

A REVIEW ON REPURPOSED DRUGS IN COVID-19 MANAGEMENT: A PHARMACEUTICAL AND CLINICAL PERSPECTIVE

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ABSTRACT

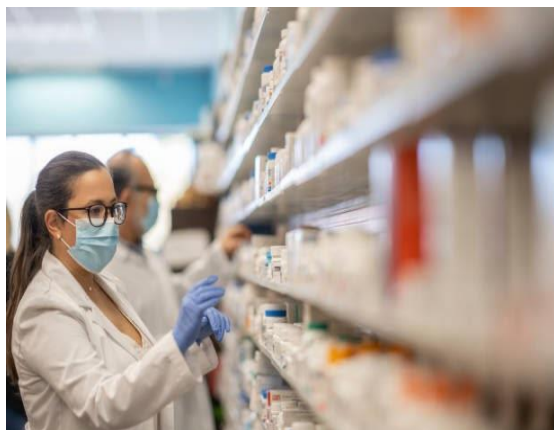
The COVID-19 pandemic, caused by SARS-CoV-2 in late 2019, created an urgent need for immediate treatments in the absence of specific vaccines and antivirals, making drug repurposing the most feasible strategy. This review evaluates the clinical utility of repurposed therapeutics for COVID-19 and emphasizes the vital role of pharmacy professionals. Initially, treatment was based on in-vitro evidence using antivirals, antimalarials, and antibiotics; however, as understanding of the disease progressed, management became more targeted. Antivirals like remdesivir and nirmatrelvir/ritonavir were used to control early viral replication, while immunomodulators such as dexamethasone, tocilizumab, and baricitinib proved life-saving in severe cases by controlling hyperinflammation. Additionally, anticoagulants addressed the thrombotic complications and monoclonal antibodies benefited high-risk outpatients. Furthermore, the review focuses on the safety, adverse effects, and the significant contributions of clinical pharmacists in dose optimization, drug interaction management, and pharmacovigilance, alongside pharmaceutical scientists who ensured formulation and supply chain stability. Despite challenges like the early use of ineffective drugs and inequitable global access, adaptive trials provided rapid evidence. Ultimately, lessons from COVID-19 repurposing offer a valuable blueprint for future pandemics through prepared drug libraries, AI-based screening, and permanent trial networks to build a more resilient healthcare system.

KEYWORDS: Drug Repurposing; COVID-19; SARS-CoV-2; Clinical Efficacy; Safety Profile; Clinical Pharmacy; Pharmaceutical Sciences; Pandemic Preparedness; Therapeutic Interventions.

1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): has been recognized as the most consequential global health crisis of the modern era. Initially reported in Wuhan, China in December 2019, the pathogen demonstrated remarkable transmissibility and within a few months spread to virtually every country. Consequently, on 11th March 2020, the World Health Organization officially declared COVID-19 a pandemic. Moreover, according to global surveillance data updated in 2025, more than 770 million confirmed cases and over 7 million deaths have been recorded worldwide. In addition, the pandemic has resulted in unprecedented disruptions to healthcare

delivery, economic stability, education, and social systems across the globe.^[1-3]



At the onset of the pandemic, the scientific and medical communities were confronted with a critical therapeutic gap. Specifically, there were no approved antiviral drugs or vaccines available for SARS-CoV-2. Therefore, there was an immediate and pressing need to identify treatment options that could be deployed rapidly. In this context, drug repurposing emerged as the most feasible and time-efficient strategy. Furthermore, drug repurposing, also referred to as drug repositioning or drug re-tasking, is defined as the application of existing, approved drugs for new therapeutic indications. Indeed, this approach presents multiple advantages compared to traditional drug discovery. To illustrate, repurposed agents have established pharmacokinetic and pharmacodynamic profiles, well-documented safety and toxicity data, and existing manufacturing infrastructure. As a result, the time required for preclinical development and regulatory approval can be reduced from several years to a few months.^[4-6]

The scientific rationale for repurposing in COVID-19 was further supported by growing knowledge of SARS-CoV-2 biology and pathogenesis. The virus enters host cells primarily via binding of the spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, followed by priming by TMPRSS2. Subsequently, viral replication depends on essential enzymes such as RNA-dependent RNA polymerase (RdRp) and the 3-chymotrypsin-like protease (3CLpro). Accordingly, antiviral agents that inhibit these targets in other RNA viruses became immediate candidates for testing. In parallel, it became evident that severe COVID-19 was associated with a dysregulated host immune response, often termed a "cytokine storm". Hence, immunomodulatory drugs previously used for rheumatoid arthritis, cancer, and transplantation were also considered for repurposing.^[7-9]

During the first year of the pandemic, 2020-2021, numerous drug classes were evaluated in clinical trials and real-world settings. Initially, broad-spectrum antivirals were among the first to be investigated. For example, remdesivir, a nucleotide analog originally developed for Ebola, and lopinavir/ritonavir, an HIV protease inhibitor combination, were among the earliest

candidates. Similarly, favipiravir, an influenza antiviral, was widely used in several countries. In contrast, antimalarial drugs such as hydroxychloroquine and chloroquine received significant public and political attention. However, large randomized controlled trials including the RECOVERY and SOLIDARITY trials subsequently demonstrated no clinical benefit and potential harms associated with these agents. On the other hand, a major breakthrough occurred with corticosteroids. Specifically, the RECOVERY trial showed that dexamethasone reduced 28-day mortality by one-third in patients receiving mechanical ventilation and by one-fifth in those receiving oxygen. Thus, dexamethasone became the first drug proven to reduce mortality and was rapidly incorporated into treatment guidelines globally.^[10-12]

As understanding of COVID-19 pathophysiology evolved, the therapeutic focus shifted toward host-directed therapies. For instance, elevated levels of interleukin-6 (IL-6) and other inflammatory cytokines were correlated with disease severity. Consequently, IL-6 receptor antagonists such as tocilizumab and sarilumab were repurposed from rheumatology. Likewise, Janus kinase (JAK) inhibitors including baricitinib, which modulate multiple cytokine signaling pathways, received emergency use authorization. Furthermore, the prothrombotic complications of COVID-19 led to widespread use of anticoagulants for both prophylaxis and treatment. In addition, antibiotics were frequently prescribed to manage suspected bacterial co-infections, although their benefit was limited in pure viral pneumonia.^[13-15]

