

# Negative Evidence: Repurposed Drugs for COVID-19: the Partisan Bone of Contention. Part I

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*"Omne Vetus Novum Est Iterum" [Everything Old Is New Again]*

## Introduction

Partisan conflict over the efficacy of repurposed drugs emerged as one of most divisive elements of the highly politicized response to the COVID-19 pandemic. This dispute continues today with no prospect for resolution. As a result, patients' access to early treatment of COVID-19 remains limited. Novel strategies are necessary to remove those detrimental limitations.

Drug repurposing is an old concept of using already approved medications for the treatment of new conditions. It used to be a random practice dependent upon serendipity. However, due to the advancement of science it is becoming a rigorous biocomputation-based method of drug discovery. All types of drug repurposing have enjoyed enthusiastic bipartisan support. Interestingly, during the COVID-19 pandemic left-wing-controlled officialdom suddenly became averse to its previously favored methodology. One can only speculate why.

This editorial will focus on the general discussion of drug repurposing and related scientific and regulatory matters, with specific application to hydroxychloroquine (HCQ). Ivermectin (IVM) and other medications that can be repurposed for COVID-19 will be considered in Part II.

The debate over the use of HCQ and IVM in the management of COVID-19 is a typical example of a clinical matter that became politicized in the current settings of extreme ideological polarization. This article does not replicate countless existing reviews that are tainted with partisan bias. Rather, it aims to provide readers with the information on this topic that is being omitted, from a political perspective. This editorial does not advocate for any ideology, but for the benefit of the patient, in accordance with the motto *"Omnia pro Aegroto"* [all for the patient].

This discussion will follow the past approach of searching for and discussing the significance of negative evidence.<sup>1-8</sup> This term refers to situations in which the expected data is unexpectedly missing. Negative evidence does not simply mean "the absence of evidence," but it suggests that relevant information has been intentionally concealed, typically to cover up wrongdoing. Any thorough investigative process should involve a careful search for negative evidence.

## The Quintessential Bone of Partisan Contention

Two repurposed drugs for COVID-19, HCQ and IVM, gained enormous public notoriety, such as has been seen with few other medications. But was what the public heard true?

It is irrefutably true that both medications were initially promoted as a potential COVID-19 treatment by right-wing-aligned medical politicians and influencers.<sup>9</sup> Both drugs were approved for a long time for other uses than COVID-19. Hence

their safety profile was known. The idea to repurpose them to treat COVID-19 came from their known biological properties, in vitro studies, informal clinical observations, and some formal clinical research.<sup>10-12</sup> The right-wing-oriented public embraced those medications with great enthusiasm.<sup>9,13</sup>

Virtually from the onset, left-wing-affiliated scientists, physicians, politicians, regulators, and journalists were skeptical about these drugs. Left-wing experts criticized the theoretical basis and in vitro and clinical research as substandard level of evidence inconsistent with principles of evidence-based medicine.<sup>14-16</sup> The left-leaning public rejected those meds. Left-affiliated regulators revoked HCQ's Emergency Use Authorization, and never endorsed IVM for use in COVID-19.<sup>17,18</sup> The lines in the sand were drawn and as discussed below HCQ and IVM became and remain until today the **Quintessential Partisan Bone of Contention** (Figure 1).



**Figure 1.** Metaphor for current partisan dispute over the efficacy and safety of certain repurposed drugs. Inspired by Pieter Brueghel the Younger and generated by AI (DALL-E 3). VETUS = NOVUM is the abbreviation for *"Omne Vetus Novum Est Iterum"* [Everything Old Is New Again].

## Beyond Partisan Narratives: Patient-Centered Recommendations

Is it possible in this politically polarized world to make a rational, politically neutral recommendation about using HCQ and IVM as early treatment for COVID-19 that would be solely focused on patients' benefits and risks? A treatment recommendation that would ignore all the popular right-wing talking heads and the left-wing (allegedly impeccable) "population based" clinical trials? And—while making such treatment decision—also follow the most universal tenets of *"Primum non Nocere"* and *"Omnia pro Aegroto"*?

Yes, it is possible. Making this sort of recommendation is especially easy in the case of old drugs with well-known safety profiles. It is also known that numerous credible, practicing physicians saw improvement in their patients with the use of those drugs. One shall always keep in mind the “*post hoc, ergo propter hoc*” fallacy, but correlation does often suggest causation in clinical medicine.

Allegedly impeccable clinical trials performed by officialdom had contrary results, but as discussed in detail below, those cannot be trusted for numerous reasons. Moreover, clinical trials involve populations. Physicians treat patients, not “populations.” But even if HCQ and IVM are indeed therapeutically inert and reported improvements are a placebo effect, their use is still acceptable. Since the official recommendation was “no treatment for outpatients,” giving an HCQ or IVM placebo would have been virtually the same [non]treatment as recommended by the official guidelines.

***In summary, patients with no contraindications and who are capable of giving informed consent should have the option to receive HCQ or IVM as early treatment of COVID-19.***

All one needs in today's world to secure this option for patients is the full acknowledgment of legality and acceptability by federal or state regulatory agencies (not the risky “off label” option) and assurance that the state medical boards will not punish prescribers and pharmacists who want to provide patients with this treatment.

## Political Context of the Controversy about Repurposed Drugs

Political context is key to understanding the controversy over the role of repurposed drugs in the early treatment of the COVID-19. Yet, it is typically glossed over, perhaps due to the assumption that this “self-evident.” This is not necessarily true in the era of political information bubbles and echo chambers.<sup>19-21</sup> Some may be shocked to learn that there is a controversy. Others' perception does not reflect objective reality but rather the political narrative in which they are immersed.<sup>19,22-24</sup> A brief overview of the political situation surrounding drug repurposing is provided below, and more detailed discussion is available.<sup>19,25-31</sup>

