The Pharmacist Activist

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"Be strong and courageous. Do not be terrified, do not be discouraged, for the Lord your God will be with you wherever you go." Joshua 1:9b

Editorial

Are Microorganisms Contributing Factors to Alzheimer's Disease?

As my chronological giftedness (aka aging) and my forgetfulness increase, I give a lot more thought to Alzheimer's Disease (AD), its devastating consequences, the limitations of our understanding of its pathology, the limited effectiveness of medications that have been developed to date, and the identification of strategies that might reduce risk. The cholinesterase inhibitors (e.g., donepezil [e.g., Aricept]), as well as memantine (e.g., Namenda), are of limited benefit in slowing cognitive decline in some patients. The recently approved amyloid-beta targeted monoclonal antibodies (i.e., aducanumab [Aduhelm; no longer marketed], lecanemab [Leqembi], and donanemab [Kisunla]) have been promoted as the first medications to target the underlying pathology of AD. I have learned as much as I can about them in preparing my reviews of new drugs. One of the first realizations is, as more is learned about one of the factors (e.g., amyloid-beta) pertaining to AD, the greater is the recognition that AD is a complex puzzle of many pieces that are contributing factors in its pathology and effective treatment. As an example regarding just one piece of the puzzle, the recently approved medications deplete the amount of amyloid-beta that has accumulated in brain tissues. But this advance also raises a question that needs to be addressed – Would research to identify agents that reduce the formation and deposition of amyloid-beta in brain tissues have been more productive than depleting the accumulation of this material in the tissues?

I commend the research initiatives that have resulted in the development of the amyloid-beta-depleting medications. However, I have reached the conclusion and shared it with immediate family that, if I experience mild cognitive impairment, dementia, and/or AD, I do not want to be treated with one of the new amyloid-directed drugs. There are several reasons for this conclusion. Clinical benefit was not demonstrated in numerous patients in the

clinical trials, and those for whom there was benefit experienced just a modest slowing of cognitive decline/impairment; the drugs do not cure, reverse, or stop cognitive decline. Brain MRI scans must be performed at baseline and periodically during treatment, and amyloid-related imaging abnormalities (ARIA) are often experienced. Although ARIA may not be associated with symptoms, brain swelling and bleeding have been reported, as well as rare reports of serious and life-threatening complications. The need to administer these drugs by intravenous infusion was not a factor in my conclusion but infusion-related reactions occur in some patients. In my opinion, the risks of these agents exceed the limited benefits some patients may experience, and this evaluation does not take into account the very high cost of treatment even for those who have the best prescription plan coverage.

A role for antimicrobial agents?

There was a time when I taught the topics of infectious diseases and antimicrobial therapy in the Therapeutics course sequence for my students at the Philadelphia College of Pharmacy. In my introductory comments at the beginning of each unit of instruction, I made the following observations:

1. Of all the diseases that have been identified, infectious diseases are among the very few that can be CURED and it is possible to prevent some of them from occurring (i.e., with vaccines).

2. I also made a prediction that when we reached the point at which there was a clear understanding of the pathology of diverse diseases, we would learn that microorganisms/infection were causative or contributing factors in most of them. The following are examples of what I anticipate will be future discoveries regarding the pathology of many diseases.

Lyme disease is now well recognized as an infectious disease. However, when the condition was first characterized primarily by arthritic/inflammatory symptoms in an unexpectedly high number of young people in the small community of Lyme, Connecticut, it was designated as "Lyme arthritis." Subsequent evaluation of afflicted patients and their activities, research investigations, and environmental studies in the community revealed that the condition originates as an infectious disease that is caused by the spirochete *Borrelia burgdorferi* that is transmitted via the bite of ticks. If the infection is not diagnosed and treated promptly with antibiotics, it can be disseminated to numerous body systems and cause a wide range of symptoms (e.g., dermatologic, arthritic/inflammatory, neurologic, cardiac), some of which may be irreversible.

Gastric ulcers are now well recognized as being caused by the bacterium *Helicobacter pylori*. For many years health professionals and research scientists thought we had a complete understanding of the pathology (excessive secretion of gastric acid) and treatment of gastrointestinal (GI) ulcers and related symptoms with antacids, histamine H_2-receptor antagonists, and proton pump inhibitors. The remarkable self-experimentation and research of the Australian physician Barry Marshall resulted in our current understanding of the important role of *H. pylori* in the occurrence and persistence of these GI conditions. The recommended treatment regimen includes antimicrobial agents and an acid suppressive drug.