The period between 2022 and 2023 marked a significant transition with the availability of oral antiviral therapies for outpatient use. Although nirmatrelvir/ritonavir (Paxlovid) and molnupiravir were developed specifically for coronaviruses, their mechanisms leveraged two decades of antiviral research. More importantly, clinical trials demonstrated that early administration of these agents significantly reduced the risk of hospitalization and death in high-risk individuals. Nevertheless, the use of Paxlovid was complicated by numerous drug-drug interactions due to ritonavir, a potent CYP3A4 inhibitor. Therefore, clinical pharmacists played an essential role in medication reconciliation and interaction screening.^[16-18]

Throughout the pandemic, the contribution of pharmaceutical sciences and clinical pharmacy extended far beyond traditional dispensing roles. Specifically, hospital and community pharmacists were at the forefront of evidence synthesis, guideline development, and therapeutic decision-making. In addition, they were responsible for dose adjustments in patients with renal or hepatic impairment, therapeutic drug monitoring, and identification of adverse drug reactions. Moreover, pharmacists led institutional pharmacovigilance programs to monitor the safety of drugs used off-label

under emergency authorizations. Consequently, the pandemic highlighted and expanded the scope of pharmacy practice in public health emergencies and underscored the need for greater integration of pharmacists into multidisciplinary care teams.^[19-21]

Despite the successes, the strategy of drug repurposing was not without significant small, single-center, and observational studies with methodological limitations. As a result, early in the pandemic there was considerable confusion and conflicting evidence. Second, the pressure to "do something" resulted in widespread off-label prescribing before robust data were available. Third, global demand surges led to critical shortages of essential medicines such as dexamethasone, tocilizumab, and sedatives in many low- and middle-income countries. Nevertheless, these challenges provided important lessons for pandemic preparedness, including the need for coordinated clinical trial networks and ethical frameworks for resource allocation.^[22-24]

Looking forward to 2026, COVID-19 has transitioned from a pandemic to an endemic respiratory illness in most parts of the world. However, the impact of drug repurposing on the COVID-19 response remains highly relevant. In essence, repurposing provided the only immediate therapeutic options during the first two years and saved countless lives. Beyond that, the experience accelerated drug development science, improved understanding of host-virus interactions, and demonstrated the value of adaptive platform trials. Furthermore, it emphasized the importance of maintaining libraries of approved drugs with potential broad-spectrum activity and investing in real-world evidence infrastructure. Therefore, future pandemic preparedness plans must prioritize these elements.^{[5][75]}

In conclusion, drug repurposing was central to the therapeutic response to COVID-19. While not every candidate proved effective, key successes including remdesivir, dexamethasone, tocilizumab, baricitinib, and oral antivirals significantly altered the course of the disease. Most importantly, the pandemic demonstrated that pharmaceutical expertise is indispensable in a public health crisis. Accordingly, this review seeks to provide a comprehensive pharmaceutical and clinical perspective on repurposed drugs in COVID-19 management, focusing on mechanisms of action, clinical evidence, safety considerations, and the evolving role of pharmacy practice in pandemic care.^[28,29]

2. Virology and Therapeutic Targets of SARS-CoV-2

Coronaviruses are large, enveloped, positive-sense RNA viruses belonging to the family *_Coronaviridae_*. Specifically, SARS-CoV-2 is a member of the *_Betacoronavirus_* genus, which also includes SARS-CoV and MERS-CoV. Structurally, the virion consists of four major structural proteins: spike (S): envelope (E): membrane (M): and nucleocapsid (N). Moreover, the genome of SARS-CoV-2 is approximately 30 kb in

length and encodes 16 non-structural proteins, 4 structural proteins, and several accessory proteins. Consequently, understanding the molecular architecture of the virus is fundamental to identifying druggable targets for therapeutic intervention.^[8]

The initial and most critical step in the SARS-CoV-2 life cycle is viral entry into host cells. This process is primarily mediated by the interaction between the viral spike protein and the host cell receptor angiotensin-converting enzyme 2 (ACE2). Furthermore, for efficient entry, the spike protein must be primed by host proteases, most notably transmembrane protease serine 2 (TMPRSS2) and cathepsin L. In addition, recent evidence suggests that other co-receptors such as neuropilin-1 and CD147 may facilitate viral attachment in certain tissues. Therefore, both ACE2 and TMPRSS2 represent logical targets for entry inhibitors. Indeed, monoclonal antibodies and soluble ACE2 decoys were among the earliest strategies explored to block this interaction.^[7,31]

Following receptor binding and membrane fusion, the viral RNA genome is released into the cytoplasm. Subsequently, the 5' two-thirds of the genome is translated to produce two large polyproteins, pp1a and pp1ab. Thereafter, these polyproteins are cleaved by two virally encoded proteases to generate 16 non-structural proteins that form the replication-transcription complex. Of these, the 3-chymotrypsin-like protease (3CLpro or Mpro) and the papain-like protease (PLpro) are essential for processing. In parallel, the RNA-dependent RNA polymerase (RdRp): encoded by nsp12, is responsible for viral RNA synthesis. Accordingly, both proteases and RdRp have been prioritized as primary targets for antiviral drug development because inhibiting them halts viral replication.^[33,36]

The replication process of SARS-CoV-2 involves the synthesis of both genomic and subgenomic RNAs. During this process, RdRp utilizes host cell machinery and requires cofactors such as nsp7 and nsp8 for processivity. In contrast to DNA viruses, RNA viruses lack proofreading capability, which results in a relatively high mutation rate. Nevertheless, coronaviruses possess an exonuclease activity, nsp14, that provides limited proofreading. As a result, the mutation rate of SARS-CoV-2 is moderate compared to other RNA viruses. This genetic plasticity has led to the emergence of multiple variants of concern, which further emphasizes the need for broad-spectrum antivirals targeting conserved viral enzymes.^[30]

Beyond viral replication, the pathogenesis of severe COVID-19 is largely driven by the host immune response. Specifically, SARS-CoV-2 infection triggers the activation of innate immune pathways, leading to the release of pro-inflammatory cytokines such as IL-6, IL-1 β , and TNF- α . Subsequently, in a subset of patients, this response becomes dysregulated and results in a

hyperinflammatory state commonly referred to as a "cytokine storm". Moreover, this immune dysregulation contributes to acute respiratory distress syndrome, multi-organ failure, and increased mortality. Hence, immunomodulatory agents that dampen excessive inflammation without impairing viral clearance became a key therapeutic strategy.^[9]