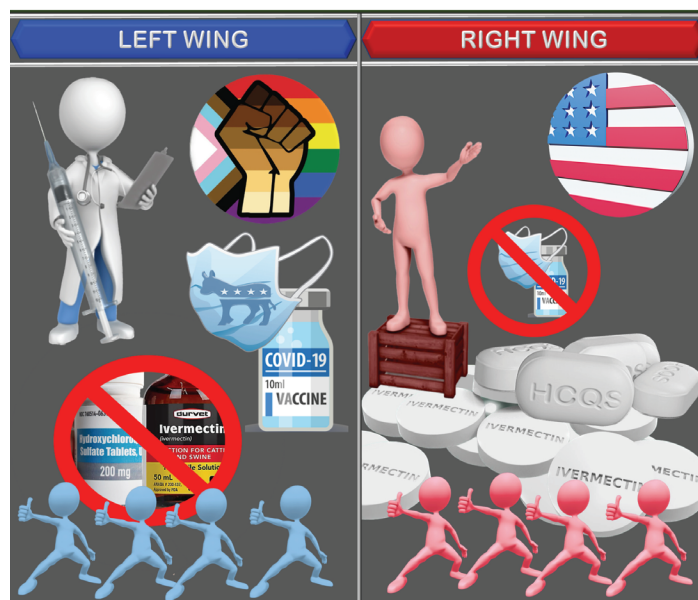
Even before the COVID-19 pandemic, a formerly cohesive American public became divided into two contradictory ideological camps.<sup>26,32,33</sup> Terminology describing those factions is imprecise but commonly they are called: right wing (a.k.a. conservatives who are mostly Republicans) and left wing (a.k.a. progressives/liberals who are mostly Democrats).<sup>26</sup> For clarity we will refer to them as right or left wing since other labels have multiple meanings. Additionally, the term “partisan” will be used to denote the broad socio-ideological identity of the person (right or left wing) and not a mere membership in the Democratic or Republican party.<sup>25</sup>

This profound partisan polarization was associated with politicization of all aspects of life including science and medicine.<sup>25,26,29,34-36</sup> Simultaneously, a covert power shift has occurred. The left wing captured the sources of influence and power that used to be either neutral or under right-wing control. This resulted in the partisan power asymmetry.<sup>26,37,38</sup> The left wing took over all education, academia, science, medicine, entertainment, legacy news, administrative agencies (such as FDA, CDC), law enforcement (police, FBI), the court system and even large parts of organized religion and the armed forces.

These changes are hard to fathom for many. Older right-wing Americans remember the old U.S.A. where political differences were respected yet everybody was united by patriotism. In that U.S.A., the FBI was targeting real gangsters, top scientists were making sense, and academic physicians did not poison or mutilate healthy bodies. American experts were trusted, and governmental institutions were respected. However, things changed.

Irreconcilable ideological differences related to polarization have driven political factions to self-segregate into echo chambers both online and in real life.<sup>19</sup> Americans are captured in the partisan information bubbles where they are being fed slanted political narratives and not reading critically objective news reports.<sup>20</sup> This reinforces their biases and impedes their ability to make realistic assessments. Partisan insulation combined with political propaganda creates the illusion for both factions of being in the righteous, powerful, and rational majority while seeing their enemies as a weak, irrational, and self-entitled minority.

The ghastly crisis of the COVID-19 pandemic descended upon the U.S. during a time when the political polarization, politicization of medicine and science, and partisan power asymmetry had reached unprecedented levels.<sup>25,26,29,34-36</sup> Immediately, politically polarized Americans started to develop rapidly diverging opinions about the pandemic.<sup>29,39,40</sup> Ultimately, two contradictory partisan narratives were established, concerning the origin of COVID-19, its significance, its treatment, and its prevention (Figure 2).



**Figure 2.** Graphic representation of the partisan divide over COVID-19.<sup>25</sup> Figure used and modified with permission.

The draconian policies enacted during COVID-19 have damaged more people in the right-wing camp.<sup>8,29</sup> Meanwhile, some left-aligned businesses made huge profits from the pandemic-related wealth shift, an unfair outcome enabled by the power asymmetry.<sup>8</sup> After the COVID-19 Public Health Emergency ended in 2023, the left-wing leaders who had abused their power are eager to erase the public memory of their misdeeds.<sup>8</sup> At the same time, many wronged right wingers, while very well-intentioned, became confused about

what should realistically be done now in the interest of justice and to protect themselves and their loved ones from further damages.<sup>8</sup> Some of them are distracted by issues that are sensational and emotional, but objectively not so relevant currently.<sup>8</sup> Among the several urgent matters that should be addressed promptly<sup>8</sup> is the issue of securing patients' access to early COVID-19 treatment with affordable repurposed drugs.

## Current Status of the Dispute

Since the COVID-19 pandemic started more than 4 years ago, a lot of formal research and a massive amount of tacit clinical data have been gathered regarding the effectiveness and safety of two established drugs, HCQ and IVM, for the early treatment of COVID-19. Surprisingly, despite this abundance of evidence, these remain a partisan bone of contention.

- The right wing continues to vigorously promote this new use of HCQ and IVM. Right-wing-aligned lay people, physicians, and activists remain unconvinced by the results of the allegedly impeccable research performed by the left-aligned academic scientists, arguing that those academic researchers cannot be trusted because of their partisan bias, which allegedly cause them to prioritize the interests of pharmaceutical companies, which are generous political donors, over proper patient care.
- The left wing staunchly opposes prescribing HCQ and IVM for COVID-19, claiming that numerous high-quality clinical research trials<sup>16,41-44</sup> have definitively proven these drugs to be ineffective and unsafe when used for this purpose. Some left-wing activists assert that these "ineffective" medications are unethically marketed to the gullible public by right-wing "misinformation spreaders" who cloak their actions in the guise of medical freedom,<sup>14,45,46</sup> while their true motivation allegedly lies in enabling unlawful enrichment of the charlatans who in turn contribute to right-wing political campaigns.<sup>47</sup>

While the partisan tug of war continues as of May 2024, asymmetrically powerful left-wing-favoring entities—including the Food and Drug Administration (FDA),<sup>48-49</sup> the National Institutes of Health (NIH),<sup>50</sup> the Centers for Disease Control and Prevention (CDC),<sup>51</sup> medical societies such as the American College of Emergency Physicians (ACEP),<sup>52</sup> and clinical decision support resources such as UpToDate<sup>53</sup>—have been issuing statements clarifying that these medicines are not indicated for COVID-19. Notably, in August 2023 FDA posted on its official X (formerly Twitter) account a statement reasserting that FDA has not approved IVM for use in preventing or treating COVID-19, but added the following clarification: *"Health care professionals generally may choose to prescribe an approved human drug for an unapproved use when they judge that the unapproved use is medically appropriate for an individual patient."*<sup>54</sup> Interestingly, some comments to this post pointed out that medical workers can be still subjected to punitive actions by their regulatory board for engaging in off-label practices.<sup>54</sup>

Despite this negativism displayed by the official regulatory agencies, prescribing of HCQ and IVM increased substantially in the U.S. during first year of the pandemic and has not decreased dramatically since.<sup>14,55,56</sup> It has been suggested that the increase in prescription pattern varied regionally, following the expected correlation with the partisan characteristic of the regions.<sup>13</sup> The amount of HCQ and IVM obtained by American patients may be much greater than official statistics are showing, since those

medications are being acquired by unofficial channels. This indicates that substantial numbers of American patients remain committed to the notion that they can benefit from treatment with those two repurposed medications, despite the escalating efforts of officialdom to suppress the availability of this option for them.

