The Pharmacist Activist

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"Jesus Christ is the same yesterday, today, and forever." Hebrews 13:8b

Editorial

# COVID-19 – Two Years Later

## Early 2020

COVID-19, hospitalizations, deaths, over-crowded hospitals, fear, hand-washing, masking, social distancing, supply chain issues, school, business, and entertainment closures, mandates, economic challenges, profit motivation, partisan politics, withheld information, false and misleading information, publications retracted, sensational and politicized media coverage, hypocrisy, accusations, threats, distrust, and more.

## Early 2022

Two years and trillions of dollars later --- We still have *all of the above*, although with some to varying degrees. We now have COVID-19 tests, COVID-19 vaccines, and medications that are active against COVID-19, and their development represent important advances. However, even these accomplishments are also replete with questions and allegations regarding availability, effectiveness, and long-term safety, and clarification of important questions is not being actively sought or ignored.

There are many whose knowledge of immunology, viruses, and vaccines far exceeds mine. I learn from them and my additional study of often diverse views of these issues to form my opinions and recommendations, as well as to identify questions for which objective information and clarification are not currently available. In the May, 2021 issue of The Pharmacist Activist, I identified my opinions and questions with respect to COVID-19. As additional information and products (e.g., vaccines, oral antiviral agents) become available, I have endeavored to integrate it with previous knowledge, reasoning, common sense and risk aversion in providing my current perspectives and opinions that follow.

## Perspectives and opinions

1. COVID-19 can cause fatal complications, and efforts to prevent and treat the infection must continue to receive a very high priority.
2. The most credible explanation is that the SARS-CoV-2 (COVID-19) virus originated in the laboratories of the Wuhan Institute of Virology and was accidentally released from this facility. There have been intentional efforts to discredit this explanation on the part of some of those who could be at fault for the occurrence and consequences of the pandemic.
3. The risk of serious complications including death from COVID-19 is greatest in the elderly as well as those with other important risk factors (e.g., immunocompromised, confined living environments). However, the incidence of infection in healthy adults, including the elderly, is low and there is not a need to isolate or restrict cautious socialization with others.
4. The risk of serious complications in children and young adults is very low, and priority should be given to protecting and treating individuals at greatest risk.
5. Frequent handwashing is highly recommended in reducing the transmission of the virus.
6. Cloth masks have not been demonstrated to be effective in substantially reducing the incidence of infection. Children should not be required or encouraged to wear masks. Wearing of masks should be optional in adults.
7. Schools, businesses, entertainment venues, and other indoor facilities/activities should be open at regular hours. In situations in which there is strong concern about close proximity of many individuals, attendance can be restricted. Accommodations (e.g., virtual instruction, delivery services) should be provided for individuals who are at greater risk or who otherwise consider additional precautions necessary.

Contents

8. Numerous tests for the presence of COVID-19 are available that have varying wait-times for results, accuracy, and reliability. As with other laboratory tests, there may be false/inaccurate results and, if there is urgency for obtaining confirmation/clarification, additional tests should be conducted.

9. COVID-19 vaccines are the most effective intervention to protect against serious complications, hospitalizations, and deaths associated with COVID-19. Individuals at high or moderate risk of experiencing COVID-19 infection should be strongly encouraged to receive the vaccine. The Moderna vaccine (Spikevax) has the strongest efficacy data, followed by the Pfizer/BioNTech vaccine (Comirnaty).

   Limitations regarding the use of COVID-19 vaccines include questions regarding some of the clinical trial data and the benefits/risks of use, the brief duration of protection against COVID-19 that may require frequent booster doses, protection of the vaccine against new variants of the virus that emerge, the lack of definitive information regarding short-term and long-term risks/adverse events, and the recognition that immunization does not prevent the individual from experiencing COVID-19 infection or transmitting the virus (in contrast to initial suggestions). In addition, there is insufficient information regarding the association and risks of the vaccines with respect to the occurrence of events such as myocarditis, myelitis, and Guillain-Barre syndrome.

10. Individuals must have the liberty to make their own personal decisions with respect to receiving the vaccine. Immunization must not be a condition for restricting employment responsibilities, school attendance, travel, etc., with limited exceptions for situations in which there is a high risk of transmission of the virus to others.

11. Although I consider the benefits of the vaccines to greatly exceed the risks in adults and others with important risk factors, I do not consider immunization important for children and young adults who are at much lower risk of serious complications of COVID-19, but may experience adverse events from use of the vaccines.

12. The obsession of some healthcare and government officials to develop, approve, and achieve widespread use of vaccines has precluded sufficient attention to studies of acquired immunity as a consequence of virus exposure, and the development, approval, and widespread availability of highly accurate tests for COVID-19 and effective oral antiviral agents.

13. Some healthcare and government officials have not been transparent in revealing pertinent information and, indeed, have provided misleading and/or false information. As one example, considerable time elapsed before it was discovered that U.S. officials had provided funding to support gain-of-function research at the Wuhan Institute of Technology and, thus, were at least indirectly aware of and involved in programs that contributed to the occurrence of the pandemic. There must be transparency and accountability of healthcare and government officials with respect to their prior and current involvement with individuals and programs associated with COVID-19, as well as potential conflicts of interest.

