The Pharmacist Activist

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Editorial

Behind-the-Counter (BTC) – Long Overdue but Let's Seize the Day!

For many decades pharmacists and some of our pharmacy organizations have sought to have established a "third class" of drugs that would be available without a prescription from a pharmacist. Variations of this theme (e.g., a "transitional" class) have also been promoted but, until recently, these efforts were an exercise in futility. The highest barrier was the long-standing position of the Food and Drug Administration (FDA) that it did not have the authority (or it did not know whether it had the authority) to establish such a class of medications. Some of the pharmaceutical companies also strongly opposed a third class of drugs because they felt that this would reduce the sales and profits from their products.

A recent event has significantly changed the context in which such issues and questions should now be considered. In late 2006, the FDA approved the nonprescription behind-the-counter availability in pharmacies of levonorgestrel (Plan B) for use as "emergency contraception" by women 18 years of age and older. This decision was made without any enabling legislation or without any new measure of authority being granted to the FDA. After decades of ambivalence the FDA concluded it had the authority to establish parameters with respect to the availability of nonprescription medications. Although debates regarding Plan B appear destined to continue indefinitely, the debate whether the FDA has the authority to limit the nonprescription availability of medications to behind the pharmacy counter should be considered concluded.

On October 4, 2007, the FDA published in the Federal Register a notice regarding a public meeting scheduled for November 14, 2007 on the topic, "Behind the Counter Availability of Certain Drugs." The notice includes the following statements: "The FDA is interested in obtaining public comment as it explores the public health benefit of certain drugs being available without a prescription but only after intervention by a pharmacist. The purpose of the meeting is to solicit information and views from interested persons on specific issues associated with BTC availability, including the impact on patient access to safe and effective products." The notice identifies numerous related issues for which the FDA is seeking comments.

This initiative by the FDA has the potential for multiple benefits. For various reasons many individuals rarely, if ever, see a physician unless there is a need for emergency treatment. Making certain medications available BTC will greatly increase the access these and other people will have to therapies from which they can benefit. Both individual patients and society in general will benefit from increased access to these medications. The involvement of pharmacists in counseling patients will be of great value in assuring the effective and safe use of these medications, and also enhance the recognition of pharmacists as a source of useful information regarding other medications and healthcare issues.

There are numerous medications that are excellent candidates for nonprescription BTC

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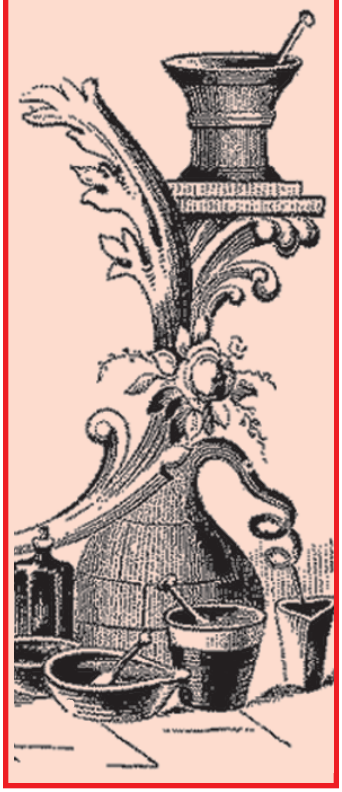

availability in pharmacies. I have selected the following examples to illustrate different reasons for which it is in the interest of patients, society, and the health care system to transfer these agents to nonprescription BTC pharmacy status.

Varenicline, nicotine nasal spray, and nicotine inhalation system

More than 440,000 Americans die each year as a result of smoking-related illnesses. Although some smokers have been successful in quitting with the use of nonprescription nicotine replacement therapy formulations (gum, lozenge, patch) or other strategies, others have not had a successful experience with these products. There are many smokers who want to quit but who will not set up an appointment with a physician to discuss other options. For these individuals, the nonprescription BTC availability of varenicline (Chantix), nicotine nasal spray (Nicotrol), and nicotine inhalation system (Nicotrol) will provide a pharmacist-monitored opportunity for a successful effort to stop smoking.