Such patients are supported by many physicians who disagree with the contrived rationale and the coercive methods used by left-wing-controlled officialdom. Therefore, in response to the above repressive efforts of officialdom, updated treatment guidelines incorporating the use of HCQ and IVM have been issued by independent medical societies and foundations. Moreover, some practitioners continued to rely on previously published medical papers that included HCQ and IVM.<sup>57-59</sup> In addition, legal efforts have been undertaken to secure patients' access to those drugs.<sup>60</sup> While those actions are important and meaningful, they still constitute mere asymmetric warfare given the significant power advantage held by the Left. Yet even such guerilla tactics are helpful since despite its tremendous power advantage the Left is still unable to win in this contest. Instead of expected easy victory it remains locked in an unexpected stalemate. Unfortunately, the robust Left can outlast the embattled Right in such a deadlock.<sup>61</sup> Moreover, many unsavory characters can benefit from this continuous impasse by exploiting desperate patients.<sup>61</sup> Hence, those who want HCQ and IVM to be approved as a legitimate treatment option need to intensify their efforts. Most importantly, they must deploy a different strategy, because the current one is not yielding the desired results.

## New Strategies for Achieving Regulatory Approval

Many medical freedom activists are trying to obtain approval for the repurposed drugs by relying on the following approaches:

- **Presenting officials and the public with mainstream scientific publications containing original research that in their opinion contradict the official narrative:** Such efforts are typically deflected by various left-wing "fact checkers" and "debunkers," who state that medical freedom activists do not understand the science behind those papers and are confused about the quality of evidence.
- **Trying to find the flaws in the research studies that are used by officialdom to support its negative opinions about repurposed drugs:** This is an extremely difficult approach since the dissidents are trying to outplay academia in the game that academia has fully mastered. A good academic clinical trialist has immense knowledge and experience. He can be rarely outplayed by someone who is not on his level, and very few dissidents are. They are successful on occasions (see below) but like with the heads of a hydra numerous heads grow in the place of the one that is cut off.
- **Appealing for the support to an authority (e.g., courts) they consider to be truly impartial and powerful enough to force the regulators to issue their approval:** However, the majority of courts are not impartial and are not siding with dissidents.
- **Challenging prominent members of officialdom to in-person debates in front of an audience:** Most prominent members of officialdom will never fall for this trap. They will use the concepts of the Gish Gallop (overwhelming

the opponent with possibly specious arguments) and Brandolini's law (the asymmetry between the difficulty of debunking as opposed to creating nonsense) as reasons for rejecting such invitations.

Predictably, while those methods have some public relations value, reliance on them has not resulted in any significant progress. It is very possible that activists are underestimating the severity of partisan polarization, pervasiveness of politicization of both science and regulatory agencies, and the degree of the power asymmetry between the Left and the Right. Perhaps many honest activists assume that the existing disagreement between them and regulators is the result of easily debunked "faulty research data" produced by the politically biased research that confuses still-objective decision makers. Activists believe that as soon as they "enlighten" the administrators they will change their opinions and grant their approval. And if that scenario fails, there will always be the option for fair adjudication in the courts by impartial judges.

All the above assumptions are incorrect, and thus the methods based upon them will be futile. The current controversy over the role of repurposed drugs is not a matter of faulty science or remediable "misunderstanding." It is rather a result of a deep ideological divide, mutual distrust, philosophical incompatibility, and irreconcilability between the Right and the Left. Both political camps loathe each other. They both claim that their opponents are the ones who are spreading misinformation, silencing dissent, and engaging in dishonest practices. Neither is particularly interested in a respectful dialogue. However, the right wing wants to be left alone while the left wing is interested only in coercing its opponents to follow its will.

In addition, the agreement about the role of repurposed drugs in the early treatment of COVID and many other matters between two partisan sides cannot be achieved since those two sides rely on different sources of information and evidence. They have different concepts of the character, role, and relevance of science. They reason in different ways and have incompatible value systems.

Reliance of the right-wing activists on winning the "scientific dispute" with opponents who control both the traditional source of scientific expertise and the regulatory agencies is a failing strategy. This is not to say that science should not be of importance to the Right, as some claim. It should be important, but not as a "tool to persuade the Left." It should be used to assure that the repurposed remedy is indeed safe for the patient and that it holds at least a theoretical promise of therapeutic effectiveness.

Therefore, while continuing to strive to achieve scientific excellence and promote scientific literacy among their fellows, the Right should shift its strategy for securing access to repurposed drugs from the futile scientific disputes to a two-step strategy involving immediate action focused on legislation and long-term efforts to retake the instruments of power from the control of the Left.

Action to pass laws to make HCQ and IVM available can be modeled on initiatives that were successfully used by Republican politicians to curb the proliferation of harmful transgender treatments of children.<sup>62-63</sup> In fact, some Republican lawmakers have already proposed and even passed legislation related to the availability of HCQ and IVM for COVID-19 treatment. Here are some notable instances:

- **Kansas:** In Kansas, Republican lawmakers introduced legislation to limit medical licensing boards' ability to act against providers who prescribe HCQ and IVM for COVID-19. The bill aimed to leave such decisions to medical professionals rather than bureaucrats.<sup>64</sup>
- **Ohio:** Several Ohio House Republicans revived efforts to expand COVID-19 patients' access to IVM, HCQ, and other repurposed drugs.<sup>65</sup>
- **Missouri:** Governor Mike Parson signed a law shielding medical practitioners from losing their medical licenses when prescribing IVM or HCQ to treat COVID-19.<sup>66</sup>

## Understanding Drug Repurposing and Related Concepts

HCQ and IVM are only two examples of many repurposed drugs. A large part of the public has heard about "drug repurposing" only in the context of the COVID-19 pandemic. Hence, many people assume that this is a brand-new idea developed as the *ad hoc* response to the therapeutic challenge posed by the novel coronavirus SARS-CoV-2. In addition, there is a tendency among the public and even in a part of the medical community to confuse drug repurposing with related but different concepts such as "off-label use," various types of "drug substitutions," "conventional to nonconventional treatment conversions," and "selective optimization of side activities" (SOSA).