14. Statistics have been selectively used to support a favored narrative. The numbers of COVID cases include individuals who may have tested positive to COVID-19 but have experienced no symptoms, as well as those who have experienced active, symptomatic infections. Some hospitalizations and deaths that have resulted from different types of medical problems have been classified as COVID casualties because the patients may have tested positive.

15. Some individuals who have voiced opinions and recommendations that differ from those of the government and healthcare officials have been strongly criticized and discredited, and characterized as conspiracy theorists and/or science-deniers. Some thoughtful viewpoints have been dismissed as "misinformation" and suppressed by many in the media, and there is no willingness to have objective and informative discussions/debates of individuals having differing points of view.

16. Some of those who are the strongest advocates of "following the science" are among the worst offenders in betraying the value of science as a result of certain of their comments and actions that are unsubstantiated and not based on evidence or reason.

17. Objective and well-designed (i.e., not "designed to fail") clinical trials of fluvoxamine, hydroxychloroquine, ivermectin, zinc/quercetin/vitamins should be conducted to determine if they have effectiveness and safety in at least the early stages of COVID-19. When U.S. health agencies can provide financial support for research programs conducted in other countries (e.g., China) to investigate how microorganisms can become more pathogenic, they must also be responsible for funding research to determine the most effective treatments for the resulting infections. The agents noted above have been suggested by some to be of value, but they are off-patent and pharmaceutical companies do not have monetary incentives to conduct such research.

18. The FDA has provided emergency use authorizations for the orally-administered antiviral agents, Paxlovid and molnupiravir, for the treatment of adults with mild to moderate COVID-19 infection. These agents are most effective when treatment is initiated as soon as possible following diagnosis, and pharmacists should be authorized to dispense these agents without a prescription when infection is confirmed to avoid unnecessary delays in starting therapy and decreased effectiveness.

19. Actions should be taken to prohibit on a world-wide basis gain-of-function research that results in the formation of more pathogenic microorganisms. The possibility that the COVID-19 virus is man-made rather than one that naturally evolved, and the millions of deaths that have resulted, represent a tragedy that must not be allowed to occur again.

20. The indemnification for pharmaceutical manufacturers which develop vaccines should be revoked or substantially revised. These companies must have the appropriate responsibility and liability for the effectiveness and safety of their products from which they anticipate substantial profits.

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# New Drug Review

## Alzheimer's disease

## Aducanumab-avwa (Aduhelm – Biogen)

### Description:
An amyloid beta-directed antibody.

### Indication:
Administered intravenously for the treatment of patients with Alzheimer's disease; (indication was subsequently revised to note that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials).

### New Drug Comparison Rating (NDCR) = 1
important disadvantages (in a scale of 1 to 5 with 5 being the highest rating)

### Comparable drugs:
Cholinesterase inhibitors (e.g., donepezil) and memantine (e.g., Namenda).

### Advantages:
- Has a unique mechanism of action (reduces amyloid beta plaques in the brain).

### Disadvantages:
- Clinical benefit has not been established;
- Must be administered intravenously (whereas comparable drugs are administered orally);
- Treatment requires brain magnetic resonance imaging (MRI) monitoring;
- May cause amyloid related imaging abnormalities (ARIA);
- Has not been directly compared with comparable drugs in clinical trials.

### Recommended dosage:
Administered by intravenous infusion over approximately one hour every four weeks and at least 21 days apart; initial dosage is 1 mg/kg (infusions 1 and 2), that is increased to 3 mg/kg (infusions 3 and 4), 6 mg/kg (infusions 5 and 6), and 10 mg/kg (infusion 7 and beyond); brain MRIs should be obtained prior to initiating treatment, and prior to the 7th and 12th infusions.

### Products:
Injection: single-dose vials – 170 mg/1.7 mL, 300 mg/3 mL (should be stored in a refrigerator); solution with the appropriate dose/volume should be added to an infusion bag of 100 mL of 0.9% Sodium Chloride Injection; immediate administration following dilution is recommended using an intravenous line containing a sterile, low-protein binding, 0.2 or 0.22 micron in-line filter.

### Contraindications/most important risks:
- Amyloid related imaging abnormalities (ARIA; e.g., edema, hemosiderin deposition; enhanced clinical vigilance is recommended during the first 8 doses of treatment);
- Hypersensitivity reactions (e.g., urticaria, angioedema).

### Most common adverse events:
ARIA-edema (35%); ARIA-H microhemorrhage (19%), ARIA-H superficial siderosis (15%), headache (21%), falls (15%).

