is to collect preclinical data from *in vitro*, *in vivo* (animal), and in silico investigations to provide a firm biological basis for the study. Phase I and II clinical trials typically assess how well a drug works for the new purpose. The trials can be shorter if the treatment is already approved for other uses. Different places have different ways of doing things. One example is the 505(b)(2) method or EUAs in the U. S. It uses safety and efficacy data already available to reduce the requirement for extra clinical studies. In the EU or India, quick approval processes also permit submissions based on literature and real-world examples. Ethical considerations, including transparency, informed consent, and the hazards associated with off-label use, are paramount, even when the drug's safety profile is well established. A successful transition from care to clinic is generally propelled by robust mechanistic evidence, such as molecular docking or omics-based signatures, and facilitated through pilot dosing studies (often utilizing platforms like AGILE), ultimately advancing to larger adaptive or conventional randomized controlled trials (RCTs) contingent upon favourable initial outcomes. Drugs that show promising early results enter structured study formats, including adaptive trial systems, with this foundation.

Adaptive clinical trial designs for repurposing

Clinical evaluation of repurposed pharmaceuticals is made more flexible, quicker, and less resource-intensive by adaptive trial designs, particularly platform trials, which allow real-time adjustment of study arms, dosing, and recruitment tactics. Platform and multi-arm multi-stage studies enable you to simultaneously test numerous drugs or drug combinations against a common control group. This means that if one treatment arm isn't working, it may be stopped or replaced throughout the trial, which saves resources. With Bayesian adaptive systems, such as the agile platform in the UK, you can adjust the dose or treatment allocation immediately. This makes first-in-human repurposing studies go faster. Major COVID-19 platform trials, including Recovery, Solidarity, and Remap-Cap, featured many participants worldwide. They gave us over 90% of the clinical data to make international treatment guidelines. Adaptive designs have significantly reduced trial completion times relative to conventional RCTs, achieving a median reduction of approximately 56 days, while maintaining stringent oversight of statistical error rates. These adaptive platforms reinforce evidence generation required for guidelines and regulatory decision-making, and they significantly reduce development timelines.

The COVID-19 pandemic as a catalyst: case studies and outcomes

Speeding up computational methods

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The COVID-19 pandemic accelerated and expedited the use of AI, machine learning, systems biology, and *in silico* screening platforms, enabling rapid identification, screening, and prioritization of drug repurposing options. These methods made it feasible to look at thousands of FDA-approved medications online to determine if they can fight viruses, reduce inflammation, or change the immune system. Deep learning models such asDeepDrug and Mol2Vec could accurately predict how medications interact with their targets. Gordon *et al.* (2020) demonstrated that network pharmacology made it easier to map host-pathogen interactomes and find therapeutic nodes. By mapping disease genes onto protein–protein interactions and aligning them with known therapeutic targets, network pharmacology sees diseases as perturbations in interconnected gene and protein networks. For complicated circumstances like COVID-19, this systems-level method is useful since it finds multi-target processes. Nevertheless, inadequate interactome data and noise might result in false positives, necessitating additional biological validation. These projects relied on several specialist databases. CORDITE, ReFRAME, and the COVID-19 OpenData Portal all had real-time datasets on drug candidates, mechanisms, and clinical trial outcomes. Using ML algorithms, RepurposeDB and DrugBank ranked candidates for repurposing based on their performance and biological relevancee. AI-assisted screening discovered BARI, a Janus kinase inhibitor approved for treating COVID-19. These new concepts showed that employing computers can significantly accelerate the discovery of new drugs. The pandemic has shown that computational drug repurposing can shorten the discovery cycle from years to months [39]. This shift in how pharmaceuticals are manufactured highlights the importance of using data-driven methods to respond quickly to global health catastrophes. The evaluation of regulatory responses such as EUAs, and the subsequent mixed results were made possible by these computational gains.