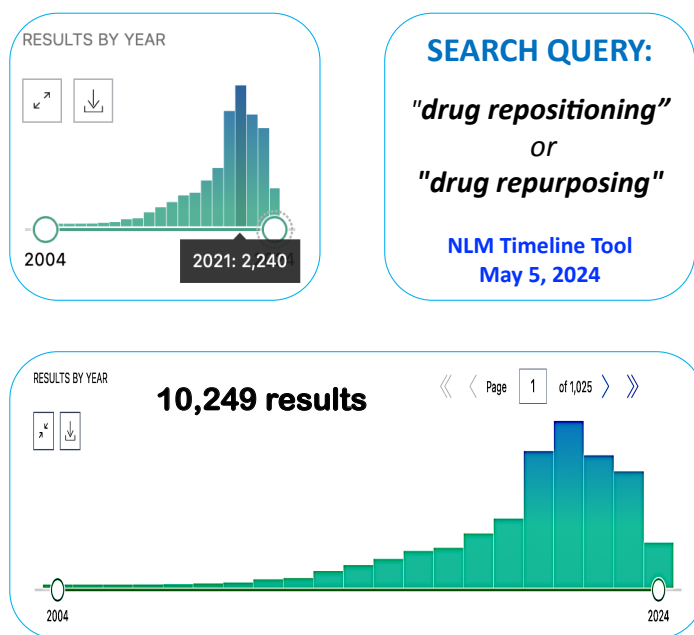
Moreover, it is imperative to correctly understand the background of those issues since they constitute important elements of the fierce partisan debates between left-wing-oriented officialdom (academia and industry) and right-wing-leaning medical and scientific dissenters that go beyond the single topic of repurposed drugs. Those crucial debates involve the ways of practicing medicine, the regulation of the medical profession, and the nature of the patient-physician relationship. The partisan divide on those matters preceded COVID-19 pandemic, but it was increased further by that historical event and related to its policies.

### Drug Repurposing

Drug repurposing, also known as drug repositioning, drug reprofiling, or drug rediscovery is formally defined as the process of finding new indications for existing drugs that are already approved, or failed the approval process, or are still investigated for other uses.<sup>67-73</sup> The informal practice of using the old drug to treat a different disease from the one for which the drug is primarily used is not new. It is as old as medicine itself.<sup>67,68,74,75</sup> Unbeknownst to public and even to part of medical community, many currently prescribed drugs were originally used for different purposes.<sup>76</sup> Those repurposed medications include the very old preparations like **aspirin** (first produced in 1853),<sup>77,78</sup> **dimethyl fumarate** (synthesized in 1819),<sup>79</sup> and more modern pharmaceuticals like **thalidomide**,<sup>80</sup> **sildenafil**,<sup>81</sup> **metformin**,<sup>82</sup> **semaglutide**,<sup>83</sup> **colchicine**,<sup>84</sup> **minoxidil**,<sup>85</sup> and others.

This *informal and serendipitous practice* of using an old drug to treat new conditions is obviously ancient. In contrast, the *formal, rigorous, and deliberate method* of drug repurposing was formulated in the year 2004 by Ashburn and Thor, who are also credited with developing the formal definition of this process.<sup>67,68</sup> Therefore, both as the informal practice and the formal drug discovery method of repurposing predate the COVID-19 pandemic by many years.

As shown in Figure 3, the number of publications related to “drug repositioning” or “drug repurposing” increased from single numbers per year before 2004 to the peak of 2,240 publications in 2021.

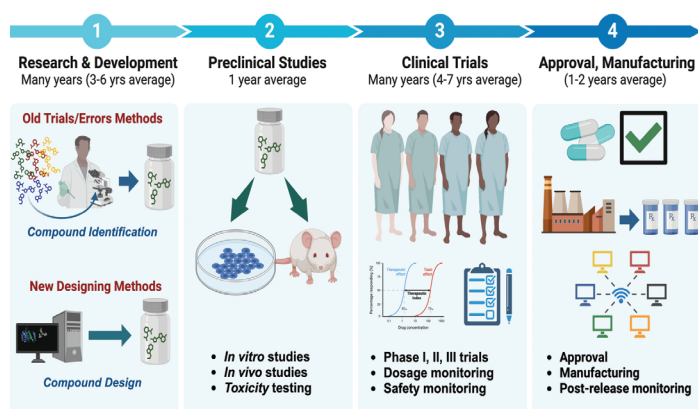


**Figure 3.** Publications related to “drug repositioning” or “drug repurposing” 2004-2024. NLM Timeline Tool, National Library of Medicine, Bethesda, Md.<sup>86</sup>

Figure 2 demonstrates that while the response to the COVID-19 pandemic cannot be credited with the discovery of drug repurposing, it increased its momentum. However, the impetus for drug repositioning had already been accelerating before the COVID-19 Global Emergency. The new journal *Drug Repurposing, Rescue, and Repositioning*, dedicated exclusively to drug repurposing, was founded in 2015.<sup>67,87</sup> Various drugs repurposing resources have been created, including internet hubs such as the “**Drug Repurposing Hub**” in 2017<sup>88</sup> and “**Drug Repurposing Central**.”<sup>88,89</sup> In addition, general open-access databases, such as **DrugBank**,<sup>90</sup> **ChEMBL**,<sup>91</sup> or **Open Targets**,<sup>92</sup> started to facilitate the drug repurposing by integrating the information on drugs, their targets, diseases, and clinical trials across different sources.<sup>90-92</sup> For more than a decade now, the growing global community of the drug-repurposing scientists could meet in person at their own international conferences. The 11th Annual Drug Repositioning & Repurposing Conference is scheduled to take place in 2024.<sup>93</sup> Numerous new startups focused solely on drug repurposing started to appear since 2004 and many achieved lasting success by 2017.<sup>67,94,95</sup>

