The Pharmacist Activist

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"You will keep in perfect peace him whose mind is steadfast, because he trusts in you. Trust in the Lord forever, for the Lord, the Lord, is the Rock eternal." Isaiah 26: 3-4

Editorial

Which is Stronger (Weaker) – AMA or APhA?

It Doesn't Matter – They Need a Synergistic Working Relationship!

Until approximately 50 years ago, almost all states had "anti-substitution" laws that prohibited a pharmacist from substituting a less-costly equivalent generic product when a physician prescribed the trade name product. The American Pharmacists Association (APhA) provided leadership in convincing legislators and the public that these laws should be repealed, and these efforts were successful in spite of strong opposition from physicians, the American Medical Association (AMA), and the large pharmaceutical companies. Today, generic products are used for a large majority of prescriptions that are dispensed, although the concerns about the high costs of medications continue.

I recall participating in a program that involved both pharmacists and physicians that was held during the time in which the anti-substitution laws were being repealed. A physician with whom I was speaking was lamenting that he wished that the AMA and physicians had as much strength and influence as APhA and the profession of pharmacy were demonstrating. I was struck by the irony of his statement because then, as well as now, many pharmacists think that AMA and the profession of medicine have much more strength and influence than the profession of pharmacy. In fact, they DON'T! However, that is no consolation when recognizing the current reality in which neither profession can claim strength or influence with respect to important decisions and policies concerning health care. Indeed, in many situations medicine and pharmacy take opposing positions regarding issues.

It would seem that the professions of medicine and pharmacy would have many more similar goals and services on behalf of their patients and the public than they have differences. Therefore, it would be of value to learn from the situations in which our professions (AMA and APhA) have taken a strong and united position. My memory is not serving me well in recalling examples of such situations and I would appreciate your assistance. I choose to not include the joint position of the AMA, APhA, and ASHP regarding the use of ivermectin in a COVID-19 context because I consider it to be the wrong position on the wrong issue and, with very limited influence, but which places members of our professions at risk if they exercise their personal professional judgment in individual patient situations (please see my commentary, "The AMA, APhA, and ASHP Collaborate! – But Undermine the Rights of Their Members!" in the September, 2021 issue of *The Pharmacist Activist*).

Test to Treat

The AMA's interest in collaborating with APhA lasted only for several months until the FDA provided emergency use authorizations for nirmatrelvir/ritonavir (Paxlovid) and molnupiravir (Lagevrio) for the treatment of mild-to-moderate COVID-19, and President Biden announced that patients could be tested and treated in just one stop at a pharmacy. Many did not initially

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recognize the serious deficiencies of the program that include insufficient supplies of the medications, availability only at selected pharmacies, refusal to let pharmacists prescribe the medications when testing demonstrated the need for timely treatment, and failure to provide a mechanism through which pharmacists would be equitably compensated for their services, although the medications themselves would be "free" because of the federal government's purchase of the drugs (approximately $530 for a course of treatment of Paxlovid).

The AMA responded by voicing strong criticism that pharmacists could be involved even to the extent possible under the limitations of the program, but supported its criticism with the ludicrous explanation that pharmacists would not be able to recognize and intervene when the ritonavir component of Paxlovid might interact with dozens of other medications. Conveniently ignored by the AMA in its self-serving statements are the thousands of interventions by pharmacists that have prevented potentially life-threatening drug interactions in patients and protected the reputation and wealth of prescribers.

Pharmacy responds

APhA, the National Association of Chain Drug Stores, and other pharmacy organizations responded quickly to the AMA criticisms. The scheduling of the APhA annual meeting in March in San Antonio was timely in enabling the Board of Trustees to submit an urgent item of new business for consideration by the House of Delegates and its overwhelming approval of the following positions:

1. APhA opposes policies, practices, and statements by the American Medical Association (AMA) and other professional organizations that impede interprofessional care, patient access to pharmacist-provided care, and health equity.

2. APhA calls on the American Medical Association (AMA) to rescind its policies opposing expanded scopes of practice for pharmacists.

3. APhA adamantly supports the continuation and expansion of collaborative patient care models among pharmacists, physicians, and other healthcare professionals to improve patient access to care, health equity, and health outcomes.

I consider it important that APhA take this strong position in response to the AMA criticisms, and I commend the APhA leaders who initiated this response. But what will now happen? Will the two associations quickly move on to other pressing matters, will the inflammatory rhetoric escalate tensions and further reduce communication between the associations, or might a truce be declared for the purpose of having the associations communicate and collaborate on issues of mutual importance that can also be of value for the patients served by both professions?

Which is Stronger?

There is no answer but that doesn't matter! What matters most is that both associations need to be much stronger and more effective. It can't be about professional turf or competition. If the associations communicated and collaborated with each other much more extensively, they would both be stronger and achieve interdisciplinary and synergistic outcomes that would improve healthcare outcomes for patients and society.

Daniel A. Hussar
DanH@pharmacistactivist.com

Walgreens Passes CVS in a Metric on the Race to the Bottom!