EUAs and failures

EUAs were granted by regulatory organizations during the COVID-19 pandemic to facilitate the quick distribution of potentially useful repurposed medications based on preliminary data. There was considerable debate about this procedure because of the data quality that backed it up, but it was essential to offer speedy treatment options. Many medications used for other things received EUAs, which had a significant effect. During COVID-19, the repurposing of various existing drugs under EUAs. The US FDAapproved REM in October 2020, created for Ebola. DXM, an anti-inflammatory corticosteroid, has been shownto help reduce mortality in ventilated patients. Furthermore, BARI, a JAK inhibitor, received a grant from the EUAs to be used along with REM in inpatient COVID-19 patients. Not all repurposed drugs may respond clinically as expected. Clinical trials revealed that HCQ, once widely promoted, was found ineffective and had safety concerns, resulting in withdrawal from EUAs. Another antiviral combination, lopinavir/ritonavir, failed in randomised clinical trials. Despite global research, ivermectinhas not shown any benefits in studies such as the TOGETHER trials. These results highlighted the importance of strong and reliable scientific evidence even when the results are uncertain. Insufficient or poorly designed drugs can show misleading results, or uncertain recommendations can erode the public's confidence and complicate policymakers' challenges. Thus, the EUAsspecify both the benefits and limitations of the regulatory emergencies during a global crisis. Stronger frameworks for generating evidence and more systematic learning for future outbreaks were highlighted by the mixed success of EUA-approved drugs.

Table 6: Timeline of EUAs and repurposed drugs during COVID-19

Drug	Original indication	Repurposed use	EUAs/approval date	Outcome	Key supporting evidence
REM	Ebola virus (antiviral)	COVID-19	EUAs: May 2020 FDA approval: Oct 2020	Approved; modest effect on recovery time.	ACTT-1 trial
HCQ	Malaria, lupus	COVID-19	EUAs: March 2020 Revoked: June 2020	Ineffective; cardiac risks observed.	Observational studies; halted RCT arms.
Lopinavir/ritonavir	HIV	COVID-19	N/A (trial use only)	Failed in multiple trials	RECOVERY; SOLIDARITY trials
DXM	Inflammation, arthritis	Severe COVID-19	Widely adopted: June 2020	Proven reduction in mortality	RECOVERY trial
BARI	Rheumatoid arthritis (JAK inhibitor)	COVID-19 inflammation	EUAs: Nov 2020	Later included in treatment guidelines	ACTT-2 trial
Tocilizumab (TCZ)	Rheumatoid arthritis (IL-6 inhibitor)	Cytokine storm in COVID-19	EUAs: June 2021	Approved for certain severe cases	RECOVERY and REMAP-CAP trials
Fluvoxamine	Depression, OCD	COVID-19	Trial stage	Promising, under further investigation	TOGETHER trial

EUAs: Emergency use authorization, REM: Remdesivir, FDA: Food and Drug Administration, ACTT: Adaptive COVID-19 treatment trial-1, HCQ: Hydroxychloroquine, RCT: Randomized controlled trial, HIV: Human immunodeficiency virus, DXM: Dexamethasone, BARI: Baricitinib, IL: Interleukin, OCD: Obsessive compulsive disorder.

Consequences for future repurposing after COVID

Drug repurposing is now a crucial part of global health planning as post-pandemic global health organizations explicitly incorporate it into preparedness and response plans. Implementingrepurposing frameworks within institutions is an important step forward. The US National Institutes of Health, the EMA, and the Indian Council of Medical Research all have plans on how to respond to and prepare for a pandemic that include drug repurposing. The WHO solidarity trials demonstrated that large, flexible clinical trials can rapidly uncover proof that drugs can be used in different groups of individuals. Adding AI and RWD to new ways of repurposing is another crucial step. Wearable gadgets, genomic analysis, and electronic health records (EHRs) are all used to match medications to specific patient categories more efficiently. This plan aligns RWE with RCTs, thereby speeding up the process of making evidence-based decisions. The epidemic has also led to new rules that make it easier and safer to provide the go-ahead for emergency medications. There is a growing movement to make conditional approval for repurposed pharmaceuticals official, especially in emergencies. There is also extensive post-marketing surveillance to keep track of long-term impacts. The principles of drug repurposing applynot only to infectious diseases but also other therapeutic areas. The efficacy of anti-inflammatory medications such as DXM in managing severe COVID-19 has resulted in the adoption of analogous therapies in oncology, neurology, and other rare disorders. Researchers are looking into antidepressants like fluvoxamine for neuroinflammation and long-term COVID symptoms. In Nature Reviews Medicinal Discovery Mullard contends that "COVID-19 has transformed drug repurposing from a side strategy into a mainstream tool for public health defense." Repurposing will be essential for robust, flexible, and adaptable treatment frameworks [3, 8, 13, 41-43]. This change also highlights the importance of actual results, such as which therapeutic candidates ultimately succeeded or failed.