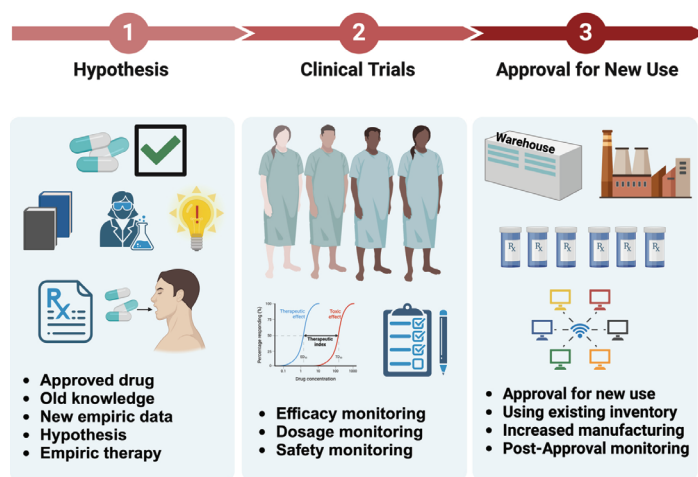
There were many good reasons for this meteoric rise of the concept of drug repurposing that started at the beginning of this century. This drug development strategy offers numerous advantages over the traditional drug discovery pipeline.<sup>75,96,97</sup> Those benefits include reduced cost, time, risk, regulatory hassles, and manufacturing issues; improved safety, and overall increased chances for both clinical and economic success of the drug.<sup>75</sup> Figures 4 and 5 show the novel drug development process and the drug repurposing pathways, respectively.

## Novel Drug Development Process



**Figure 4.** Novel drug development process

## Drug Repurposing



**Figure 5.** Drug repurposing method

The novel drug development process is lengthy, complex, and very expensive; includes elaborate and time-consuming approval proceedings; and is fraught with many risks including emergence of long-term side effects. Clearly, the repurposing pathway appears to be superior to novel drug development. Since the repurposed drug has been approved for other uses it already went through the mandated thorough safety testing.<sup>97,98</sup> The medication is already on the market, its manufacturing has been mastered, and there is typically a large inventory of it already stored in warehouses. The approval process (including clinical trials) for the drug's new use is the only significant impediment that repurposed drug faces. Regulators require this step to confirm the purported efficacy and safety of the repurposed drug for its new indication. Their specific concerns are: (1) the repurposed drug may not perform as well in the real world as the theory-driven conclusions, laboratory experiments, anecdotal data, and limited clinical research would imply and (2) it can cause new adverse effects, unexpected interactions with other drugs, and/or unpredicted pharmacokinetic issues when used for different conditions and in different settings and populations.<sup>97-99</sup>

Fortunately, in certain circumstances a repurposed drug can be prescribed for “off label” indications (see below) while its formal validation takes place.

Before the 21st century, all the advantages of drug repurposing were hampered by the purely serendipitous nature of discovering new indications for established drugs.<sup>96,98,100</sup> Due to scientific and technological limitations, the repurposing process was based upon sheer luck. However, during the last two decades, rapid advances in genomics, bioinformatics, computation, and artificial intelligence have caused a significant paradigm shift. Those emerging technologies have made it possible to identify on demand new molecular targets, pathways, and mechanisms of action for existing drugs based on large-scale data analysis.<sup>101-107</sup> To describe those changes, the newly coalesced “repurposing industry” has formulated the following quite self-promoting narrative:<sup>89</sup> ***The informal and haphazard-based practice of drugs repurposing has been replaced by the much better formal mechanism-based and in silico modeling-aided methodology.***<sup>89,97,98</sup>

That narrative has been adopted without much questioning by mainstream academia.<sup>96</sup> In accordance with the modern academicians’ modus operandi, a “consensus” has been reached among them that those improved drug-repurposing methods are formidably more agile and robust alternatives to the traditional sluggish and cumbersome drug development techniques.<sup>96,98,108,109</sup>

It is more difficult to study the views of medical dissidents regarding drug repurposing as compared to those of mainstream academicians. Medical dissenters are not bound by the imperative of totalitarian “consensus.”<sup>110,111</sup> They are not as ideologically uniform in their opinions and education as the members of academia. Unlike academia, the medical freedom community (MFC) has no strict vetting process, formal credentialing, or quality control.<sup>5</sup> That can be both a blessing and a curse. Medical dissidents are not given a large platform within the mainstream scientific publications to express their views. Even if their work is occasionally published in the mainstream scientific journals, it is frequently subjected to mobbing and ultimately retracted.<sup>15,112,113</sup> As a result, their opinions must be published on platforms not indexed by the National Library of Medicine such as independent journals, Substack, X (formerly Twitter), or disseminated as lectures on video platforms resistant to censorship such as Rumble.<sup>114-118</sup> Moreover, many nonconforming clinicians are too busy with treating their patients and defending themselves from the lawfare unleashed on them by officialdom. Hence, they do not have a lot of time for disseminating their opinions. Nevertheless, one can identify the general characteristic of the attitudes the MFC towards drug repurposing. Drug repurposing of any type is welcomed and encouraged by the MFC since it is perceived as benefiting patients by providing them with more affordable options. MFC has no problem with the “serendipitous” type of repurposing, recognizing the fact that many independent right-wing clinicians may in fact be able to make such “serendipitous” discoveries as demonstrated by case of Dr. Vladimir Zelenko.<sup>119</sup> The MFC has, however, understandable skepticism about the claims of the newly formed “mechanism-based” repurposing industry.

### Off-label Use

While drug repurposing aims to discover new therapeutic indications for existing drugs, off-label use refers to the prescription of a drug for an indication, population, dose, or route of administration that is not approved by the regulatory

authorities.<sup>120</sup> Theoretically, off-label use is a common and legal practice in many countries, especially when there is a lack of alternative treatments or evidence-based guidelines.<sup>121</sup> However, off-label use can also pose ethical, legal, and clinical challenges, such as increased risk of adverse events and liability issues.<sup>122</sup> This can be especially true if the prescribed off-label treatment is considered to be not “politically correct” by the authorities. Therefore, off-label use should be used very carefully and judiciously and always based on sound scientific rationale, clinical judgment, and patient consent.

Drug repurposing and off-label use are related but distinct concepts. Drug repurposing can lead to off-label use if the new indication is not formally approved by the regulators. Conversely, off-label use can provide clues for drug repurposing if the observed clinical outcomes suggest a new mechanism of action or a new target population.