Another critical aspect of COVID-19 pathology is its prothrombotic nature. Endothelial dysfunction, platelet activation, and coagulation cascade abnormalities are frequently observed in hospitalized patients. In addition, elevated D-dimer levels and thromboembolic events are associated with poor prognosis. Consequently, the virus-induced endotheliitis and systemic inflammation create a hypercoagulable state. Therefore, anticoagulants and antiplatelet agents were repurposed to prevent and treat thrombotic complications. Likewise, the extrapulmonary manifestations of COVID-19, including cardiac, renal, and neurological involvement, broadened the scope of therapeutic targets beyond the lungs.^[15]

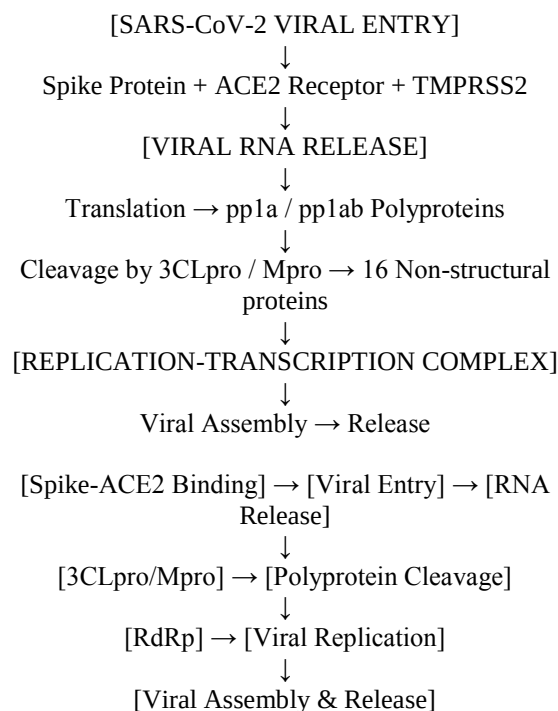
Based on this understanding of virology and pathogenesis, several classes of drugs were identified for repurposing. First, antivirals targeting RdRp, such as remdesivir and favipiravir, were investigated to directly inhibit viral RNA synthesis. Second, protease inhibitors like lopinavir/ritonavir and the 3CLpro inhibitor nirmatrelvir were developed to block polyprotein processing. Third, host-directed therapies including TMPRSS2 inhibitors and ACE2 blockers were explored to prevent viral entry. Fourth, immunomodulators such as corticosteroids, IL-6 inhibitors, and JAK inhibitors were used to control inflammation. Finally, supportive therapies including anticoagulants and antibiotics addressed secondary complications.^[10,47]

The success of a repurposed drug depends not only on its antiviral activity but also on its pharmacokinetic properties and safety profile. For instance, drugs must achieve adequate concentrations in the respiratory tract to be effective against SARS-CoV-2. Similarly, the timing of administration is crucial, with antivirals being most effective in the early viral phase and immunomodulators in the later inflammatory phase. In addition, drug-drug interactions, particularly with agents metabolized by CYP3A4, posed significant challenges in clinical management. Thus, a deep understanding of both virology and clinical pharmacology was essential for rational drug repurposing.^[63,64]

In summary, the virology of SARS-CoV-2 provides multiple actionable therapeutic targets across the viral life cycle. The spike-ACE2 interaction, viral proteases, and RdRp represent direct-acting antiviral targets. Meanwhile, host factors such as TMPRSS2 and immune mediators like IL-6 and JAK represent host-directed targets. Ultimately, the integration of virological knowledge with clinical data enabled the rapid identification and deployment of repurposed drugs

during the pandemic. Therefore, this section lays the foundation for the subsequent discussion on specific repurposed agents, their mechanisms, and clinical evidence.^[28,47]

Flow chart



Drug targets

- Target 1: ACE2, TMPRSS2 → Entry Inhibitors
- Target 2: 3CLpro/Mpro → Protease Inhibitors
- Target 3: RdRp → Nucleoside Analogues

Therapeutic Agents

1. Entry: ACE2, TMPRSS2 inhibitors
2. Replication: 3CLpro inhibitors, RdRp inhibitors

3. Major classes of repurposed drugs for covid19

The therapeutic response to COVID-19 was largely dependent on the rapid repurposing of existing drugs. Given the absence of specific therapies at the onset of the pandemic, the global research community systematically evaluated drugs from diverse pharmacological classes. Consequently, several major categories emerged based on their mechanism of action and stage of disease in which they were applied. Moreover, these classes can be broadly grouped into antivirals, immunomodulators, anticoagulants, and supportive agents. Therefore, understanding the rationale, clinical evidence, and limitations of each class is essential for appreciating the role of drug repurposing in pandemic management.^[47]

3.1 Antiviral Agents Targeting Viral Replication

The first line of pharmacological attack focused on directly inhibiting SARS-CoV-2 replication. To this end, nucleoside and nucleotide analogs were among the earliest candidates. Specifically, remdesivir, originally

developed for Ebola virus, functions as an adenosine analog that inhibits the viral RNA-dependent RNA polymerase (RdRp). Furthermore, the ACTT-1 trial demonstrated that remdesivir shortened the time to recovery in hospitalized patients. Similarly, favipiravir,

an influenza antiviral, and ribavirin were tested for their ability to terminate viral RNA synthesis. In contrast, the clinical benefit of these agents remained modest, particularly in severe disease, likely due to late administration.^[48-50]

Figure 3.1: SARS-CoV-2 Virion Structure

Schematic cross-section illustrating the structural components of the SARS-CoV-2 viral particle