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Table 5: Key AI platforms

Platform/tool	Function	Notable output
Benevolent AI	Knowledge graph-based ML for drug-target prediction	Predicted BARI for COVID-19
Deep drug	Deep learning model for drug-protein interactions	Predicted antivirals and JAK inhibitors
Alpha fold (Deep Mind)	Protein structure prediction	Provided 3D models of SARS-CoV-2 proteins
CANDO	Shotgun multitarget repurposing platform	Ranked candidate antivirals
AI4COVID-19	NLP-based literature screening	Identified high-value clinical trial data

Important examples: candidates who did and didn't make it

Despite initial optimism, several repurposed drugs showed convincing clinical success, while others failed to show meaningful benefit. AI-driven screening initially found BARI. Then, the ACTT-2 and COV-BARRIER trials verified this by showing that it cut down on recovery time and death rates. This led to an EUA in November 2020 and full FDA clearance for hospital patients in 2022. The UK RECOVERY trial showed that DXM dramatically cut the fatality rate among patients on ventilators. It was rapidly incorporated into treatment guidelines all around the world. TCZ was studied in the RECOVERY and REMAP-CAP trials, and it was found to lessen the death rate in patients who needed oxygen assistance after 28 days. It is now routinely utilized in severe conditions. On the other hand, several candidates who were given new jobs failed or caused problems. In March 2020, HCQ and chloroquine were given EUAs, but big trials after, including RECOVERY, proved that they didn't help and were dangerous; therefore, the EUAswere taken away by June 2020. Lopinavir/ritonavir did not work in pivotal trials like SOLIDARITY and RECOVERY, even though it was thought it would. Several countries utilized favipiravir (FPV) and umifenovir in an emergency. Still, a 2024 Cochrane review and meta-analyses indicated that they didn't significantly change the number of deaths or the requirement for ventilation. Fluvoxamine showed promise in small outpatient trials, but the FDA turned down its EUAs in 2022 because there wasn't enough evidence to support it [44-46]. A deeper analysis of individual case studies to understand what drives clinical success in repurposing was prompted by these differentiated outcomes.

Case studies in post-COVID drug repurposing

In-depth case studies helpilluminate how different mechanisms, developmental trajectories, and evidence quality impacted actual clinical adoption. Antiviral agents provide the first major category among these case studies, demonstrating varied but instructive clinical experiences.

Reusing antivirals (REM, FPV)

REM and FPV, two repurposed antivirals, demonstrated inconsistent efficacy across various patient populations and study designs. The FDA grantedfull REM approval for use in on children aged 12 and older with COVID-19 in the hospital in October 2020. In 2022, it was also used on high-risk outpatients 28 days old or older. Clinical studies and meta-analyses demonstrated that REM lowers the risk of death by a moderate amount that is statistically significant, as well as the time it takes to recover from a clinical condition by about four days. It also lowers the risk of serious side effects. A Phase II randomized experiment in the UK examines how well giving individuals with long-term COVID once-daily intravenous REM for 10 days works. The results are expected to be announced in early 2024. FPV EUAsweregiven to treat mild to moderate COVID-19 in several countries, such as Japan, India, and Turkey. A meta-review from September 2020 indicated that the infection resolved more quicklyand showed awaysome improvement on X-rays, but it didn't establish that it was better at preventing death. A Cochrane review published in February 2024 found that FPV exerted minimal impact on mortality, hospitalization duration, mechanical ventilation requirements, or adverse outcomes. These results prompted researchers to investigate other drug classes, especially immunomodulatory and anti-inflammatory treatments.