Research programs designed to better understand the pathology of AD and develop treatment options have focused primarily on acetylcholine concentrations and the roles of the proteins amyloid-beta and tau. There have been tantalizing suggestions for a number of years that microorganisms (e.g., certain bacteria, viruses, fungi) may have a role in the development of AD and that antimicrobial agents might be effective components of a treatment regimen. Most of these suggestions are based on labora-

tory research and the experience in patients is very limited and primarily consists of anecdotal reports in individual patients.

It would be anticipated that any reasonable hypothesis or clue that might be of value in the occurrence and treatment of a disease as devastating as AD would be quickly studied in randomized clinical trials (RCT). However, the microorganisms that have been most prominently suggested as contributing to the occurrence of AD are susceptible to antimicrobial agents that have been available for many years and are available in inexpensive generic formulations. As a consequence, pharmaceutical companies are not going to spend millions of dollars to conduct clinical trials of a drug, even one with "blockbuster" importance, if the drug is off-patent and will not provide the company with "blockbuster" profits. Many of the foundations and organizations that are advocates for patients with AD and research initiatives, receive much of their funding from the pharmaceutical companies that make the drugs that are currently available for the treatment of AD. Therefore, they are unlikely to possibly jeopardize their current sources of substantial funding to support research of antimicrobial agents that would be available at much lower costs.

It is estimated that approximately 6.5 million individuals are afflicted with AD. In addition to the anguish and mental and physical consequences for patients and their families, the cost of treatment and care for patients, government agencies (e.g., Medicare), and others is astronomical. It can't be expected that pharmaceutical companies will conduct the necessary research programs. Therefore, the federal government through its agencies such as the National Institutes of Health should provide the funding and conduct the research to evaluate the role of microorganisms as a contributing factor in AD and the potential benefit of antimicrobial agents for prevention and treatment. What better use could there be for the substantial taxes we pay?

From curiosity to activism

My long-standing interest in the areas of infectious disease and antimicrobial therapy has maintained my strong curiosity regarding the unsolved or still unknown roles of microorganisms in the occurrence and treatment of chronic diseases. Over the last year I have endeavored to learn as much as I can about the microbial hypothesis of AD. A friend, Dorothy Rivers, introduced me via email to Herbert Allen, a physician who has done extensive research utilizing the pathology and microbiology found in tissue from patients with documented AD. His research identified *Borrelia burgdorferi* (the causative agent of Lyme disease) and *Treponema denticola* (a prominent component of the mouth flora) in the brain tissue. Periodontal disease is frequently referred to as the second highest risk factor for AD, just behind age. Both of these organisms are spirochetes that pass through the blood-brain barrier and have an affinity for neural tissues. Once in the brain, these spirochetes make biofilms (a community of microbial organisms encased in a slime coating) that create the pathology including the formation of amyloid-beta that then interacts with tau protein. Dr. Allen's research also suggests that the combination of bacteria and the biofilms they form are also the cause of other chronic diseases such as atopic dermatitis and psoriasis.

Treponema denticola is just one of the species of Treponema that also includes *Treponema pallidum*, the causative agent of syphilis. If syphilis is not diagnosed and effectively treated on a timely basis, infected patients may eventually experience dementia with characteristics that are very similar to those associated with dementia of AD. It has been observed that "if you know syphilis, you also know AD."

Syphilis is one of the very few infections that is still highly susceptible to "narrow spectrum" penicillins such as penicillin G. Dr. Allen has proposed that the oral use of penicillin V or amoxicillin (to

which *Borrelia burgdorferi* is also susceptible) could prevent AD by killing the spirochetes before they make biofilms. Azithromycin could be used in patients who are allergic to penicillin. Preliminary evaluation of this strategy has been conducted in approximately 150 patients who have risk factors for AD (e.g., parents with the disease). With respect to the treatment of early AD in an attempt to prevent or slow further cognitive decline, it is proposed that the penicillin be used together with a biofilm disperser ("buster") such as rifampin that would disrupt the biofilm coating and enable penicillin to kill the spirochetes. (Reference: Allen, Herbert B., Journal of Alzheimer's Disease, 84, no.1, pp. 61-67, 2021).

Several weeks ago Dr. Allen introduced me via email to Anna Shelander, the President of The Curing Alzheimer's Disease Foundation (curingalzheimersdisease.com). Her father, the late Dr. David E. Crandall, was a dentist who recognized the importance of periodontal disease as a risk factor for AD and was convinced that oral bacteria are intimately involved. He experienced progressively worsening symptoms of AD, Ms. Shelander notes that he "treated himself with anti-inflammatory agents and antibiotics that specifically treat periodontal disease and in so doing was able to reverse symptoms (dramatically). At autopsy the drug combination was determined to have preserved the brain structures normally destroyed by this disease."