### Generic and Therapeutic Drug Substitution

Drug repurposing and drug substitution are also different concepts. **Drug substitution** refers to the replacement of a prescribed drug with another drug that has the same active ingredient, strength, dosage form, and route of administration.<sup>123</sup> Drug substitution can be either **generic** or **therapeutic**.<sup>124</sup> Generic substitution involves switching a brand-name drug with a generic version that has the same active ingredient and bioequivalence. Therapeutic substitution involves switching a drug with another drug in the same pharmacological class that has similar therapeutic effects but may have a different active ingredient.<sup>125</sup> Drug substitution is usually motivated by cost savings, availability, or formulary restrictions. However, drug substitution can also have potential risks, such as drug interactions, allergies, or reduced efficacy.

### Conventional to Nonconventional Treatment Conversion

The practice of replacing conventional pharmaceuticals with a variety of unapproved substances such as dietary supplements, investigational drugs, “natural products,” etc. does not have a specific term that is widely recognized or used in professional medical contexts. Yet, this occurs frequently especially in “non-orthodox” practices. As can be expected, officialdom is not supportive of those practices. According to FDA: “*Substituting an unapproved drug for the FDA-approved drug prescribed by a patient’s healthcare practitioner can negatively affect patient outcomes because the healthcare practitioner may unknowingly make subsequent treatment decisions based on the patient’s response to the unapproved drug.*”<sup>126,127</sup> Such an attitude is unfortunate since selected individual patients in certain circumstances can benefit greatly from such interventions.

### Selective Optimization of Side Activities (SOSA)

This is mentioned here for the sake of completeness. The elegantly clever drug discovery method known as the selective optimization of side activities (SOSA) described by Wermuth is sometimes lumped into the drug repurposing cluster.<sup>128,129</sup> However, this approach falls outside the scope of repurposing. In the SOSA approach, the biological properties deemed responsible for a drug’s adverse effects in a particular indication are isolated and amplified through chemical modification so that the modified drug can be proposed for a new indication.

## Conflicting Views of Authorities on Drug Repurposing during COVID-19 Pandemic

Before the outbreak of the COVID-19 pandemic, “settled opinion” within academe held that advanced “mechanism-based” drug repurposing is capable of instantaneously developing safe and effective remedies in case of sudden massive emergencies including pandemics. And such crises were anticipated by both medical experts and intelligence agencies,<sup>130-132</sup> long before the COVID-19 Global Emergency. While the public was mostly unaware of those developments, after the onset of the COVID-19 pandemic many mainstream academic and industry scientists turned their attention to advanced drug repurposing.<sup>108,109,133,134</sup> They were hoping that it would deliver on its promise of promptly furnishing an efficient therapeutic solution to the scourge of COVID-19.<sup>109</sup> Interestingly, for some reason the results were either “mixed” or disappointing for the mainstream experts.<sup>16,134-138</sup> More than 1,800 trials for possible COVID drugs have been initiated according to the NIH ClinicalTrials.gov website.<sup>139-140</sup> In those trials, a vast number of pharmaceuticals including variety of antiviral, anti-inflammatory, and immunomodulating medications as well as oncological, pulmonary, cardiological, and many other types of drugs were tested.<sup>140,141</sup> The selection of candidates for repurposing followed the officially favored “mechanism-based paradigm” that considered both in vitro and in silico activity against SARS-CoV-2, or previous therapeutic success in treatment of diseases related to COVID-19 viral diseases.<sup>44, 142</sup> And yet, from the viewpoint of the mainstream scientists none of the tested drugs has showed the efficacy that they hoped for.<sup>44,140,143,144</sup> It is notable that the undesired tacit clinical success of HCQ and IVM is never discussed by members of the mainstream medicine in this context.

At any rate, it is clear that before the COVID-19 pandemic, officialdom was very fond of the idea of repurposing. Indeed, since 2016, drug repositioning is becoming strongly supported by governments, non-trading organizations and academic institutions.<sup>105</sup> For example, both the U.S. (National Center for Advancing Translational Sciences) and the United Kingdom (Medical Research Council) launched large-scale funding programs in this area with a goal to extend molecules that already have undergone significant research and development by the pharmaceutical industry to more new indications. Somehow the COVID-19 pandemic has mysteriously changed that enthusiasm. The official explanation given is that while repurposing is an attractive option for drug discovery it also poses significant scientific, technical, and ethical challenges that require multidisciplinary collaboration and coordination among various stakeholders, such as researchers, clinicians, regulators, industry, and patients, which is sometimes hard to achieve. Furthermore, it was observed that the regulatory and intellectual property aspects and profit margins of the drug repurposing processes must be carefully considered, as they may affect the incentives and rewards for the developers.<sup>96,145</sup>

### The History of Hydroxychloroquine Repurposing

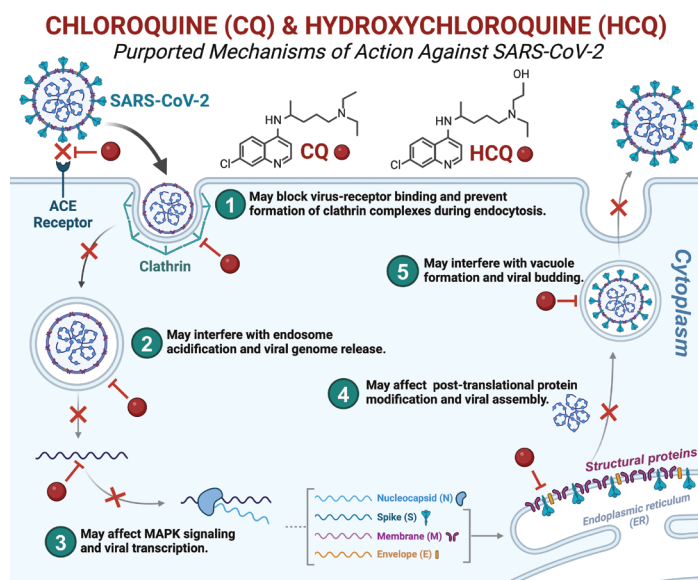
The initial history of repurposing HCQ is described below, with refutation of the official narrative about this, and the presence of negative evidence is pointed out.

