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Viewpoint

The regrettable story of the “Covid Kit” and the “Early Treatment of Covid-19” in Brazil

Leonardo Furlan^{1,*}, Bruno Caramelli^{1,2}¹ University of São Paulo Medical School, São Paulo, Brazil² Interdisciplinary Medicine in Cardiology Unit, InCor, São Paulo, Brazil

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From an evidence-based medicine perspective, drug prescriptions should be based on credible systematic reviews with meta-analyses of randomised controlled trials that provide sufficiently trustworthy estimates of the efficacy and safety of the respective drugs [1]. Otherwise, physician and patient may mistakenly balance benefits and harms during the application of values and preferences, which can compromise clinical decision making and bring unwanted consequences [2].

At the beginning of the Covid-19 pandemic, facing growing numbers of hospitalisations and deaths due to SARS-CoV-2 infections, physicians around the world were taken over by despair and an emotional need to offer “something” to their patients. This, and the severity of the whole situation, motivated a worldwide search for potential treatments for Covid-19, which in turn led to the repositioning of several drugs that started to be investigated in research and used off-label in clinical practice, mainly in severely/critically ill hospitalised patients. The off-label utilisation of repositioned medications against Covid-19 at that time became quite problematic when prominent politicians such as Donald Trump started to promote unproven drugs as silver bullets for fighting the disease [3]. This “infusion of politics into science” [4] likely sparked the widespread off-label use of several medications against Covid-19 in many countries, including in the US and Brazil, despite the international scientific community advising against this practice [3].

In Brazil, already from March 2020, largely spearheaded by president Bolsonaro, several actions that favour the spread of the new coronavirus were put into practice in the country, not only by public authorities but also by physicians [5]. These actions in-

cluded, among others, the blatant promotion of unproven drugs against Covid-19, such as hydroxychloroquine, ivermectin, and nitazoxanide, on one hand, and the sabotage of established interventions, such as social distancing, mask-wearing, and vaccination, on the other hand [5]. In a politically inflamed and understandably frightened population in which many people have difficulties in making informed health choices, this can have catastrophic consequences.

In 2020, prescriptions and sales of hydroxychloroquine, ivermectin, and nitazoxanide skyrocketed in Brazil [6], which led to a shortage of some of these medications on the market and hence adversely affected those who made on-label use of these drugs. For instance, hydroxychloroquine is commonly used in Brazil for the treatment of malaria, lupus, and rheumatoid arthritis. According to a survey performed in July 2020, some cities faced problems of hydroxychloroquine shortage in their pharmacies at that time, which impaired the treatment of many rheumatic patients who made continuous use of the drug [7].

Physicians prescribing drugs off-label to Covid-19 outpatients in Brazil have been backed and encouraged by a decision from the Brazilian Federal Board of Medicine issued in April 2020 that authorised, in the name of “physician’s autonomy,” the prescription of hydroxychloroquine to early/mild Covid-19 cases, [8] and by a protocol from the Brazilian Ministry of Health guiding the use of hydroxychloroquine and azithromycin in the treatment of non-hospitalised Covid-19 patients, that remained in effect from May 2020 to May 2021 [9]. The main goal of this protocol was to increase patients’ access to the so-called “Early Treatment of Covid-19” through the Brazilian public healthcare system [9]. It is noteworthy that, in late August 2021, the Federal Board of Medicine’s decision is still in effect.

Drugs like hydroxychloroquine, ivermectin, and nitazoxanide have been prescribed for Covid-19 in Brazil (even to unconfirmed

* Corresponding Author: Leonardo Furlan, Address: Av. Dr. Arnaldo, 455 – Cerqueira César, CEP: 01246903, São Paulo, SP, Brasil, Telephone: +55 11 3061 7379
E-mail address: leonardo.furlan@fm.usp.br (L. Furlan).

cases) often by means of the so-called “Covid Kit,” which usually also includes other medications such as azithromycin and systemic corticosteroids. The “Covid Kit” came up in Brazil early in the pandemic and has since been promoted by the “Physicians for Life,” a medical organisation created for disseminating the “Early Treatment of Covid-19” in the country. The rationale underpinning this initiative is that by treating patients precociously with these drugs it is possible to prevent disease worsening and hence avoid hospitalisation, intubation, and death. Both the conception and creation of this organisation found great support in the Federal Board of Medicine’s decision and in the Ministry of Health’s protocol. Moreover, at the beginning of the pandemic, also contributing to the dissemination of the “Early Treatment of Covid-19” in Brazil, private healthcare providers and municipal governments started to distribute the “Covid Kit” to their physicians, for both personal use and prescription to patients.