In the April issue of *The Pharmacist Activist*, I commented on the CVS agreement to pay Florida $484 million to settle opioid-related claims. It was also noted that Walgreens had not settled because of its opinions that the claims were covered in a previous settlement in 2012 and that they were unjustified. It has now been reported that Walgreens will pay $683 million to settle with Florida to resolve opioid-related claims. Neither CVS nor Walgreens acknowledges wrongdoing but they don't want juries to evaluate the credibility of their "innocence," so they reach settlements. The Drug Enforcement Administration should take action to prohibit CVS and Walgreens from dispensing any controlled substances! Very unfortunately, I feel these settlements only represent the tip of the iceberg, and that these and other chains will also be sued in other states and by the federal government for the opioid-related destruction of lives and families.

I discussed this situation with a pharmacist friend who works for CVS and his pessimistic response was, "More fines just mean less hours of pharmacist/tech staffing."

National Day of Prayer

May 5 was the National Day of Prayer. If you missed observing it, you can catch up as prayer has value every day.

Paxlovid – A Blemished Success Story

The development of nirmatrelvir has been an important step in the oral treatment of COVID-19. Nirmatrelvir has a relatively short duration of action that, if used alone, would probably require four doses a day during the 5-day course of treatment that is recommended. Accordingly, because nirmatrelvir is extensively metabolized via the CYP3A4 pathway, Pfizer evaluated it in combination with ritonavir, a strong CYP3A4 inhibitor. Ritonavir is an HIV-1 protease inhibitor that has been available for many years for use in combination with other antiretroviral agents in the treatment of HIV-1 infection/AIDS. However, it is used with nirmatrelvir, not because of its antiviral activity, but because it will inhibit the metabolism of nirmatrelvir and prolong its duration of action to the extent that the product can be administered twice a day instead of more frequently. The FDA has enabled the availability of nirmatrelvir/ritonavir (Paxlovid), as well as molnupiravir (Lagevrio), via its emergency use authorization (EUA) process. My review of nirmatrelvir/ritonavir is included in the February issue of *The Pharmacist Activist*, and I gave the product a positive New Drug Comparison Rating of 4 (with 5 being the highest rating) that reflects its value and advantages. Although the nirmatrelvir and molnupiravir products have not been directly compared in clinical studies, the results of separate trials of the individual products suggest that nirmatrelvir is far more effective against COVID-19 and also has other advantages.

Hindsight is often 20/20 but the decision to use ritonavir with nirmatrelvir can be questioned. Nirmatrelvir, if used alone, appears to be very well tolerated. However, ritonavir, in addition to interacting with (i.e., inhibiting the metabolism of) nirmatrelvir, interacts with dozens of other medications and also introduces other risks. The fact sheet for Paxlovid identifies 22 other medications (e.g., clozapine, amiodarone) with which concurrent use of the new product is *contraindicated*, because of the potential severity of interactions with ritonavir. There are numerous other medications with which ritonavir may interact but the risk does not rise to the level of necessitating a contraindication because other interventions and/or monitoring would be sufficient precautionary measures.

Nirmatrelvir is clearly the most effective treatment, that also provides the convenience of oral administration, for mild to moderate COVID-19 in patients who are at high risk for progression to severe COVID-19, including hospitalization or death. The unanswered question with respect to the combined use with ritonavir is whether the trade-off of the added benefit of administration just twice a day is more important than the contraindications that will preclude use of the product in many individuals who may experience worsening of the infection, hospitalization, or death as consequences.

As one who has had long-standing concerns regarding the challenges of achieving compliance with instructions for using medications, I fully recognize the extent of that challenge with the use of medications that must be administered frequently on a continuing basis. However, the recommended dosage regimen for nirmatrelvir involves only a 5-day course of treatment. Even if nirmatrelvir had to be administered four (or even six) times a day if ritonavir was not used concurrently, could we not persuade patients of the importance of doing that over a period of just 5 days, particularly with the added motivations of achieving relief and control of symptoms and their likely awareness of a family member or friend who has experienced more severe consequences from the infection?

Some of us recall the time when zidovudine (Retrovir) was the first antiretroviral agent to be approved for the treatment of HIV infection/AIDS. The recommended dose was administered every 4 hours on a continuing basis and patients complied with that instruction because the drug was viewed as the only hope to escape the death sentence that a diagnosis of AIDS represented at that time. COVID-19 is a threat to many more people than AIDS. The use of any effective treatment strategy must not be compromised, but we are doing just that in the situation described above and for other reasons!