HCQ is a derivative of chloroquine (CQ), a synthetic compound that was first developed in the 1930s as a treatment

for malaria. CQ and HCQ have also been used to treat other diseases, such as rheumatoid arthritis and lupus, because of their anti-inflammatory and immunomodulatory effects.<sup>146</sup> Other potential applications of this medication, including use in infectious, neoplastic, and neurological diseases, were considered in the not-so-remote past.<sup>147</sup>

It has been known that HCQ, like any effective therapeutic, can have potential serious side effects including cardiac toxicity, retinal damage, and neuropsychiatric disorders, and require careful monitoring and dosage adjustment.<sup>48,148</sup> However, as an outstanding clinician once noted: one should not use drugs with no potential significant side effects since such drugs would be therapeutically inert.<sup>149</sup>

The idea that HCQ might be effective against COVID-19 emerged from the observation that the drug could inhibit the entry and replication of some coronaviruses in vitro, by interfering with the pH-dependent fusion of the virus with the host cell membrane.<sup>10</sup> As presented in Figure 6, other antiviral mechanisms have been proposed as well.<sup>150-151</sup>



**Figure 6.** Hydroxychloroquine: purported mechanisms of actions against SARS-CoV-2

A number of frequently cited basic studies prompted the idea that HCQ could be effective against COVID-19. Yao et al.<sup>152</sup> showed that HCQ had a higher potency than CQ in inhibiting SARS-CoV-2 infection in Vero cells, a monkey kidney cell line commonly used for viral studies. The study also estimated the optimal dose and duration of HCQ for COVID-19 patients based on pharmacokinetic and pharmacodynamic modeling.

Liu et al.<sup>153</sup> showed that HCQ was more effective than CQ in blocking the entry and fusion of SARS-CoV-2 with human lung cells (A549) and African green monkey kidney cells (Vero E6). The study also suggested that HCQ could interfere with the glycosylation of the angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, and thus reduce its binding affinity to the viral spike protein.

Wang et al.<sup>154</sup> showed that both remdesivir, an antiviral drug, and CQ, an antimalarial drug, could inhibit SARS-CoV-2 infection in Vero E6 cells at low-micromolar concentrations. The study also reported that CQ was highly effective in preventing the spread of SARS-CoV-2 in cell culture. Since HCQ is a less

toxic derivative of CQ, this study raised the possibility that HCQ might be useful against SARS-CoV-2.

It is worth noting that many of those effects were only observed at concentrations that were much higher than those that could be achieved in human plasma without causing toxic effects to human cells. Also, in vitro studies do not necessarily translate to in vivo results, as many factors, such as pharmacokinetics, pharmacodynamics, immune response, and viral mutation, can affect the outcome. Hence the in vitro studies are only the first step in the journey of drug discovery.

The first clinical studies that suggested a possible benefit of HCQ for COVID-19 were conducted by a French team led by Dr. Didier Raoult.<sup>12,134</sup> The study, published in March 2020, involved 36 patients with COVID-19, who were divided into two groups: one received HCQ alone or in combination with azithromycin, an antibiotic, and the other received standard care. The study claimed that HCQ, especially when combined with azithromycin, reduced the viral load, and shortened the duration of symptoms. This study has been heavily criticized. It has been pointed out that it had many methodological flaws, such as lack of randomization, blinding, and a control group; small sample size; selective reporting of outcome; and confounding factors. The study was also disparaged for ethical violations, such as lack of informed consent and peer review, and potential conflicts of interest, as Raoult had filed a patent for the use of HCQ and azithromycin for COVID-19. Ultimately, the research of Dr. Raoult has been retracted due to the pressure of mainstream scientists.<sup>15</sup>

While Dr. Raoult delivered research data about the utility of HCQ in the treatment of COVID-19, Dr. Vladimir Zelenko, a New York-based physician, provided tacit clinical observations. He claimed to have cured hundreds of patients with a combination of HCQ, azithromycin, and zinc, and wrote an open letter to President Trump, urging him to adopt his protocol.<sup>11,119</sup> Zelenko's claims were widely circulated online and were cited by Trump and other politicians as evidence of HCQ's efficacy.

In view of its hopeful potential in desperate times, Dr. Raoult's research and Dr. Zelenko's anecdotal data received widespread attention and endorsement from various influential figures including U.S. President Donald Trump, who repeatedly praised HCQ as a "game changer" and a "miracle drug" for COVID-19, and claimed to have taken it himself as a preventive measure.<sup>13</sup> Trump's statements were amplified by conservative media outlets, such as Fox News, and social media platforms, such as Twitter and Facebook, where HCQ was a trending item.<sup>42</sup> Eventually, the FDA authorized the use of HCQ for COVID-19 under an Emergency Use Authorization (EUA), which it ultimately revoked.<sup>17</sup>

While the majority of right wingers embraced HCQ after endorsement by President Trump, the initial response of left-wing-aligned mainstream scientists was politely speaking "cautious" since President Trump was not a very popular figure within this community.<sup>14,16</sup>

Due to public pressure several initial clinical trials were launched to evaluate the efficacy and safety of HCQ for COVID-19, both as a treatment and as a prophylaxis.<sup>155-157</sup> According to mainstream scientists, those results were not encouraging. With time, more clinical trials were conducted:

- The RECOVERY Trial,<sup>158</sup> conducted by the University of Oxford, involved more than 11,000 patients with COVID-19 in the UK, and compared HCQ with standard care. The trial found no difference in mortality, hospitalization, or recovery

between the two groups, and concluded that HCQ had no clinical benefit for COVID-19.

- The ORCHID Trial,<sup>159</sup> conducted by the National Institutes of Health, involved more than 470 patients with COVID-19 in the U.S., and compared HCQ with placebo. The trial was stopped early due to lack of efficacy, as HCQ did not improve clinical outcomes or reduce viral load.
- The COPCOV Trial, conducted by the Mahidol Oxford Tropical Medicine Research Unit,<sup>160</sup> planned to involve more than 40,000 medical workers in 30 countries, to compare HCQ with placebo for the prevention of COVID-19. The trial was halted early due to lack of efficacy, as HCQ did not reduce the incidence of COVID-19 or its complications.

The results from these trials, along with many others, have been used by the mainstream scientific community to craft the narrative according to which irrefutable evidence shows that HCQ was not effective for COVID-19, and could even be harmful. Based on this narrative, the scientific community and regulatory agencies changed their stance and withdrew their support for HCQ. The World Health Organization (WHO) discontinued the HCQ arm of its Solidarity Trial in June 2020, citing lack of benefit. The FDA revoked the EUA for HCQ and CQ in June 2020, stating that the drugs were unlikely to be effective and could cause serious side effects. The CDC also removed its guidance for the use of HCQ and CQ for COVID-19 and advised against their use outside of clinical trials or approved programs.