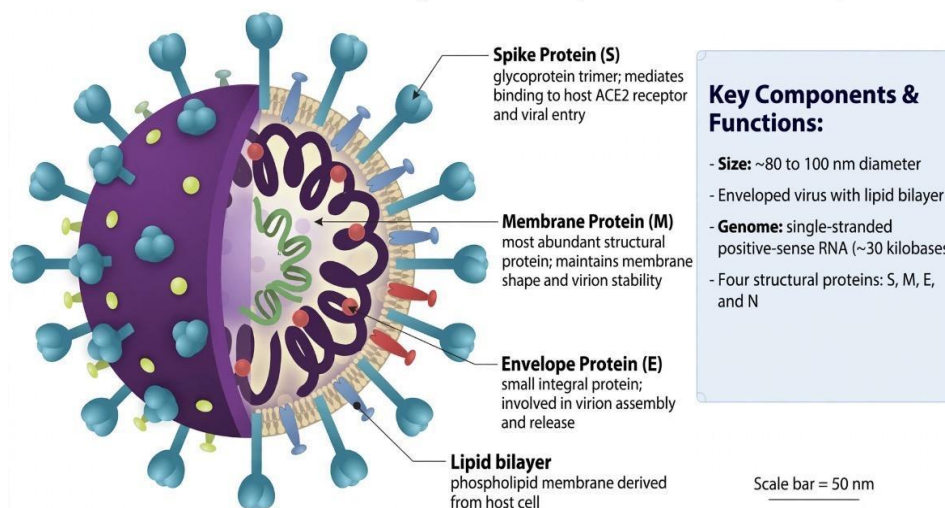


Illustration Style: Educational / Textbook

Figure 3.1. SARS-CoV-2 is an enveloped coronavirus. The ~30 kb positive-sense RNA genome is encapsidated by nucleocapsid (N) protein to form the helical nucleocapsid, which is surrounded by a lipid bilayer envelope embedded with Spike (S), Membrane (M), and Envelope (E) proteins.

In parallel, protease inhibitors represented another major antiviral strategy. The SARS-CoV-2 3-chymotrypsin-like protease (3CLpro or Mpro) is essential for cleaving viral polyproteins. Accordingly, lopinavir/ritonavir, an HIV protease inhibitor combination, was one of the first drugs to be repurposed. However, the RECOVERY and WHO SOLIDARITY trials failed to show mortality benefit. Subsequently, more specific 3CLpro inhibitors were developed. For instance, nirmatrelvir, co-administered with ritonavir as Paxlovid, demonstrated significant efficacy in reducing hospitalization and death in high-risk outpatients when given early. Thus, protease inhibition proved to be a more successful target than broad-spectrum RdRp.^[36,18]

3.2 Immunomodulatory and Antiinflammatory agents

As the pandemic progressed, it became clear that mortality in severe COVID-19 was driven more by host inflammation than by viral load. Therefore, immunomodulation became a central therapeutic pillar. Initially, corticosteroids were evaluated based on their broad anti-inflammatory effects. In particular, dexamethasone emerged as a landmark success. The RECOVERY trial showed a 28-day mortality reduction of 35% in patients on mechanical ventilation. As a result, low-dose dexamethasone became the standard of care for patients requiring oxygen support.^[13]

Subsequently, targeted cytokine inhibitors were investigated to address the "cytokine storm". Interleukin-6 (IL-6) is a key mediator of inflammation, and thus IL-6

receptor antagonists such as tocilizumab and sarilumab were repurposed from rheumatology. Moreover, meta-analyses of large platform trials including REMAP-CAP and RECOVERY confirmed survival benefit when combined with corticosteroids in critically ill patients. In addition, Janus kinase (JAK) inhibitors, including baricitinib and tofacitinib, gained attention due to their dual antiviral and anti-inflammatory properties. Notably, baricitinib plus remdesivir improved recovery time and reduced mortality. Hence, JAK inhibition offered a mechanistically distinct approach to immunomodulation.^[52-55]

During the early phase of the pandemic, antimalarial drugs received unprecedented attention. Hydroxychloroquine and chloroquine were hypothesized to have antiviral activity through interference with endosomal entry and immunomodulatory effects. Furthermore, initial small studies suggested potential benefit. However, large randomized trials including RECOVERY and WHO SOLIDARITY conclusively demonstrated no clinical benefit and potential cardiac toxicity. Consequently, regulatory agencies revoked emergency use authorizations. Nevertheless, this episode highlighted the importance of rigorous evidence before widespread adoption of repurposed drugs.^[37]

3.3 Monoclonal antibodies and Immune-Based Therapies

Another major class involved passive immunotherapy. Convalescent plasma was among the first to be used,

based on historical precedent in other viral infections. However, randomized trials showed limited and inconsistent benefit. In contrast, monoclonal antibodies targeting the spike protein, such as casirivimab/imdevimab and sotrovimab, demonstrated significant efficacy in preventing progression in early disease. Nevertheless, the emergence of viral variants led to reduced effectiveness of many early antibodies. Accordingly, this class underscored both the potential and the challenge of targeting a rapidly mutating virus.^[59-61]

3.4 Antibiotic and Antithrombotic Agents

A distinctive feature of severe COVID-19 is the prothrombotic state associated with endothelial injury and systemic inflammation. As a result, venous thromboembolism, pulmonary embolism, and microvascular thrombosis were commonly observed. Therefore, anticoagulants were widely repurposed for both prophylaxis and treatment. Specifically, low-molecular-weight heparin became standard for hospitalized patients. In addition, therapeutic-dose anticoagulation was evaluated in moderately ill patients, with some trials showing benefit. However, in critically ill patients, therapeutic anticoagulation increased bleeding risk without improving outcomes. Thus, risk stratification became essential for anticoagulant use.^[57,58]

3.5 Supportive and Adjunctive Agents

Beyond direct antivirals and immunomodulators, several supportive agents played a role. Antibiotics were frequently prescribed to cover secondary bacterial infections, although true co-infection rates were low. Similarly, vitamins D and C, zinc, and other supplements were widely used despite limited evidence. Furthermore, inhaled budesonide was shown to reduce recovery time in community-treated patients. Therefore, while not all supportive agents proved effective, they reflected the urgent need to explore every possible therapeutic avenue during the crisis.^[62,64]

3.6 challenges and clinical considerations in Drug Repurposing

Despite the successes, the repurposing strategy faced several challenges. First, the heterogeneity of patient populations and disease stages made it difficult to identify who would benefit most from a given drug. Second, pharmacokinetic issues such as lung penetration and drug-drug interactions, particularly with ritonavir, complicated clinical use. Third, supply chain disruptions led to shortages of key drugs like dexamethasone and tocilizumab. In addition, the rapid pace of publication led to misinformation and premature adoption. Nevertheless, the experience provided critical lessons for future pandemics, including the need for adaptive trial platforms and real-time evidence synthesis.^[24-26]