Anti-inflammatory and immunomodulatory drugs

During COVID-19, targeting the inflammatory cascade provided an alternative therapeutic pathway that resulted in several successful repurposed treatments. BARI is a JAK1/2 inhibitor that also stops AAK1, preventingit from working to combat viruses. It has been demonstrated to be effective in the clinic for treating COVID-19. The ACTT-2 study found that taking BARI and REM combined sped up both the healing process and the progression of the disease. The COV-BARRIER experiment (n = 1,525) also showed that the probability of death within 28 days decreased by 38.2%, and 20 persons had to be treated to see this benefit. The drug obtained EUAs in November 2020, full FDA approval in May 2022 the WHO now says it should be used for severe or critical COVID-19 cases. Anakinra is an interleukin (IL)-1 receptor blocker that helps with hyperinflammation. A meta-analysis of nine studies, involving approximately 1,119 people, demonstrated its efficacy. The results reveal that patients who are in the hospital but not on a ventilator need less mechanical breathing and have a decreased chance of death, with no increase in bad events. The EMA approved expanding Kineret's use in December 2021 for high-risk COVID-19 patients with greater soluble urokinase-type plasminogen activator receptor levels. The RECOVERY and REMAP-CAP investigations found that TCZ, an IL-6 receptor antagonist, helped lower the fatality rate in severe cases when used with frequent corticosteroid therapy. Infliximab, an anti-TNFα medication, has shown initial promise in observational studies for improving oxygenation, with ongoing trials assessing its efficacy. A Cochrane review highlightsthat many repurposed drugs now under investigation, such as colchicine, canakinumab, nintedanib, pirfenidone, ivermectin, N-acetylcysteine, and sildenafil, have been chosen for their potential to modulate cytokine storms or enhance endothelial function in COVID-19. Expanding research into the long-term neurological and cardiovascular effects of COVID-19 was also encouraged by clinical progress in these categories.

Neurological and cardiovascular implications

Interest in repurposing cardiovascular and neuroactive drugs for post-acute complications was sparked by the long-term vascular and neurological symptoms of COVID-19. Endothelial dysfunction is a significant symptom of long-term COVID. The TUN EndCOV study, which included 290 patients, demonstrated a substantialimprovement in endothelial function and a decrease in symptoms, including chest pain and palpitations, following three weeks of sulodexide treatment. A larger, placebo-controlled experiment (NCT05371925) is currently undergoing to assess effectiveness over a longer period, with a focus on a broader range of thrombotic and inflammatory outcomes. Researchers are investigating pharmacological therapies for those who have postural tachycardia syndrome and heart palpitations after getting COVID-19. Beta-blocker metoprolol is being studied in an open-label randomized controlled study (NCT05096884). In a tiny research, ivabradine, a medication that lowers heart rate, worked better than carvedilol without causing low blood pressure. COVID-19 raises the long-term risk of cardiac problems like stroke, atrial fibrillation, acute coronary syndrome, myocarditis, and heart failure. The hazard ratios range from 1.5 to 1.7, indicating that every 1,000 survivors has much work to do. Repurposing cardiovascular preventive drugs such as statins, ACE inhibitors, and anti-inflammatory pharmaceuticals like sulodexide, which stabilize the endothelium, may mitigate cardiovascular problems associated with extended COVID [2, 7, 8, 47]. This necessitates validation through randomized studies. To confirm their long-term clinical value and inform standardized treatment protocols, many of these applications still require large, controlled studies.

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Challenges and limitations

Data bias and model overfitting

Despite tremendous advancements, the quality, completeness, and balance of underlying datasets continue to pose substantial challenges to AI-based drug repurposing, thereby limiting its current utility in clinical settings and reducing its reliability. Datasets that are not balanced or skewed are a big problem. Many models use old data that doesn't really show how drugs are used or how well they work. This hinders predictions and makes it hard for the model to find effective treatments for drug-disease combinations that aren't well represented. Supervised learning models that perform well on training datasets but have trouble using what they've learnt in new contexts, without much testing, commonly overfit. Deep learning architectures and GNNs are examples of complex models that are often "black boxes," meaning they are difficult to understand. This makes it harder for doctors and regulators to trust AI predictions. Secular trend bias is a big problem in clinical predictive modeling. If not handled correctly, changes in clinical processes and new standard-of-care medications could induce temporal confounding, making algorithmic outcomes less trustworthy and accurate. To improve clinical reliability, these analytical challenges underscore the need for more transparent interpretable models and continuously updated data resources.