Some will contend that there is not enough experience to conclude that varenicline is safe enough to be available BTC without a prescription. However, of all the medications approved for use in recent years, it has one of, if not the, "cleanest" safety profiles as reflected by the approved labeling. It is also very unlikely that any unanticipated adverse event that might be recognized with more extensive use of the drug could be worse than the consequences of continuing to smoke. It is an unacceptable irony that only proof of age is required to purchase a dangerous product like cigarettes whereas a prescription is required to obtain products that will help individuals stop smoking. Effective and safe smoking cessation aids should be conveniently available for smokers who choose not to visit a physician, and barriers to such access must be reduced.

Epinephrine auto-injector

Some individuals experience very serious and even life-threatening reactions following insect bites or stings, or exposure to other allergens. Epinephrine is the drug of choice for the emergency treatment of severe allergic reactions, and the administration of this medication with a product such as Epipen can be a life-saving intervention. Epipen requires a prescription. Many individuals who are at risk of experiencing a serious allergic reaction will usually have an Epipen readily available. However, even these individuals may not always be prepared or have overlooked the fact that their Epipen is well past the expiration date and may not provide a reliable response.

Emergencies such as anaphylactic reactions seldom occur in a convenient location such as a block away from a hospital in which needed treatment can be quickly provided. Often these events occur in an area and/or at a time in which the local pharmacy is more quickly accessible than a physician or a hospital. The nonprescription BTC pharmacy availability of Epipen or a similar product can be life-saving.

Oseltamavir

In recent years there has been considerable publicity about the possibility of an influenza pandemic. Oseltamavir (Tamiflu) is one of a very small number of antiviral agents that is effective in the treatment of influenza. However, for this drug to be optimally effective, it is very important that treatment be initiated as soon as possible (within two days) following the onset of symptoms. Patients who experience influenza symptoms should be provided the fastest access possible to medication that might be of significant benefit, and even the delay in seeing a physician (who can be expected to be even busier than usual during "flu season") for a prescription may compromise the effectiveness of therapy.

Although there have been some reports (mostly in Japan) of neuropsychiatric adverse events in children and adolescents, oseltamavir is well tolerated by most patients. The anticipated benefits (possibly life-saving in vulnerable patients) of making this medication more readily accessible on a timely basis, without the limitation and delay of requiring a prescription, far exceed the low risk associated with its use.

Statins

The statins are among the most widely prescribed of all therapeutic agents. They are the most effective medications in lowering cholesterol concentrations and are well tolerated by most patients, notwithstanding the potential for musculoskeletal adverse events. Requests to transfer lovastatin (e.g., Mevacor) and pravastatin (e.g., Pravachol) from prescription-only to nonprescription status were initiated several years ago but were not approved by the FDA. Merck is currently planning another request in support of nonprescription status for lovastatin.

A primary concern voiced by those who oppose nonprescription status for the statins is that patients will have difficulty determining their need for and subsequent monitoring of a statin, particularly because hypercholesterolemia is not associated with symptoms. Although this is a valid concern, it must also be recognized that many individuals, rather than seeing a physician and receiving prescribed medications, are purchasing herbal products and dietary/nutritional supplements for the purpose of decreasing their cholesterol and deriving the suggested accompanying benefits. These products have not been evaluated in clinical studies, there are little or no safety data, and there is often no assurance of standardization of active ingredients. In this context, a strong case can be made for the nonprescription BTC pharmacy availability of statins that have been extensively studied, have a known safety profile, and can be monitored by a pharmacist.

In addition to these four examples, there are numerous other medications that are strong candidates for nonprescription BTC pharmacy availability. With certain agents, there will be a need for specific parameters and guidelines to assure appropriate use and these will vary depending on the medication. However, this should not be reason to delay consideration of medications for which a change in status should be made quickly.

The increase in number of nonprescription BTC pharmacy available medications will not only result in increased patient access to helpful medications, but will also make them available on a more cost-effective basis. The opportunity that the FDA is providing is one in which all participants can "win" – individual patients, society in general, the healthcare system, pharmacists, pharmaceutical

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New Drug Review

Raltegravir
(Isentress – Merck)
Antiviral Agent

New Drug Comparison Rating (NDCR) = 4
(significant advantages) in a scale of 1 to 5, with 5 being the highest rating

Indication:

In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Most important risks/adverse events:

Immune reconstitution syndrome; is primarily eliminated by metabolism via a uridine diphosphate glucuronosyltransferase (UGT) 1A1-mediated glucuronidation pathway and action may be reduced by the concurrent use of a strong inducer of UGT1A1 such as rifampin (e.g., Rifadin); may increase creatine kinase (CK) concentrations—myopathy and rhabdomyolysis have been reported and caution should be exercised in patients who are also being treated with other medications (e.g., statins [e.g., atorvastatin (Lipitor)]) that are known to cause these conditions.