In conclusion, drug repurposing provided the backbone of COVID-19 therapeutics in the absence of novel agents. The major classes, including antivirals,

immunomodulators, anticoagulants, and supportive therapies, each addressed a specific aspect of the disease. While not all candidates succeeded, the identification of dexamethasone, tocilizumab, baricitinib, and Paxlovid saved millions of lives. Ultimately, the COVID-19 experience has redefined the role of repurposing in modern medicine and established a blueprint for rapid therapeutic response in future outbreaks.^[10]

4. Role of pharmaceutical science and clinical pharmacy in Covid 19 management

The COVID-19 pandemic fundamentally transformed the scope and responsibilities of pharmaceutical sciences and clinical pharmacy. Traditionally, pharmacists were primarily involved in drug dispensing and basic counseling. However, during the pandemic, their role expanded dramatically to include evidence evaluation, therapeutic decision-making, and public health leadership. Consequently, clinical pharmacists emerged as essential members of multidisciplinary COVID-19 teams. Moreover, pharmaceutical scientists played a critical role in formulation development, stability testing, and supply chain management. Therefore, this section highlights the multifaceted contributions of pharmacy professionals throughout the pandemic.^[21]

CLINICAL PHARMACIST IN COVID 19

PATIENT CARE SAFETY	MEDICATION HEALTH	PUBLIC
- Counseling	- DDI Check	Education-
- Education	- Dose Adjust	- Guidelines
- Follow-up	- ADR Monitor	- Stewardship

4.1 Evidence Appraisal and guidelines development

In the early months of the pandemic, healthcare providers were overwhelmed with rapidly published and often conflicting data. As a result, there was an urgent need for professionals who could critically appraise emerging literature. In this context, hospital and clinical pharmacists took the lead in evaluating the efficacy and safety of repurposed drugs. Furthermore, they systematically reviewed trial designs, endpoints, and statistical analyses to determine the validity of findings. In addition, pharmacy departments collaborated with infectious disease and critical care teams to develop institutional treatment protocols. Accordingly, pharmacists ensured that guidelines were updated in real-time as new evidence from trials like RECOVERY and REMAP-CAP became available. Thus, their expertise prevented the adoption of ineffective or potentially harmful therapies.^[21-23]

4.2 Therapeutic Drug monitoring and Dose optimisation

The pharmacotherapy of COVID-19 was complicated by the unique characteristics of the patient population. Specifically, many patients had renal impairment, hepatic dysfunction, or were receiving multiple concomitant medications. Therefore, dose adjustment

became a critical responsibility of clinical pharmacists. For instance, antivirals such as remdesivir required renal function monitoring, while immunomodulators like tocilizumab needed liver enzyme surveillance. Similarly, drugs with narrow therapeutic indices, including anticoagulants, demanded careful titration. In parallel, pharmacists conducted therapeutic drug monitoring for agents where levels correlated with efficacy or toxicity. As a consequence, individualized dosing strategies improved patient outcomes and minimized adverse events.^[66-68]

4.3 Drug-Drug interactions management

A major challenge during COVID-19 was the high potential for drug-drug interactions, particularly with the widespread use of ritonavir-boosted therapies. Ritonavir is a potent inhibitor of CYP3A4 and can significantly alter the metabolism of hundreds of commonly used medications. Hence, pharmacists performed comprehensive medication reconciliation for every patient initiated on Paxlovid. Furthermore, they identified interactions with statins, antiarrhythmics, immunosuppressants, and psychiatric medications. In addition, they recommended dose adjustments, alternative agents, or temporary discontinuation where necessary. Moreover, electronic health record alerts were optimized by pharmacy informatics teams to flag high-risk combinations. Thus, pharmacist-led interaction screening became a cornerstone of patient safety.^[69-70]



4.4 Pharmacovigilance and Adverse Drug Reaction Monitoring

The emergency use of repurposed drugs under crisis conditions created uncertainty regarding their safety profiles. Consequently, robust pharmacovigilance systems were essential. Hospital pharmacists led institutional adverse drug reaction (ADR) monitoring programs specifically for COVID-19 therapies. For example, they tracked cardiac events associated with hydroxychloroquine, hepatotoxicity with remdesivir, and secondary infections with immunosuppressants. In addition, they reported ADRs to national and international databases such as WHO's Vigibase and the FDA's FAERS. Furthermore, they educated healthcare providers on recognizing and managing toxicities. As a

result, real-world safety data complemented clinical trial findings and informed regulatory decisions.^[70]

4.5 Supply chain management and drug shortages

The global surge in demand for COVID-19 medications led to unprecedented drug shortages. Key agents such as dexamethasone, propofol, midazolam, and tocilizumab became critically scarce, particularly in low- and middle-income countries. Therefore, hospital pharmacists played a vital role in inventory management and allocation. Specifically, they implemented conservation strategies, therapeutic interchange protocols, and prioritization criteria. Moreover, pharmaceutical scientists worked with manufacturers to address formulation challenges and scale-up production. In addition, they evaluated alternative suppliers and compounded medications when commercial products were unavailable. Accordingly, pharmacy leadership ensured continuity of care despite supply disruptions.^[72]

4.6 Patient counseling and community pharmacy services

Beyond the hospital setting, community pharmacists served as the most accessible healthcare providers during the pandemic. They were responsible for educating the public on medication use, symptom management, and when to seek medical care. Furthermore, as vaccines became available, community pharmacies emerged as primary vaccination sites. In addition, they provided counseling on post-COVID medications, managed chronic diseases during lockdowns, and addressed vaccine hesitancy. Consequently, the pandemic highlighted the importance of community pharmacy in public health emergency response and expanded their scope of practice.^[22,64,65]

4.7 Research and pharmaceutical Development

Pharmaceutical scientists contributed significantly to the rapid development of new formulations. For instance, the need for intravenous to oral step-down therapy led to the development of oral antivirals like nirmatrelvir/ritonavir. Similarly, researchers optimized drug delivery systems to improve lung targeting of inhaled therapies. In parallel, academic and industry pharmacists participated in adaptive platform trials, providing expertise in pharmacokinetics and pharmacodynamics. Moreover, they utilized in-silico modeling and AI-based drug repurposing to screen thousands of approved drugs. Thus, pharmaceutical sciences accelerated the translation of basic science into clinical therapies.^[18]