Off-target effects and drug-drug interactions (DDIs)

Drug repurposing still raises serious safety and pharmacological issues despite its therapeutic benefits, especially when it comes to polypharmacology and changed dosage schedules. Polypharmacology is hard because many small medicines work on more than one protein target. This could lead to new ways to cure illnesses, but also raises the risk of side effects and other problems. In polypharmacy, repurposed drugs may be utilized without a DDI assessment. AI-based DDI prediction models are in the development works, but must be tested in a clinical setting first. New uses may require different dose schedules, which could alter how a drug works and its safety. It's hard to trust repurposed agents because there isn't enough or up-to-date toxicological data, especially for those who are more likely to be harmed, such as the elderly, children, or people with numerous health problems. New safety studies are needed to make sure they are used correctly. Therefore, to guarantee that repurposed candidates can be used safely across diverse patient populations, systematic preclinical and clinical validation remains essential.

IP and regulatory gaps

Drug repurposing holds as great scientific promise, but in addition to scientific difficulties, legal, regulatory, and commercial obstacles frequently prevent it from being implemented. Even when new uses for off-patent pharmaceuticals have been clinically proven, they still lack intellectual property protection, which makes them less appealing to businesses due to competition from generic drugs. With patent ever greening and complicated patent landscapes, such as secondary or overlapping family patents, it can be challenging to get chemicals on the shelf. Beingunable to assess data is a significant problem. Pharmaceutical corporations typically keep the outcomes of unsuccessful experiments or information regarding substances no longer being utilized a secret. Researchers also face challenges in working together more efficientlybecause of proprietary issues and Material Transfer Agreements. Regulatory problems are enormous, especially for academic or non-profit entities that can't sell their goods. Agencies are requesting more precise toxicological data, which may be challenging to find or procure for older medications. Many academic repurposing initiatives lack motivation or knowledge of the rules. Generics don't have commercial support and a regulatory environment that considers risks, making it hard to turn repurposed candidates into approved medicines and get funding [48–52]. As a result, many successful repurposing opportunities fail to achieve market adoption, underscoring the need for more transparent incentives and streamlined regulatory pathways.

Regulatory and commercial challenges in drug repurposing

Due to the lack of intellectual property protection for off-patent medications, which lowers investment incentives and restricts their advancement from discovery to clinical approval and practical usage, drug repurposing confronts significant financial and regulatory obstacles. Several lawshelps lower these obstacles. The FDA 505(b)(2) pathway permits the use of current safety and clinical data while giving limited exclusivity, which accelerates development and increases commercial viability. By offering monetary value through tradable awards that prolong exclusivity for another product, proposed transferable data-exclusivity vouchers could encourage repurposing even in the absence of patents.

Drug repurposing can be advanced in global health sectors where typical market incentives are weak through mission-driven funding, shared resources, and open-science collaboration, as demonstrated by non-profit and public-private models such as DNDi and Cures Within Reach. Finding a balance between quick patient access and rigorous evidentiary criteria is a significant regulatory challenge. During the COVID-19 pandemic, EUAs expedited access; however, early approvals, such as HCQ without sufficient data, led to misunderstandings and decline in public confidence. On the other hand, adaptive trials like RECOVERY and SOLIDARITY have shown that repurposed medications can be assessed rapidly without sacrificing scientific integrity. In the future, a viable drug-repurposing ecosystem will require more stringent evidence criteria, enhanced regulatory frameworks, and creative funding mechanisms [2, 53].

Table 7: Key challenges

Challenge domain	Mainissues	Potential mitigations
Data and algorithms	Biased datasets, overfitting, model opacity, and secular trend confounders	Development of transparent models, diverse datasets, bias-correction pipelines, rigorous external validation
Safety and pharmacology	Off-target risks, DDIs, mismatched dosing, and outdated toxicology	Adaptive PKs/PD modeling, improved preclinical profiling, real-world safety analytics, and dose-optimization trials
IP and regulation	Weak patents, data silos, regulatory burdens, and economic disincentives	Patent-extension incentives, open-science consortia, harmonized regulatory pathways, public-private funding models

DDIs: Drug-drug interactions, PKs/PD: Pharmacokinetics/Pharmacodynamics. IP: Intellectual property.