This CAD Foundation has recently announced its agreement to fund the Alzheimer's Legacy Lab at the University of Minnesota. Scientists at this Lab will be actively investigating the Microbial/Infectious Hypothesis of Alzheimer's, the relationship between periodontal disease and AD, and the identification of strategies to prevent/delay symptoms of AD, as well as regimens for treatment. These initiatives are exciting! Because agencies of the federal government have not historically favored the microbial/infectious hypothesis in their funding, and as all grant guidelines continue to narrow, the CAD Foundation has stepped up to provide 100% of the funding for this research with no time limit. Ms. Shelander insists that the CAD Foundation's revolutionary (privatized) way of funding will allow the lab to investigate the spontaneous discovery inherent to the research process (via an agile pivot vs. being relegated to document the the finding in their paper's conclusion." By removing the time-intensive administration required of a government grant, Ms. Shelander expects the lab will be more efficient and the work to progress much faster. The CAD Foundation states on their website that their mission is "To See the Science Through." Individuals and organizations should also provide financial support and advocacy for these investigations and their anticipated value for individual patients and society.

I fully recognize the importance of evidence-based medicine. I also quickly acknowledge that the clinical experience with antimicrobial agents for the purposes discussed is very limited, and that evidence of efficacy and safety are not yet available. However, without effective intervention, the consequences of AD will become even more devastating. The need for such intervention is URGENT and we must not wait for the availability of "evidence."

Some will voice concerns regarding potential adverse events with the off-label use of antibiotics and that more extensive use of these agents will increase the emergence of resistance. In my opinion, the potential benefits from such use far exceed the risks. I have learned enough from the excellent, albeit preliminary, work of others to conclude that, if I had risk factors for AD, I would arrange to take an appropriate antibiotic. I am also determined to strengthen my advocacy in urging individuals who have these risk factors or early symptoms of AD to consult with their physician(s) about these interventions. The potential benefits of avoiding the consequences of AD are great and the risk is small.

Daniel A. Hussar
DanH@pharmacistactivist.com

More Deception from Express Scripts!

The lead commentary in the August issue of *The Pharmacist Activist* was, "Express Scripts Attempts to Change its Identity," that responds to its full-page advertisement in major newspapers. The PBM has followed that with another full-page ad that continues the deception and lies, but provides no transparency regarding its operations, rebates from pharmaceutical companies, steering patients to its own pharmacies, and other "facts" which they accuse its critics of ignoring. The new ad begins with the following pronouncement in large type.

WE FIGHT FOR YOUR HELP EVERY DAY. TODAY, THAT MEANS FIGHTING THE FTC.

The text of the ad notes:

> "We feel we have no choice but to sue the Federal Trade Commission. This was an extremely difficult decision to make so we want to make ourselves unequivocally clear as to why."

(Editor's comment: This may be the first time that Express Scripts has attempted to be "unequivocally clear," but it is just another charade).

> "But their report about the Pharmacy Benefit Manager industry published on July 9, 2024, leads us, as well as an FTC Commissioner, to believe that the agency is not acting in the public interest. That is why we are calling on the FTC to retract the report."

(Editor's comment: A majority of the FTC Commissioners approved the report but Express Scripts prefers that the public knows the opinion of the one Commissioner who dissented).

> "We're advocates for affordability, not misinformation."

(Editor's comment: The large increase in drug prices during Express Scripts' "watch" contradicts any claims of success in achieving affordability).

> "…programs we've developed result in up to 27% higher medication adherence and 23% fewer inpatient hospitalizations. The FTC's report fails to acknowledge any of these findings."

(Editor's comment: Express Scripts can provide very specific data when it considers it to be in its own interest to do so. There are some references provided in very small type at the bottom of the advertisement. The two references provided as the source of the two statistics noted are attributed to Evernorth, the parent company of Express Scripts. There is no reason to think that this self-generated report is any more credible than the other claims made by Express Scripts).

> "Reports outlining how PBMs pass nearly 100% of rebates and fees to employers, labor unions, government agencies, and health plans."

(Editor's comment: The most revealing word in this statement is "nearly." Express Scripts is able to identify the specific percentage of rebates but refuses to do so. Does 90% qualify as "nearly?" 75%? 51%? The claims processed by the three major PBMs have a cost of billions of dollars. Even if they retain only a small percentage of the fees and rebates, the amount is huge. The rebate game is a self-enrichment contest that creates an incentive for

higher drug prices and benefits only the PBMs and pharmaceutical companies. Everyone else loses – it is fraudulent and must be terminated).