4.8 Challenges and future directions

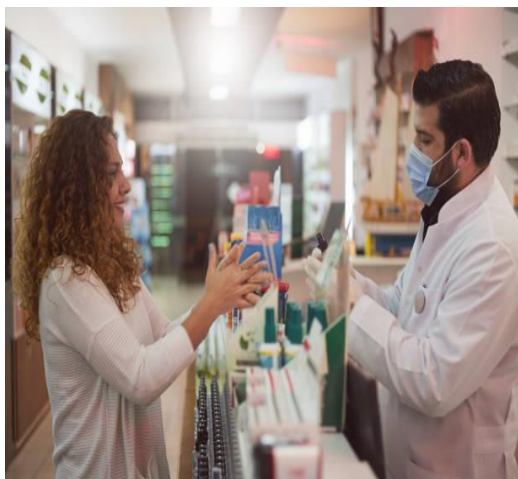
Despite their critical contributions, pharmacy professionals faced numerous challenges. First, the rapid pace of information required continuous learning and adaptation. Second, staffing shortages and burnout affected both hospital and community pharmacists. Third, the lack of standardized protocols in the early phase led to practice variability. Nevertheless, the pandemic demonstrated that pharmacists are

indispensable in crisis management. Looking forward, it is essential to formally integrate pharmacists into pandemic preparedness plans, expand prescribing authority, and invest in pharmacy research infrastructure. Ultimately, the lessons learned will strengthen the role of pharmacy in future public health emergencies.^[22]

In summary, the COVID-19 pandemic redefined the role of pharmaceutical sciences and clinical pharmacy. From evidence appraisal and dose optimization to pharmacovigilance and supply management, pharmacists were at the forefront of the therapeutic response. Most importantly, the pandemic underscored that optimal patient care requires the integration of pharmaceutical expertise at every stage. Therefore, strengthening the pharmacy workforce and expanding their scope will be crucial for future pandemic preparedness.^[21]

5. Clinical efficacy and safety profile of Repurposed drugs

The evaluation of any therapeutic agent during a pandemic requires a careful balance between clinical efficacy and safety. In the context of COVID-19, repurposed drugs were deployed under emergency conditions with limited initial data. Consequently, understanding their real-world effectiveness and adverse effect profile became critical for clinical decision-making. Moreover, the risk-benefit assessment varied significantly depending on disease severity, timing of administration, and patient comorbidities. Therefore, this section provides a comprehensive review of the clinical efficacy and safety of the major repurposed drug classes used in COVID-19 management.^[29]



5.1 Antiviral Agents: Efficacy and Safety

Antivirals were primarily aimed at reducing viral replication and preventing disease progression. Among them, remdesivir was the first drug to receive FDA approval. Clinical trials demonstrated that remdesivir shortened median time to recovery from 15 to 10 days in hospitalized patients. However, it did not show a consistent mortality benefit across all trials. Regarding safety, the most common adverse events were hepatotoxicity, infusion-related reactions, and renal

impairment. As a result, liver and kidney function monitoring was recommended during therapy.^[48-50]

In contrast, oral antivirals showed more promising results in the outpatient setting. Nirmatrelvir/ritonavir (Paxlovid) reduced the risk of hospitalization or death by 89% in high-risk, unvaccinated individuals when initiated within 5 days of symptom onset. Nevertheless, its safety profile was complicated by numerous drug-drug interactions due to ritonavir. Similarly, molnupiravir demonstrated a 30% reduction in hospitalization and was generally well-tolerated, although concerns about mutagenicity required careful patient selection.^[18-20]

5.2 Corticosteroid: The cornerstone of severe disease

Dexamethasone remains the most definitive success story in COVID-19 therapeutics. The RECOVERY trial established that 6 mg daily for 10 days reduced 28-day mortality by 35% in patients requiring mechanical ventilation and by 20% in those on oxygen. Importantly, no benefit was observed in patients not requiring respiratory support, and potential harm was noted. Regarding safety, short-term dexamethasone was well-tolerated, but risks included hyperglycemia, secondary infections, and psychiatric effects. Therefore, its use was restricted to patients with hypoxia.^[13]

5.3 Immunomodulators: Targeted Anti-inflammatory therapy

The role of immunomodulators was most evident in patients with hyperinflammation. Tocilizumab, an IL-6 receptor antagonist, showed a mortality benefit when combined with corticosteroids in critically ill patients. Meta-analyses reported a 13% relative reduction in 28-day mortality. However, safety concerns included increased risk of secondary bacterial and fungal infections, as well as hepatotoxicity and neutropenia. Consequently, patient selection based on inflammatory markers was advised.^[14]

Similarly, baricitinib, a JAK inhibitor, demonstrated efficacy in reducing mortality and accelerating recovery when combined with remdesivir. The ACTT-2 trial showed a 1-day improvement in time to recovery. In terms of safety, baricitinib was associated with venous thromboembolism, serious infections, and laboratory abnormalities. Thus, screening for tuberculosis and viral hepatitis was recommended prior to initiation.^[54]

5.4 Anticoagulants: Balancing Thrombosis and Bleeding

Given the prothrombotic nature of COVID-19, anticoagulation became standard care. Prophylactic-dose low-molecular-weight heparin reduced thrombotic events without significantly increasing bleeding. Furthermore, therapeutic-dose anticoagulation showed benefit in moderately ill, non-critically ill patients, improving organ support-free days. However, in critically ill patients, therapeutic anticoagulation increased major

bleeding without improving survival. Therefore, a stratified approach based on disease severity was essential. Common adverse effects included bleeding, heparin-induced thrombocytopenia, and injection site reactions.^[57]

5.5 Antimalarials and Failed Candidates: Lessons in safety

Hydroxychloroquine and chloroquine provide an important lesson in safety. Despite initial enthusiasm, large randomized trials showed no efficacy and highlighted significant cardiac toxicity, including QT prolongation and arrhythmias. As a result, emergency use authorizations were revoked. Similarly, lopinavir/ritonavir failed to demonstrate clinical benefit and was associated with gastrointestinal toxicity and drug interactions. Accordingly, these experiences emphasized that efficacy must be proven before widespread adoption, and safety monitoring is non-negotiable.^[12,55,56]