Future paths andopportunities

Incorporation of RWE

The integration of RWE has emerged as a key driver of identifying and validating new therapeutic uses more efficiently as repurposing strategies continue to mature. Drug repurposing benefits from RWD's capacity to develop and test novel ideas. EHRs, insurance claims, patient registries, and wearable devices facilitate extensive analysis to identify potential new applications for existing drugs. A scoping review of studies conducted from 2010 to 2022 identified 250 relevant investigations, comprising 36 focused on hypothesis generation and 101 on hypothesis validation. There are

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still issues, such as a lack of precise data, factors that complicate things more complicated, and rules that aren't clear. Regulatory frameworks are shifting to make it easier to use RWE. The 21st Century Cures Act in the US and later FDA guidelines clarify that RWE should be used to add information to medicine labels and approve drugs that have been repurposed. The FDA-supported CURE Drug Repurposing Collaboratory and other harmonization tools have made platforms like the Edge Tool better for people to use RWD. This application streamlines the process of making and put it into standard data models by automating the steps. Federated real-world networks, such as DARWIN EU, which began in 2022, employ the OMOP standard data model to bring together health data from various European sources while keeping the identities of the people involved private. This facilitates drug repurposing programs and enables regulators tocollaborate across borders. When taken as a whole, these developments show that standardized, regulator-accepted RWE ecosystems will increasingly support approval, labeling expansion, and post-marketing refinement of repurposed drugs.

Personalized repurposing and medicine with precision

Repurposing is moving away from broad population strategies and toward precision frameworks tailored to individual biological and clinical characteristics due to advancements in genomics and patient-level profiling. More and more, new drug repurposing frameworks combineRWD and molecular profiling to make the process more accurate and efficient. STEDR demonstrates that EHR-integrated subgroup emulation facilitates the execution of several "virtual trials" to evaluate the effects of medications on various patient groups. In Alzheimer's disease, STEDR identified 14 prospective drugs precisely tailored for distinct qualities. Phenome-wide association studies, which connect genome-wide association studies with EHRs, have shown roughly 53,000 links between diseases and medications. One-third of these have been corroborated by clinical trials or literature, indicating that genetics-informed drug repurposing possesses significant promise. Tools like ASGARD, which use single-cell RNA sequencing data, are far more accurate (AUC 0.92) than bulk-cell methods for finding new uses for drugs for diseases like breast cancer, leukemia, and COVID-19. In oncology, drug repurposing platforms for leukemia and other cancers highlight the significance of genetic tumor characterisation in broadening therapeutic alternatives. These approaches are so exact that they only work for a few people. It is challenging to set rates, get paid back, and ensure everyone has equal access. We need to develop value-based frameworks and clear regulations to remedy this. Wider adoption in the future will depend on creating equitable access pathways and sustainable reimbursement models that enable precision repurposing to benefit real-world patient populations.

Public-private collaborations and open-science platforms

Data, compound libraries, and evaluation tools are being shared globally through open innovation networks and multi-institution collaborations, which are increasingly transforming drug repurposing. Nonprofit and open-science programs accelerate the process of repurposing drugs, particularly for rare or unknown diseases. Every Cure's AI platform, MATRIX, looks at several drug-disease combinations each week and assigns scores to them. It then makes the best ones public to speed up treatments for rare diseases. The PostEra COVID Moonshot and the JEDI Grand Challenge are examples of open research since they let people worldwide design, construct, and test SARS-CoV-2 inhibitors and share all the data with the public. Partnerships between the public and private sectors are very significant. For example, the European Lead Factory brings together academics, small and medium-sized businesses, and pharmaceutical companies to improve chemical screening and lead identification. Global projects like WIPO Re: Search and the GHIT Fund, facilitate the transfer intellectual property without paying royalties and encourage businesses from different fields to work together. They also allow researchers access to key compound libraries for diseases that aren't receiving sufficient attention or are still in the early stages of development, where traditional business motivations aren't as strong [54–58]. These cooperative models demonstratehowimproving shared infrastructure and reducing intellectual property barriers can speed up translation, particularly for neglected and low-commercial-value therapeutic areas.

DISCUSSION

The COVID-19 pandemic operated as both a stimulus and a stress test for global drug-repurposing efforts, exposing strengths, flaws, and vital lessons for future preparedness. It encouraged computational, clinical, and regulatory innovation while revealing methodological and ethical inadequacies.