> "We're advocates for facts, not conjecture."
>
> "We're advocates for objectivity, not bias."
>
> "We're advocates for due process, not convenient timing. Billions of data points were provided by the PBMs to the FTC in response to their demands."

(Editor's comment: "Billions of data points" suggest that the PBMs were responsive to the FTC's request for information. However, the FTC was delayed and frustrated in addressing concerns about PBMs because they did not respond in providing requested information on a timely basis and most likely are still withholding information needed for a complete analysis of its operations and monopolistic practices. The allegation by Express Scripts that the FTC used "convenient timing" in issuing its report is disingenuous. The FTC had announced its plan to sue Express Scripts and other PBMs. It is actually Express Scripts that is exercising "convenient timing" by suing the FTC as a preemptive action before the FTC filed its lawsuit. Express Scripts is taking a page out of Walmart's playbook when, several years ago in anticipation of a lawsuit by the federal government for its role in opioid overdosage deaths, Walmart sued the federal government. Walmart's lawsuit was dismissed and the one filed by Express Scripts should also be dismissed).

> "We're advocates for people. We're advocates for health."
>
> "Pharmaceutical companies set and raise drug prices. PBMs lower them."

(Editor's comment: PBMs receive larger rebates for the most expensive drugs. More expensive drugs are often placed in the more favorable tiers of their formularies, even when less expensive alternatives are available. Patients, employers, and taxpayers pay more. Pharmacists are also victims of the greed, fraud, and policies of the PBMs, and many pharmacies have closed because they can't survive financially).

The Express Scripts suit against the FTC seeks to have the agency retract its report that is critical of the PBMs… To challenge the statements in the FTC report, Express Scripts primarily relies on the "research" of an economist who essentially concludes that the FTC's claims about the PBMs "are not supported by the data." The economist's conclusions are strongly refuted in a comprehensive analysis by 46Brooklyn Research in its detailed report of September 20, "Express Scripts, Inc. vs. The Federal Trade Commission." The CEO of 46Brooklyn Research is Antonio Ciaccia whose investigations exposed the PBM fraud in Ohio several years ago.

The FTC lawsuit

On September 20 the FTC sued the three largest PBMs. The title and subtitle of the FTC press release are noted below:

> "FTC Sues Prescription Drug Middlemen for Artificially Inflating Insulin Drug Prices"
>
> "Caremark, Express Scripts, Optum, and their affiliates created a broken rebate system that inflated insulin drug prices, boosting PBM profits at the expense of vulnerable patients, the FTC alleges."

The FTC press release includes the following allegations:

> "CVS Health's Caremark, Cigna's ESI (Express Scripts), and United Health Group's Optum, and their respective GPOs (group purchasing organizations)…have abused their economic power by rigging pharmaceutical supply chain

competition in their favor, forcing patients to pay more for life-saving medication."

"The three PBMs created a perverse drug rebate system that prioritizes high rebates from drug manufacturers, leading to artificially inflated insulin list prices…even when lower list price insulins became available that could have been more affordable for vulnerable patients, the PBMs systemically excluded them in favor of high list price, highly rebated insulin products."

Rahul Rao, the Deputy Director of the FTC's Bureau of Competition, notes: "Caremark, ESI, and Optum—as medication gatekeepers—have extracted millions of dollars off the backs of patients who need life-saving medications. The FTC's administrative action seeks to put an end to the Big Three's exploitative conduct and marks an important step in fixing a broken system…"

"…the PBMs are not the only potentially culpable actors—the Bureau also remains deeply troubled by the roles that drug manufacturers like Eli Lilly, Novo Nordisk, and Sanofi play in driving up list prices of life-saving medications like insulin. Indeed all drug manufacturers should be on notice that their participation in the type of conduct challenged here raises serious concerns, and that the Bureau of Competition may recommend suing drug manufacturers in any future enforcement action."

"The PBMs financial incentives are tied to a drug's list price, also known as the wholesale acquisition cost. PBMs generate a portion of their revenue through drug rebates and fees, which are based on a percentage of a drug's list price. PBMs, through their GPOs, negotiate rebate and fee rates with drug manufacturers. Products with higher list prices generate higher rebates and fees for the PBMs and GPOs, even though the PBMs and GPOs do not provide drug manufacturers with any additional services in exchange."