Most common adverse events:

Diarrhea (17%), nausea (10%), headache (10%), pyrexia (5%).

Usual dosage:

400 mg twice a day.

Product:

Tablets – 400 mg.

Comparable drugs:

Other antiretroviral agents; comparisons are made with the HIV protease inhibitors (e.g., lopinavir/ritonavir [Kaletra], atazanavir [Reyataz], darunavir [Prezista]).

Advantages:

- Has a unique mechanism of action (inhibits HIV integrase strand transfer);
- Is effective in some patients who have become resistant to previous regimens;
- Use is associated with fewer serious adverse events;
- Interacts with fewer medications.

Disadvantages:

- Use is limited to treatment-experienced patients with evidence of resistance to other agents (except for darunavir and tipranavir (Aptivus), as well as enfuvirtide (Fuzeon) and maraviroc (Selzentry), whose use is also limited to treatment-experienced patients);
- May be more likely to increase CK concentrations and cause musculoskeletal adverse events;
- Is administered twice a day (compared with atazanavir that is administered once a day).

Comments:

Raltegravir (Isentress – Merck) is the twenty-fourth antiretroviral agent to be marketed for the treatment of HIV infection/AIDS in the United States. It has a unique mechanism of action and is designated as an HIV integrase strand transfer inhibitor (integrase inhibitor). Like HIV protease and reverse transcriptase, integrase is an HIV-1 enzyme that has an important role in the replication of the virus. This enzyme facilitates the integration of viral DNA into the DNA of host cells, and inhibition of integration by raltegravir blocks propagation of the viral infection. Additive to synergistic antiretroviral activity has been demonstrated in cell cultures when raltegravir has been combined with most other antiretroviral agents.

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companies, and the FDA. The FDA is providing the opportunity – it is now up to the profession of pharmacy to effectively articulate and demonstrate how these changes can be implemented and the value of our expertise and services. We must seize the day!

I have requested the opportunity to present comments at the meeting on November 14. I would encourage you to submit by November 28, 2007 written comments to:
Division of Dockets Mangement (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
or electronically to:
http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm

Daniel A. Hussar

New Drug Review (cont.)

Comments:

Raltegravir is specifically indicated for use, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. It joins tipranavir, darunavir, enfuvirtide, and maraviroc as antiretroviral agents that are not included in initial regimens for the treatment of HIV infection and should be reserved for use in patients who demonstrate resistance to previous regimens. The effectiveness of raltegravir in reducing HIV-1 RNA concentrations was demonstrated in two controlled studies in patients with documented resistance to at least one drug in each of three classes of antiretroviral agents. Patients received either raltegravir or placebo in addition to optimized background therapy (OBT) consisting of two to seven antiretroviral agents.

Although experience with raltegravir is limited, it appears less likely than most other antiretroviral agents to cause serious adverse events. The discontinuation rate (2%) in the clinical studies due to adverse events was similar to that in the group receiving placebo plus OBT. Serum creatine kinase (CK) elevations were experienced by some patients treated with the new drug, and myopathy and rhabdomyolysis have been reported although a causal relationship with the use of raltegravir has not been demonstrated. Caution must be exercised if a patient is also taking other medications such as a statin (e.g., atorvastatin) that are known to cause musculoskeletal adverse events. Raltegravir is not a substrate for cytochrome P450 (CYP) enzymes and, therefore, is not implicated in the numerous drug interactions with which the HIV protease inhibitors are associated. It is eliminated primarily via a UGT1A1-mediated glucuronidation pathway, the activity of which is altered by a relatively small number of drugs. However, rifampin is a strong inducer of UGT1A1 and reduces the concentration of raltegravir.

Raltegravir is administered twice a day without regard to food. Its twice-daily frequency of administration is the same as that for many of the antiretroviral agents but is not as convenient as that for selected other agents such as atazanavir that are administered once a day. The unique mechanism of action and favorable safety profile of raltegravir make it a valuable addition to the group of antiretroviral agents.

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