What if the recommended dose (300 mg) of nirmatrelvir was administered every 6 hours (or even every 4 hours) for 5 days without ritonavir instead of the present recommendation of every 12 hours for 5 days with it? Would the alternative dosage regimens be at least as effective? I consider it likely but we don't know, and there appears to be no incentive for Pfizer to conduct such a study in view of the huge revenues it anticipates with the current product. Such a study could be readily conducted, however, (e.g., by the NIH, FDA, pharmaceutical scientists, health professionals) using the currently available product. Unlike most fixed-dose combination pharmaceutical products with multiple active ingredients, Paxlovid is a co-packaged product in which nirmatrelvir and ritonavir are supplied in separate tablets, and this readily enables the evaluation of different dosage regimens of nirmatrelvir alone

Let's consider a situation in which a patient with severe schizophrenia that is effectively managed with clozapine, experiences COVID symptoms and a positive test for the virus, and would be a candidate for treatment with Paxlovid. However, the concurrent use of clozapine and Paxlovid is contraindicated, and the patient would be placed at risk if the use of clozapine was suspended. Other options include 1) using molnupiravir that does not interact with clozapine but is much less effective than Paxlovid, 2) using a monoclonal antibody or remdesivir (Veklury) intravenously, or 3) using nirmatrelvir alone "off-label," without ritonavir in a dosage of 300 mg every 6 hours (instead of every 12 hours) for 5 days, even though there are no studies or evidence for this dosage regimen that would satisfy those who insist on evidence-based guidelines/recommendations for every drug therapy decision.

If I had the authority to prescribe in this situation (for which I feel my knowledge and scientific reasoning prepare me well), I would choose option 3 without hesitation as it permits the use of the medication that is clearly most effective. I am not aware that AMA is considering any treatment recommendations such as this, but perhaps it is too busy objecting to the role of the pharmacist in these circumstances.

Other blemishes

There are other problematic situations pertaining to the availability of Paxlovid, each of which could be considered at length but will be briefly summarized below,

1. The approximate cost of $530 for a 5-day course of treatment is grossly excessive for a product for which extensive use is anticipated.

2. The federal government is purchasing the product and making the decisions as to how supplies are allocated. The product was initially available in only limited supplies that were provided to large chain pharmacies and selected other facilities. Now that larger supplies are available, they are being erratically distributed and there are large geographical areas in which access is limited.

3. Although pharmacists perform COVID tests, they are denied the authority to prescribe a product for which the effectiveness is dependent on how soon treatment is initiated.

4. The federal government is paying for the product and COVID testing but has made no provision for equitable compensation for the service of pharmacists, as is the case with the administration of COVID-19 vaccines, although some will debate whether that compensation is equitable. If compensation for Paxlovid is permitted to become the responsibility of health insurance companies and pharmacy benefit managers, compensation for pharmacists can be expected to be abysmal to the point that pharmacists who do provide it will experience a financial loss that will preclude the participation of many. Access to the product could become even more limited.

5. There have been an increasing number of reports of relapses of COVID symptoms following treatment with Paxlovid, the explanations for which require study and clarification, but could be interpreted as the product providing limited or no protection following the course of treatment, and/or one dosage recommendation not providing optimum effectiveness for all patients. When asked about the relapses, the CEO of Pfizer stated that patients can take another course of treatment, "like you do with antibiotics." The FDA quickly responded that "there is no evidence of benefit at this time for a longer course of treatment…or repeating a course of Paxlovid…" in patients in whom symptoms recur.

   The CEO of Pfizer is clearly making recommendations for off-label use of Paxlovid, as he has done with the use of Pfizer's COVID-19 vaccine and booster shots. If Pfizer sales representatives would make such statements, they would be terminated. Other pharmaceutical companies have paid huge settlements/fines for previous examples of promoting off-label use of their products. The FDA must not tolerate such statements from any employee of a company and must take appropriate actions.

6. The supply of Paxlovid has increased to the point that the supply meets or even exceeds the demand. The priority concerns of Pfizer appear to have shifted from meeting the demand to now viewing Paxlovid as being underutilized with the result that revenue forecasts are threatened. Could this situation be a contributing factor to the Pfizer CEO's promotion of off-label use that would result in greater sales?

7. In addition to the avalanche of revenue Pfizer continues to receive for its COVID-19 vaccine, the company anticipates another financial windfall with Paxlovid in forecasting $22 billion in global sales from the product in 2022. This situation exists concurrently with the dilemma pharmacists face in not knowing how they will be paid for their services and whether the amount of compensation will make it affordable to stock and provide the medication with appropriate services.

I am not aware of any action or statement that Pfizer has made that recognizes the current role of pharmacists and supports an expanded role in assuring that the criteria for using Paxlovid are met and that the product is used as effectively and safely as possible. Pfizer should work with the FDA and other federal agencies in assuring availability of the product to every pharmacy that wants to obtain it. I further recommend that Pfizer provide to pharmacies compensation in the amount of $100 for each 5-day course of treatment of Paxlovid in which pharmacists provide appropriate dispensing, counseling, and monitoring services. Pfizer can afford to do that, but many pharmacists will not be able to afford to obtain and dispense it under prevailing non-negotiable compensation terms. It would be a wise investment for Pfizer in meeting the public health needs of patients, supporting the role of pharmacists, and increasing the extent to which its valuable and unique treatment of choice will be used.

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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