"The complaint alleges that PBMs keep hundreds of millions of dollars in rebates and fees each year and use rebates to attract clients. PBMs' clients are payers such as employers, labor unions, and health insurers."

For many years, pharmacists have been victimized by the deception and fraud of the PBMs, and have been very frustrated in not having our important concerns understood and/or effectively addressed by regulators, legislators, and federal agencies. Although there is much still to be accomplished, it is very encouraging that the FTC has investigated and understands the problems, and has taken action to sue the PBMs. The leaders and membership of the National Community Pharmacists Association (NCPA) are to be highly commended for providing numerous specific examples and other information that have exposed the egregious policies and terms of the PBM programs. The American Pharmacists Association (APhA) has also been very active in this regard, and both of the organizations, as well as others, are strongly supporting proposed federal legislation with bipartisan support to accomplish PBM reform. The time to accomplish this is short. *Every* pharmacist should contact their Senator and Representative to ask them (if it is not already known) if they are supporting the legislative proposals and urge them to support them. The specific legislative proposals are:

S. 2973/H.R. 5378: the Modernizing and Ensuring PBM Accountability (MEPA) Act;

S. 127: the Pharmacy Benefit Manager Transparency Act;

S. 3430: Better Mental Health Care, Lower-Cost Drugs, and Extenders Act.

Others have also exposed the deceptive actions of the PBMs. Matt Stoller is the Director of Research at the American Economic Liberties Projects, and an expert on monopolies. He is the author of the book Goliath: The Hundred Year War Between

Monopoly Power and Democracy, and also writes the Substack publication BIG. His commentary on September 23, "Monopoly Round-Up: Lina Khan, Pharma Middlemen and 'Tasty Rebates,'" provides excellent coverage of the FTC suit. Using Lantus as an example, he notes that its list price in 2019 was $403 for a one-month supply. During 2019, its manufacturer (Sanofi) was giving OptumRx 80% of the list price to be the preferred insulin for its patients. "That's just $64 going to Sanofi for the drug, and $339 going to OptumRx as a kickback." In describing how PBMs work, he states:

"They aren't just middlemen, they are allocators of what really looks perilously close to organized crime loot to a series of conspirators, from pharmaceutical firms to insurers to benefit consultants to large employers."

Wall Street Journal editorial

The lead editorial in the September 26 issue of *The Wall Street Journal* is titled, "Higher Health Premiums for All," and the subtitle is "Lina Khan piles on the anti-PBM bandwagon, to ill effect for consumers." I responded with the following letter to the editor:

> "I usually agree with and learn from the WSJ's editorial opinions. However, the apparent obsession with criticizing Lina Khan results in undeserved support for pharmacy benefit managers (PBMs). The PBMs wield more power and control in the selection, distribution, use, and cost of medications than prescribers, pharmacists, and even the pharmaceutical companies. Ironically, the cyclical blame game between the PBMs and Pharma enriches both groups (i.e., list prices and rebates/fees both increase). The policies of the PBMs are economically motivated and override the decisions of prescribers and pharmacists who provide the services and care for individual patients. Patients/consumers are the greatest victims when the decisions regarding medications made by their healthcare providers are challenged, changed, and/or delayed by the PBMs. I and many other health professionals are of the opinion that the PBMs have had a highly destructive impact on the scope and quality of health care, and the attainment of personalized, effective, and safe drug therapy. In many situations, the non-negotiable amount that the PBMs pay pharmacists for the medications they dispense is considerably less than the cost pharmacists pay for the medication. Many pharmacist-owned independent pharmacies have not been able to survive financially and have closed, creating a much larger number of "pharmacy deserts," resulting in greater inconvenience and delays for patients in obtaining prescribed medications.
>
> The FTC is on target in challenging the PBMs. If it is to be faulted at all, its action should be applicable to all prescription medications and not just insulins."

It is unlikely that my letter will be published, but I couldn't be silent after reading it. If any readers can use any or all of the content of this letter in your communications with the media, legislators, or others, please feel free to do so in your own message. It is not necessary to identify me as the source.

Daniel A. Hussar
DanH@pharmacistactivist.com

Author/Editor/Publisher – Daniel A. Hussar, Ph.D.
Dean Emeritus and Remington Professor Emeritus at
Philadelphia College of Pharmacy
Assistant Editor – Suzanne F. Hussar, B.Sc. (Pharmacy)

The Pharmacist Activist, 1 Boulder Creek Lane, Newtown Square, PA 19073
E-mail: info@pharmacistactivist.com

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