5.6 Monoclonal Antibodies: High efficacy, limited Durability

Monoclonal antibodies targeting the spike protein showed high efficacy in preventing progression in early, mild-to-moderate COVID-19. For example, casirivimab/imdevimab reduced hospitalization and death by 70%. However, their clinical utility was limited by the emergence of viral variants that escaped neutralization. In terms of safety, infusion reactions were the most common adverse event, but overall they were well-tolerated. Nevertheless, the need for intravenous administration and cold-chain storage restricted their use.^[59]

5.7 Overall Risk: Benefit and clinical Decision making

In summary, the clinical efficacy of repurposed drugs was highly context-dependent. Antivirals were most effective early in the disease course, while immunomodulators and corticosteroids were beneficial in the later inflammatory phase. Moreover, the safety profile of each agent required individualized assessment based on comorbidities and concomitant medications. In addition, pharmacists played a key role in mitigating risks through dose adjustment, interaction screening, and ADR monitoring. Ultimately, the pandemic demonstrated that rapid deployment must be paired with rigorous post-marketing surveillance to ensure patient safety.^[28]

Therefore, the legacy of COVID-19 therapeutics is not just the drugs that worked, but the framework established for evaluating efficacy and safety in real-time during a public health emergency. This framework will be invaluable for responding to future pandemics.^[29]

6. Challenges, Limitations and future perspectives

While drug repurposing provided a rapid therapeutic response to COVID-19, the approach was not without

significant challenges. Understanding these limitations is crucial for refining strategies for future pandemics. Moreover, the lessons learned from COVID-19 offer a roadmap for improving drug repurposing frameworks. Therefore, this section critically evaluates the obstacles encountered and proposes future directions for the field.^[24]

6.1 Scientific and clinical challenges

The foremost challenge was the lack of pre-existing clinical data for COVID-19. As a result, many repurposed drugs were tested based on in-vitro activity or mechanistic rationale alone. Consequently, this led to the rapid adoption of agents like hydroxychloroquine and lopinavir/ritonavir, which later proved ineffective in large trials. Furthermore, the heterogeneity of COVID-19 disease presentation made it difficult to identify the optimal patient population and timing for intervention. For instance, antivirals were beneficial early, whereas immunomodulators worked later. In addition, the absence of validated biomarkers to guide therapy resulted in a one-size-fits-all approach initially. Thus, future efforts must prioritize disease-specific preclinical models and adaptive trial designs.^[25]

6.2 Regulatory and ethical Limitations

Regulatory agencies faced unprecedented pressure to approve therapies quickly. Therefore, Emergency Use Authorizations (EUAs) were granted based on limited data. While this accelerated access, it also led to confusion when recommendations were reversed. Moreover, the ethical dilemma of allocating scarce resources such as remdesivir and tocilizumab during shortages posed significant challenges. In parallel, conducting placebo-controlled trials during a pandemic raised ethical questions. However, platform trials like RECOVERY and REMAP-CAP demonstrated that rigorous science and ethical care can coexist. Accordingly, regulatory frameworks need to be more flexible yet evidence-driven for future emergencies.^[71]

6.3 Pharmacological and supply chain issues

From a pharmaceutical perspective, several limitations emerged. First, many repurposed drugs had suboptimal pharmacokinetics for respiratory viruses, such as poor lung penetration. Second, drug-drug interactions, especially with ritonavir-boosted regimens, complicated management in patients with comorbidities. Third, the global demand surge led to severe shortages of essential medicines including dexamethasone, sedatives, and anticoagulants. Consequently, hospitals had to implement rationing and therapeutic substitution protocols. In addition, manufacturing and distribution bottlenecks delayed access in low- and middle-income countries. Therefore, strengthening global supply chains and developing regional manufacturing hubs is essential.^[72]

6.4 Information overload and Misinformation

The pandemic was accompanied by an "infodemic". A vast number of preprints and observational studies were published rapidly, often without peer review. As a result, clinicians and the public were exposed to conflicting and sometimes misleading information. Furthermore, social media amplified anecdotal evidence, leading to premature adoption of unproven therapies. In contrast, clinical pharmacists and evidence synthesis groups played a vital role in filtering signal from noise. Nevertheless, this highlighted the need for centralized, real-time evidence platforms. Thus, future pandemic preparedness must include robust systems for rapid but reliable knowledge dissemination.^[73]

6.5 Future perspectives: Building a better Framework

Despite the challenges, COVID-19 has transformed drug repurposing. Moving forward, several key strategies should be implemented. First, the creation of global repurposing libraries with pre-characterized safety and PK data will accelerate screening. Second, investment in AI and machine learning can improve the prediction of drug-target interactions. Third, establishing permanent adaptive platform trials will allow for rapid testing of multiple agents. Fourth, integrating pharmacists and pharmaceutical scientists into pandemic task forces from day one will ensure rational drug use. Finally, international collaboration and data sharing must be prioritized to avoid duplication and ensure equity. Ultimately, these steps will enable a faster and more effective response to the next public health crisis.^[4]

In conclusion, while drug repurposing was a critical success during COVID-19, it also exposed major gaps in our preparedness. The challenges related to evidence generation, regulation, supply, and communication must be addressed proactively. Nevertheless, the unprecedented scientific collaboration and innovation during the pandemic provide optimism. Therefore, by learning from these experiences, we can build a more resilient and efficient system for drug repurposing in the future.^[5]

7. Transition to endemic phase: Lessons for future

Is the COVID-19 pandemic progressed, SARS-CoV-2 evolved from a pandemic pathogen to an endemic respiratory virus. Consequently, the role of drug repurposing has also shifted from crisis management to long-term disease control. Moreover, the experience gained over the past five years provides invaluable lessons for managing future outbreaks. Therefore, this section discusses the transition to the endemic phase and the key takeaways for future pandemic preparedness.^[27]

7.1 From pandemic Response to Endemic Management

During the acute phase of the pandemic, the focus was on rapid deployment of any potentially effective therapy. However, in the endemic phase, the priorities have changed. Specifically, the emphasis is now on targeted

treatment for high-risk populations, outpatient management, and prevention of severe disease. Furthermore, the availability of vaccines has significantly reduced hospitalizations, thereby altering the therapeutic landscape. In addition, the emergence of new variants necessitates continuous evaluation of drug efficacy. As a result, repurposed drugs are now used in a more stratified and evidence-based manner rather than empirically.^[27]