In August 2020, members and supporters of the “Physicians for Life” attended an event called “Brazil Beating Covid-19” at the Presidential Palace, when a letter promoting the “Early Treatment of Covid-19” was handed to Bolsonaro, who received it with much gratitude and enthusiasm [10]. Through online courses, conventional media appearances, an overt backing from the federal government, and a strong social media presence, the “Physicians for Life” movement has influenced many people in the country, not only health professionals but also the lay population who, understandably, is frightened and disoriented since the beginning of the pandemic. For instance, likely presuming that benefits outweigh harms, approximately one in every four individuals in Brazil has taken drugs from the “Covid Kit” as prophylaxis or treatment for Covid-19, including through self-medication [11]. Moreover, data from the “DETECToV-19” study showed that, among people with a previous Covid-19 diagnosis, 56% had taken medications as treatment for the disease, usually combining different drugs from the “Covid Kit” [12]. Nineteen percent had taken (hydroxy)chloroquine, 55% ivermectin, 8% nitazoxanide, 77% azithromycin, and 26% corticosteroids [12].

Notably, the “Covid Kit” and its drugs individually have been promoted and prescribed in Brazil based on anecdotal evidence, personal experiences and opinions, *in vitro* studies with drug dosages exceeding safety limits in humans, clinical studies of poor methodological quality yielding untrustworthy estimates of efficacy and safety, systematic reviews with meta-analyses without credibility, political ideology and, above all, “physician’s autonomy.” There has never been a sound scientific basis that would justify the promotion and prescription of these medications outside a research context.

One key point of this discussion is the importance of not extrapolating efficacy and safety evidence from the hospital setting, which usually involves people with advanced disease/severe symptoms, to the contexts of outpatient treatment and prophylaxis, which otherwise involve earlier disease/milder symptoms and healthy/non-infected people, respectively [13,14]. The therapeutic priorities and hence the outcomes of interest are likely different in each of these three situations, as well as the pathogenesis of early versus advanced Covid-19 [13,14].

Currently, the results from credible systematic reviews with meta-analyses of randomised controlled trials do not support the utilisation of the “Covid Kit” drugs for outpatient treatment and prophylaxis of Covid-19 outside clinical studies. For some of these drugs, the evidence is still either lacking or insufficiently trustworthy (very low- to low-certainty estimates of efficacy/safety), rendering their clinical effects very uncertain [15], while for others, the evidence is already trustworthy enough (moderate- to high-certainty estimates of efficacy/safety) and reveals no clinical benefit and/or an increased risk of harm [16].

Accordingly, international guidelines currently recommend/suggest against using the “Covid Kit” drugs in the contexts of outpatient treatment and prophylaxis of Covid-19 outside clinical studies, not only because of still unproven clinical benefits, but also because of the harmful potential of these drugs [17,18]. The NIH’s guideline recommends against the use of hydroxychloroquine, azithromycin, nitazoxanide, and systemic corticosteroids for both prophylaxis and outpatient treatment of Covid-19 [17]. Due to still very uncertain benefits and the possibility of serious adverse events, the IDSA’s guideline suggests not using ivermectin in non-hospitalised Covid-19 patients [18]. Notably, the Brazilian Medical Association and the Brazilian Societies of Infectious Diseases and of Pulmonology and Tisiology currently also recommend against the use of these drugs for both prophylaxis and treatment of early/mild, non-hospitalised Covid-19 cases.

Compared with placebo, hydroxychloroquine probably does not reduce the risks of SARS-CoV-2 infection and hospitalisation of Covid-19 outpatients, and its use for prophylaxis probably increases the risk of adverse effects [16]. Furthermore, hydroxychloroquine and azithromycin can both cause serious cardiac problems, even more so when in combination with each other, which is particularly worrisome in the outpatient setting [17]. Moreover, the indiscriminate use of antibiotics may increase bacterial resistance. Systemic corticosteroids have shown benefit only for hospitalised patients receiving respiratory support [13,17,18]. The use of these drugs is associated with adverse effects that might be difficult to monitor outside the hospital, and their utilisation in early Covid-19 may even increase viral replication, which in turn may result in further harm [13,17]. With regards to ivermectin, there have been reports from different countries, including Brazil and the US, of people being hospitalised after self-medicating and intoxicating themselves with the drug.