The disparate results of HCQ and BARI underscore the key important factors that determine the effectiveness of repurposing. Because AI-based predictions matched mechanistic plausibility and were verified by rigorous trials such as ACTT-2 and COV-BARRIER, which resulted in regulatory approval, BARI was successful. Despite early in vitro promise, HCQ raised safety concerns and failed in large RCTs like SOLIDARITY and RECOVERY, underscoring the risk of hasty adoption without adequate validation.

The pandemic led to change a shift in repurposing from a reactive strategy to a more methodical, data-driven science backed by AI, network pharmacology, real-world data, and extensive platform trials like Solidarity, Recovery, and Activ. These efforts stressed standardized methodology, reproducibility, and open data sharing.

There are still issues with AI bias, openness, and repeatability as the area grows more data-intensive. Meeting these expectations will require interdisciplinary collaboration, global data-sharing, and explainable AI that can earn scientific and regulatory trust.

All things considered, COVID-19 showed the promise of computational repurposing while also highlighting the necessity of collaborative infrastructures, clinical rigor, and mechanistic validation. These lessons have changed medication repurposing into a more systematic, evidence-based, and sustainable discipline for future therapeutic innovation [59].

CONCLUSION

Drug repurposing changed from an opportunistic activity to an organized, data-driven field as a result of the COVID-19 outbreak. It expedited the application of ML, network pharmacology, omics platforms, and high-throughput screening coupled with real-world data, enabling faster identification and evaluation of candidates. The quick success of REM, BARI, and DXM demonstrated how open data sharing, regulatory flexibility, and predictive analytics may reduce the time from bench to bedside. AI-driven projects such as BenevolentAI and DeepDrug, supported target prediction, while massive worldwide trials like as RECOVERY and Solidarity verified medicines at scale.

In the post-COVID era, repurposing must transition from emergency use to a long-term, evidence-based strategy. Biological plausibility, mechanistic validation, iterative clinical testing, and unambiguous regulatory pathways are all necessary to justify computational predictions. Interpretable, bias-controlled AI models, together with integrated multi-omics, EHR, genomic, and RWD systems, will increase precision medicine. Adaptive trial designs and harmonized worldwide networks will allow faster and more trustworthy assessments.

Strong data ecosystems, open-science cooperation, and solutions to data bias, trial diversity, IP hurdles, and equitable access are all necessary for future advancement. Overall, the pandemic proved that successful repurposing requires computational innovation, biological insight, and clinical

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rigor. To develop treatments for neglected and chronic diseases and to establish a robust and equitable global framework for future pandemics, politicians, researchers, and regulators must continue to collaborate.

ACKNOWLEDGEMENT

The authors acknowledge the support and encouragement provided by Bhaskar Pharmacy College and Joginapally B. R. Pharmacy College during the preparation of this review. We extend our profound gratitude to colleagues and peers for their valuable insights and feedback on the manuscript.

FUNDING

Nil

ABBREVIATIONS

PKs-Pharmacokinetics, REM-Remdesivir, DXM-Dexamethasone, BARI-Baricitinib, FDA-Food and Drug Administration, RWE-Real-World Evidence, HCQ-Hydroxychloroquine, EUAs-Emergency Use Authorizations, EMA-European Medicines Agency, NDA-New Drug Application, CORDITE-COVID-19 Open Research Dataset and Evidence, NCATS-National Center for Advancing Translational Sciences, AI-Artificial Intelligence, ML-Machine Learning, GNNs-Graph Neural Networks, RCTs-Randomized Controlled Trials, FPV-Favipiravir, IL-Interleukin, TCZ-Tocilizumab, TNF-Tumor Necrosis Factor, DDIs-Drug-Drug Interactions, RWD-Real-world data, EHRs-Electronic Health Records

AUTHORS CONTRIBUTIONS

Pedireddi Sobitha Rani carried out the literature search, wrote the review, and formulated the core idea. Pulla Udaya Chandrika, G. Susmitha, Lakshmi Devi Gottemukkula, and Mohd Abdul Hadi revised the manuscript and to ensure the references and the correctness of formatting. The final version was examined and approved by all authors.

CONFLICT OF INTERESTS

The authors declare that there are no competing interests.

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