7.2 Key Lessons for Drug Repurposing

The COVID-19 experience has yielded several critical lessons. First, *speed must be balanced with scientific rigor*. While early adoption of drugs like hydroxychloroquine proved premature, later successes with dexamethasone and Paxlovid were based on robust randomized trials. Second, *adaptive platform trials are essential*. Studies like RECOVERY and REMAP-CAP allowed multiple drugs to be tested simultaneously and results to be implemented in real-time. Third, *drug-drug interactions and safety cannot be overlooked*. The widespread use of ritonavir highlighted the need for comprehensive medication review. Accordingly, these lessons should be integrated into future pandemic response plans.^[51]

7.3 Role of pharmaceutical science in long term preparedness

Looking ahead, pharmaceutical sciences will play a central role in pandemic preparedness. To begin with, the development of global repurposing libraries containing approved drugs with known safety profiles will accelerate screening. In parallel, artificial intelligence and machine learning can be used to predict drug-target interactions and prioritize candidates. Moreover, investment in flexible manufacturing and regional supply chains will mitigate drug shortages. In addition, pharmacists must be formally included in national pandemic task forces to provide expertise in therapeutics and logistics. Thus, a proactive rather than reactive approach is needed.^[63,67]

7.4 Addressing health inequities and Global Access

A major limitation during the pandemic was unequal access to therapeutics. High-income countries had early access to monoclonal antibodies and oral antivirals, while low- and middle-income countries faced delays and shortages. Therefore, future strategies must prioritize equitable distribution. Furthermore, technology transfer and local manufacturing should be encouraged. In addition, repurposing of low-cost, widely available drugs should be emphasized to ensure accessibility. Ultimately, global health security depends on ensuring that all populations have access to effective therapies.^[26]

7.5 Future directions and Recommendations

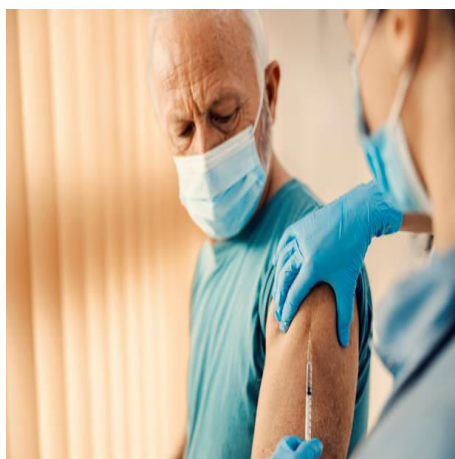
Moving forward, several recommendations can be made. Firstly, governments and funding agencies should maintain permanent clinical trial infrastructure that can be activated rapidly. Secondly, regulatory agencies

should develop clear pathways for EUA that are based on evolving evidence. Thirdly, real-world evidence and pharmacovigilance systems must be strengthened to monitor long-term safety. Fourthly, public communication strategies should be developed to combat misinformation. Finally, interdisciplinary collaboration between virologists, clinicians, pharmacists, and pharmaceutical scientists should be institutionalized. In conclusion, the transition to endemicity does not mean the end of vigilance. Rather, it provides an opportunity to build a more resilient healthcare system.^[74]

Therefore, the lessons learned from drug repurposing during COVID-19 will serve as the foundation for future pandemic response. By applying these insights, we can ensure a faster, more equitable, and more effective therapeutic response when the next public health emergency arises.^[75]

8. CONCLUSION

The COVID-19 pandemic stands as one of the most significant global health challenges of the 21st century. In the initial absence of vaccines and specific antiviral therapies, the medical and scientific community was compelled to seek rapid solutions. Consequently, drug repurposing emerged as the cornerstone of the early therapeutic response. Moreover, this strategy demonstrated that existing medications could be effectively redirected to combat a novel pathogen, thereby bridging the critical gap between outbreak onset and de novo drug development.



Throughout the course of the pandemic, the evaluation and implementation of repurposed drugs followed a dynamic trajectory. Initially, broad-spectrum antivirals and antimalarials were investigated based on in-vitro data and prior experience with other coronaviruses. Subsequently, as understanding of the disease pathophysiology evolved, the focus shifted toward immunomodulatory agents and anticoagulants to address the hyperinflammatory and thrombotic complications of severe COVID-19. Furthermore, the development and authorization of targeted oral antivirals marked a pivotal advancement in outpatient management. Nevertheless,

the journey was not without setbacks. For instance, several widely promoted candidates failed to demonstrate clinical benefit in large-scale randomized trials. Therefore, this experience underscores the fundamental principle that therapeutic decisions must be guided by robust clinical evidence rather than preliminary data or anecdotal reports.

In addition to clinical outcomes, the pandemic profoundly reshaped the role of pharmaceutical sciences and clinical pharmacy. Clinical pharmacists became essential frontline members of healthcare teams, providing expertise in drug selection, dosing, monitoring, and management of drug-drug interactions in complex, critically ill patients. Similarly, pharmaceutical scientists contributed to addressing formulation challenges, ensuring supply chain continuity, and supporting pharmacovigilance efforts. As a result, the integration of pharmaceutical expertise was recognized as vital for optimizing patient care and ensuring medication safety during a public health emergency. Thus, strengthening pharmacy practice and education must be prioritized in future pandemic preparedness plans.

Looking ahead, the transition of SARS-CoV-2 to an endemic pathogen does not diminish the relevance of the lessons learned. On the contrary, these insights provide a strategic framework for responding to future emerging infectious diseases. Specifically, the establishment of pre-prepared drug repurposing libraries, the development of adaptive clinical trial platforms, and the leveraging of artificial intelligence for drug screening represent key opportunities. In parallel, ensuring equitable global access to therapeutics and combating misinformation remain critical priorities. Accordingly, international collaboration and sustained investment in research infrastructure are imperative.

In summary, drug repurposing proved to be an indispensable tool in the fight against COVID-19. While the approach had limitations, it delivered life-saving treatments at a time when they were most needed. Ultimately, the legacy of COVID-19 therapeutics extends beyond the specific drugs used. It has redefined how the scientific community responds to urgent health crises with speed, rigor, and collaboration. Therefore, by applying these lessons, we can build a more resilient, equitable, and effective system to protect global health against future pandemics.

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