Ivermectin has long been promoted in the US as a prophylaxis and early treatment medication against Covid-19 by the “Front Line COVID-19 Critical Care (FLCCC) Alliance,” an American medical organisation created in early 2020. The group has published several Covid-19 protocols, one of which is centred on ivermectin for both prophylaxis and early treatment. This protocol was translated into several languages, including Portuguese. In July 2021, physicians from both the “Physicians for Life” and the “FLCCC Alliance” took part in the “World Ivermectin Day,” an international online conference that celebrated the end of Covid-19 with ivermectin. The event was also joined by other affiliated international groups, such as the “British Ivermectin Recommendation Development (BIRD) Group.” This is all very worrying, as currently there is no scientific basis whatsoever for such an enterprise [15]. Perhaps this is all being motivated by a strong desire to be free from the virus and out of risk, a search for prestige, or simply an interest in disseminating fake news.

Besides the toxic potential of an unsupervised and combined utilisation of the “Covid Kit” drugs, the belief that there are widely accessible harmless medications that can prevent and/or treat Covid-19 precociously might result in the abandonment of more burdensome, yet more effective and safer protective measures, such as social distancing and mask-wearing, because of a sense of protection afforded by the drugs. In support of this hypothesis, data from the “DETECToV-19” study showed that the prevalence of SARS-CoV-2 infection was 50% higher among those who self-medicated as prophylaxis for Covid-19 (25% of the study’s sample) [12].

Although belatedly and slowly, vaccination in Brazil is moving forward. However, national vaccination coverage is still low, with less than 30% of the entire population fully immunised in late August 2021, [19] and many people remain resistant to getting their shots due to concerns about vaccines’ efficacy and/or safety. People must not mistakenly choose ineffective/unproven and potentially

harmful drugs over approved, and therefore effective and safe vaccines. Indeed, full control of the Covid-19 pandemic will require, in addition to vaccines, the use of medications that can prevent and treat infections precociously and that are safe, widely accessible, and easily administered [13]. Unfortunately, these drugs do not yet exist, but many studies are being conducted.

The merit of the “Early Treatment of Covid-19” with the “Covid Kit” drugs is an essentially scientific issue, but which regrettably became political. This has resulted in serious conflicts in Brazil among physicians, scientists, and even the lay population. As a society, people should be united in the name of a common goal, which is to tackle Covid-19 in the most effective way possible. Not following recommendations from established national and international scientific/medical entities leads to a waste of efforts and resources, causes more suffering, and certainly does not contribute to achieving this goal.

The “Early Treatment of Covid-19” with the “Covid Kit” drugs is part of an international project with ongoing activities in different countries. Although praiseworthy, unfortunately, the “Covid Kit” project has all along been devoid of the required scientific basis. For the time being, the Brazilian Federal Board of Medicine should officially prohibit the “Early Treatment of Covid-19” in Brazil with the “Covid Kit” drugs. Furthermore, the efforts and resources that have long been employed by public authorities and physicians in the promotion of this project should be directed to maximise adherence to vaccination and non-pharmacological protective measures in the country. After all, the Delta variant is already here and threatens Brazil with another outbreak, [20] which demands not only the maintenance/implementation of truly effective protective measures, but also the abolition of any unscientific, distracting, and potentially harmful interventions. Moreover, it is necessary to expand and strengthen already existing initiatives of evidence-based medicine teaching and training for health professionals in Brazil. Ensuring clinicians’ adherence to an evidence-based practice is equally important. Finally, educational interventions aimed at improving people’s ability to make informed health choices are desperately needed in the country.

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LF conceptualised and wrote the first and subsequent versions of the manuscript. BC revised and commented on the first and subsequent versions of the manuscript. Both authors approved the submitted version of the manuscript.

Declaration of interests

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The interested reader may consult a more extensive bibliography on the Portuguese version of this Viewpoint (see Supplementary materials).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lana.2021.100089](https://doi.org/10.1016/j.lana.2021.100089).

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