CHAPTER 12

New Drug Update 2017/2018

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INTRODUCTION

Each year, a wide range of drugs and devices are introduced into the market. It is important for new drugs to reach the public quickly and efficiently, however patients and consumers must be protected from unsafe drugs. Before a drug reaches the public, it must undergo a rigorous approval process through a team of physicians, pharmacologists, statisticians, and scientists. Not every approved drug is 100% risk free, and the benefit should outweigh the risk; therefore it is the duty of physicians and drug manufacturers to continually monitor the drug after the approval process. The agency responsible is the US Food and Drug Administration (FDA).

BRIEF HISTORY OF THE FDA

The FDA is the oldest consumer protection agency in the US Federal Government (1). It began in the US Patent Office in 1848, then transferred to the US Department of Agriculture (USDA) in 1862, when chemist Charles M. Wetherill analyzed samples of food, soil, fertilizers, and other agricultural substances in the laboratory (2). The Pure Food and Drugs Act was passed in 1906, which prohibited adulterated and misbranded food and drugs from being transported across state lines. The FDA did not get its present name until 1930 with the passage of The Federal Food, Drugs, and Cosmetics Act in 1938, which required all drugs to be inspected for safety by the FDA. The FDA was moved from the USDA to the Federal Security Agency (FSA) in 1940; then in 1953 it was moved from the FSA to the Department of Health Education and Welfare (HEW).

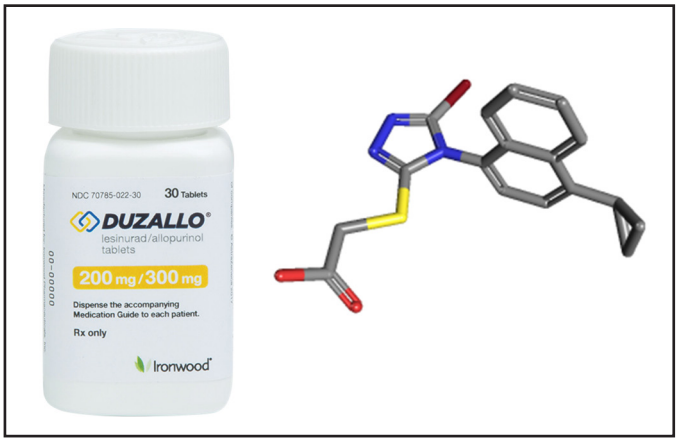

Figure 1. Lesinurad/Allopurinol (Duzallo).

In 1968, the FDA became part of the Public Health Service within HEW. The Department of Health and Human Services was formed by Congress in 1980, and the FDA became part of the department up until today. The FDA has six centers and the largest is the Center for Drug Evaluation & Research (CDER), which is responsible for both prescription and non-prescription (over-the-counter) drugs (1, 2). The remaining five FDA centers are responsible for tobacco products, biologics, veterinary drugs, medical devices, and food and cosmetics (1).

GOUT

Gout is a metabolic condition that is commonly seen in the podiatric physician's office. It is a disease that results from the deposit of monosodium urate crystals to the tissues from the extracellular fluids, due primarily to a disorder of purine metabolism causing hyperuricemia. This leads to severe inflammatory reaction translating to intense pain for the patient. Urate crystals can deposit anywhere in the body however the first metatarsophalangeal joint is a common location for crystals. Gout is a treatable and manageable condition. Common medications used to treat acute gout attacks include colchicine and nonsteroidal anti-inflammatory medications such as indomethacin. Diet management can be summarized by mainly avoiding organ meat, shellfish, and alcohol. Long-term management of gout includes the use of allupurinol, probenecid, and sulfinpyrazone. Duzallo is a new FDA-approved medication for the treatement of hyperuricemia associated with gout.