### Comments:
The accumulation of amyloid beta plaques in the brain is thought to be a factor in the development of symptoms and dementia associated with Alzheimer's disease. Aducanumab is the first treatment to be approved that is directed at the underlying pathophysiology of the disease. The drug was evaluated in two placebo-controlled studies in patients with confirmed amyloid pathology and mild cognitive impairment or mild dementia, and was determined to consistently reduce amyloid beta plaques in the brain in a dose- and time-dependent manner. The reduction is this surrogate marker is thought to predict clinical benefit but is not itself a measure of clinical benefit. In both studies patients were randomized to receive aducanumab low dose, aducanumab high dose, or placebo intravenously every 4 weeks for 18 months. At a point during the trials a "futility analysis" was conducted that appeared to indicate that aducanumab was not likely to be more effective than placebo and the company terminated both trials prior to their planned completion. Following the termination of the trials, the company continued to reanalyze the available data/results. In one of the clinical trials, no statistically significant differences on the efficacy endpoints were observed between the aducanumab-treated and the placebo-treated patients. However, in the other clinical trial the high dose (but not the low dose) of aducanumab was thought to reduce clinical decline, as reflected by a statistically significant treatment effect on the primary and secondary efficacy endpoints compared to placebo. The FDA approved the drug under the provisions of the Accelerated Approval Program.

Daniel A. Hussar

# Continued PBM Deception and Fraud

CVS Caremark has recently informed participants in many of its prescription benefit programs that "starting January 1, 2022, certain prescriptions that you may have filled will no longer be covered by your pharmacy benefit plan. We're here to help your provider choose a new covered medication." The letter to participants continues, "Generic medications approved by the U.S. Food and Drug Administration are available to treat your condition. If you choose to continue filling your prescription for your current medication(s) listed below, you will pay 100% of the cost."

The PBMs make changes in their formularies every year, and most of the changes have no ramifications with respect to the effectiveness, safety, and risk of equivalent or very similar products. However, the CVS Caremark letter that includes the excerpts noted above is to a plan participant who is taking Eliquis. The patient is informed that warfarin and Xarelto are the "covered generic medication(s)," and that if she chooses to continue using Eliquis, she will pay 100% of the cost.

Eliquis, Xarelto, and warfarin are the most commonly prescribed orally-administered anticoagulants. Although these three drugs are used to provide a beneficial anticoagulant effect, they are used in different dosages and warfarin has a different mechanism of action. The most important concern with the use of any anticoagulant is the possibility of an excessive response and the occurrence of bleeding, which may range in severity from mild to severe. Optimum use involves starting treatment with the particular anticoagulant selected, establishing/confirming the dosage that provides the best balance of benefit and risk, and continuing treatment with that medication and monitoring appropriately.

Many patients in these CVS Caremark plans will not be able to afford or will not be willing to assume the high cost of Eliquis. Every anticoagulant has the important intrinsic risk of bleeding. That risk is increased when treatment is changed from one anticoagulant to another, or even when the dosage of a particular anticoagulant is adjusted upward. Switching from the use of one anticoagulant with which treatment has been stabilized to another one adds unnecessary additional risks for the patients (e.g., bleeding adverse events, confusion regarding the different dosage regimen), as well as significant inconveniences for the affected patients, prescribers, and pharmacists.

This CVS Caremark decision is an outrageous intrusion on the rights of patients, the authority and prerogatives of prescribers to select the anticoagulant they consider best for their patients, and the responsibilities and time of pharmacists. The decision should be challenged and rescinded!

Why did CVS Caremark make this decision? They don't have to say and won't! The inescapable answer is that they have negotiated terms, rebates, etc. with the manufacturer of Xarelto that are more profitable for itself, than what they were able to negotiate with the manufacturer of Eliquis. When there is an opportunity for greater profits for CVS Caremark, the risks to patients don't matter!

## Wait! There's more

Lantus (insulin glargine) is a very widely prescribed and costly long-acting insulin product. The FDA has approved products (e.g., Basaglar) that are biosimilar to Lantus, but not interchangeable. On July 28, 2021, the FDA approved Semglee (insulin glargine-yfgn) that is both biosimilar to and interchangeable with (can be substituted for without prescriber consultation) for Lantus. The FDA press release on that date describes the action as part of its commitment "to support a competitive marketplace" that "empowers patients by helping to increase access to safe, effective, and high-quality medications at *potentially* (my emphasis) lower cost."

The manufacturer of the product is providing branded (Semglee) and unbranded (insulin glargine) versions of the product, both of which are interchangeable with Lantus. The wholesale acquisition cost (WAC) of Semglee is slightly less than that for Lantus, whereas the WAC for the unbranded insulin glargine is approximately 65% less than that for Lantus. The result is that Semglee is a high-cost, high-rebate, and insulin glargine is a low-cost, low-rebate interchangeable alternative for Lantus. How do the PBMs respond?

For 2022, the largest commercial formulary of Express Scripts includes just the high-cost, high-rebate Semglee, the comparable Optum formulary includes Lantus, and the comparable CVS Caremark formulary includes Basaglar. The manufacturer of Semglee (Viatris, a combination of a unit of Pfizer with the former Mylan) is a co-conspirator in this deception, and the FDA's dream of "potentially lower cost" is manifested as greater profits for PBMs and Viatris.

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