However, while the official narrative was very smooth on the surface, the saga of HCQ was not without controversy and confusion, as some of the research results by mainstream medical researchers had to be withdrawn due to poor quality and concerns about bias and fraud. One of the most notorious examples was a study published in *The Lancet* in May 2020, which claimed that HCQ increased the risk of death and heart problems in patients with COVID-19, purportedly based on a large database of medical records from 96,000 patients in 671 hospitals across six continents.<sup>161,162</sup> The study, led by Dr. Mandeep Mehra, a cardiologist and professor at Harvard Medical School, received widespread attention and media coverage, and prompted the WHO and several countries to suspend their HCQ studies. However, soon after its publication, the study was challenged by several scientists and clinicians, who raised questions about the validity and veracity of the data, the methodology and analysis, and the conflicts of interest of the authors. The data source, a company called Surgisphere, which was founded and owned by one of the co-authors, Dr. Sapan Desai, turned out to be obscure and unreliable, and refused to share its raw data or code for independent verification. The authors admitted that they could not vouch for the accuracy of the data, and requested *The Lancet* to retract the study, and it did so in June 2020, along with issuing an apology and an expression of concern.

A similar study, published in the *New England Journal of Medicine* in May 2020, which used the same data source and involved some of the same authors, was also retracted in June 2020, for the same reasons.<sup>164,165</sup>

The retractions of these studies, which were widely publicized and politicized, caused a major embarrassment and damage to the credibility and reputation of the scientific community and the medical journals, and fueled the distrust and skepticism of the public.<sup>163</sup> The mainstream scientific community has acknowledged the limitations and challenges of conducting and disseminating research during a pandemic

but maintained its previous narrative about “overwhelming and conclusive” evidence of inefficacy of HCQ in treatment of COVID-19. Despite this official narrative, various groups of medical dissidents continue to promote and use the drug for treatment and prevention of COVID-19 based upon their own and their colleagues’ tacit clinical experience. One of the most vocal and visible groups that advocated for HCQ was America’s Frontline Doctors, a coalition of physicians and health professionals that claimed to represent the Medical Freedom Movement. This right-wing-aligned group held a press conference in July 2020 in front of the U.S. Supreme Court, where they denounced the mainstream medical and scientific establishment, and asserted that HCQ was an effective method for COVID-19.<sup>165</sup> It is beyond the scope of this editorial to list all the individuals and groups who contributed to maintaining the opinion that repurposed HCQ is a safe and effective option for treatment of COVID-19.

From this summary one can discern that, from the beginning of the HCQ controversy, powerful medical officialdom has meticulously crafted an elaborate narrative against the use of this repurposed medication for early treatment of COVID-19. This narrative is backed by very sophisticated research studies, some of which have been discovered to be fraudulent, but still contain a formidable body of evidence—at least in officialdom’s opinion. However, despite this façade of grandeur, there are signs of unsound construction.

## Refutation of Official Reasons for Treatment Denial

### Alleged Ineffectiveness

The clinical trials data presented by officialdom, while very elaborate, appears to be untrustworthy for many reasons.

There is a **virtually unprecedented discrepancy** between allegedly perfect formal clinical trials data showing “absolute lack of efficacy” and the massive tacit informal clinical observations that show that this treatment works. In contrast to the popular evidence-based medicine fallacy, the plural of (credible) anecdotes is in fact evidence. The **negative evidence** is that there are no robust attempts on the side of the academic researchers to pre-empt the expected concerns about this discrepancy by running a modeling study or performing supplemental research.

There was demonstrated **fraud** in at least two research studies by prominent Ivy League academicians, as noted above. The fraud was discovered because the principal investigator was sloppy. The possibility that more (if not all) of the studies in officialdom’s portfolio are falsified cannot be excluded. The fraudster may have been more diligent and skillful. The **negative evidence** is that while there has been much talk about preventing the recurrence of fraudulent research, there has been little if any effective action designed to prevent fraud and provide transparency.

There is huge potential for **conflict of interest**. It is indeed all too convenient that proving ineffectiveness of this affordable repurposed drug would enormously benefit vaccine manufacturers and makers of designer antiviral drugs. Those businesses are the most generous sponsors of the involved researchers themselves as well as their institutions and political leaders. **Negative evidence** is that this subject is simply avoided by the researchers; they prefer silence to making clear denial.

It is obvious that the academic community loathes the politician who endorsed this treatment. Even academicians can

be subject to **emotional bias**. Again, silence is the preferred line of defense here.

**Clinical trials deal with populations not individuals.** Physicians treat individual patients not “populations.” Even if one single patient will respond better to this treatment than the “composite population model,” the use of HCQ is justified. The **negative evidence** is a striking lack of discussion of prominent outliers within data sets.

### Alleged Harm

Harms reported in the studies are **highly improbable**. HCQ has been approved for a long time. Its side effects are well-known in various patients who take it while being affected by a variety of accidentally concomitant diseases including severe viral illnesses. By what unexplained mechanism did an otherwise safe medication become a lethal cardiotoxic agent when administered to patients with COVID-19? Moreover, HCQ is being used for COVID-19 treatment on a much larger scale than officialdom acknowledges. **Why do we not see a massive wave of cardiac side effects** from HCQ in this country and in poor countries that use this medication heavily? The **negative evidence** is that those obvious discrepancies were never addressed.

### Alleged Low Risk: Benefit Ratio

Even if HCQ is indeed therapeutically inert in the specific patient, or worked via placebo effect, the risk: benefit ratio would be still acceptable. Officialdom itself recommended **no treatment** as the management option of choice for outpatients. Hence, even if HCQ is inactive, giving it to the patient would result in the precisely same treatment as called for by the official “evidence-based” guidelines.

### Summary

There are no valid reasons to deny HCQ to any patient who is in a suitable state of health, has no specific contraindication for taking HCQ, and is able to provide informed consent.

### Conclusion

Despite evidence for their safety and usefulness, HCQ and IVM are opposed by officialdom for use in COVID-19. “No treatment” may be recommended instead. Patients have sometimes been able to get limited access through the “off label” option, but this is very risky for physicians and pharmacists. The formal, rigorous, and deliberate method for repurposing drugs, defined in 2004, had the strong support of academia, but for some reason fell out of favor with COVID. The heavily politicized obstruction of safe, affordable, effective treatment is not acceptable and must be changed, most realistically by aggressive legislative actions.

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