Lesinurad/Allopurinol (Duzallo)

Duzallo is the newest FDA-approved drug for the treatment of hyperuricemia associated with gout (Figure 1). It was approved in August 2017 (3). Duzallo is a combination of allopurinol and lesinurad. Allopurinol disrupts the production of uric acid by inhibiting the biosynthesis of purine, a key pathway in the production of uric acid. Lesinurad works in the kidney preventing the re-absorption of uric acid. Duzallo is indicated to be used in gout patients when a medically appropriate daily dose of allupurinol alone is not enough to achieve target serum uric acid levels. It is a pill taken once daily and comes in two strengths; lesinurad 200mg/allupurinol 300mg and lesinurad 200mg/allupurinol 200mg (3). Duzallo has a drug-drug interaction with mercaptopurine, moderate cytochrome P450 2CP inhibitors, CYP3A substrate and most important

is its interaction with warfarin anticoagulants, as it is not uncommon for our patient population to be on long-term anticoagulants. Duzallo was approved after undergoing two phase III clinical trials on adult patients with gout who failed to achieve target serum uric acid levels on allupurinol alone, however with a combination of lesinurad to allupurinol, almost twice the patients achieved target uric acid levels <6 mg/dl at month 6 (4).

ANTIBIOTICS

In the last 100 years, there have been many inventions. Many will argue that the computer was the best invention in the last century, others will say the internet, some will say the airplane however the author will argue strongly in favor of antibiotics starting with the invention of penicillin in 1928. Antibiotics have saved countless lives by preventing death from treatable diseases. No doubt that the discovery of antibiotics is the greatest achievement in medicine next to vaccines. Many antibiotics have been introduced into the market since the discovery of penicillin, which has helped save lives. However, the biggest challenge scientists face today is antibiotic resistance due mostly to inappropriate use. Scientists and researchers are always in a race against time to develop the next antibiotics to kill resistant organisms. Therefore, when choosing an antibiotic, it is vital to consider targeting the most likely infecting organism for prophylaxis antibiotics and also consider the sensitivity of the organisms to the antibiotics. With all the advances in science and technology, skin and soft infections continue to have a high mortality rate and are a leading cause of non-traumatic amputation. Diabetic foot infection is a costly problem both for the patient and healthcare system, diabetic related hospital admissions are mostly due to foot infections. Next, we will review two antibiotics recently approved by the FDA.

Delafloxacin (Baxdela)

Delafloxacin is the newest approved fluoroquinolone (Figure 2). It was approved by the FDA in June 2017 for treatment of acute bacterial skin and skin structure infection in adults (5). It is effective against aerobic gram-positive organisms including MRSA and aerobic gram-negative organisms including *Pseudomonas aeruginosa.* It is available in both oral and intravenous forms. The recommended intravenous dose is 300 mg every 12 hours administered slowly over 60 minutes. The oral dose is 450 mg every 12 hours for 5-14 days (5). Just like clindamycin, delafloxacin can be started intravenously for an in-patient and converted to oral dosing upon discharge. It is renally dosed and contraindicated in patients with end-stage renal disease (ESRD). Delafloxacin works by inhibiting both topoisomerase and DNA gyrase in bacteria. Both enzymes are necessary for DNA replication, recombination, transcription and repair. In vitro, it has a concentration-dependent bactericidal activity against gram-positive and gram-negative organisms. Delafloxacin was approved after undergoing two phase III trials consisting of 1,510 randomized adults with acute bacterial skin and skin structure infections comparing delafloxacin with vancomycin plus aztreonam (6). Just like with any fluoroquinolone, serious adverse reactions include tendinitis, tendon rupture, peripheral neuropathy, central nervous system dysfunction, and exacerbation of myasthenia gravis.

Omadacycline (Nuzyra)

Omadacycline is the recently approved tetracycline (Figure 3). It was approved on October 2, 2018 by the FDA for the treatment of adults with community-acquired bacteria pneumonia (CABP) and acute skin and skin structure infectious (7). CABP can be caused by staphylococcus species, streptococcus species, Haemophilus, Klebsiella, Legionella, Mycoplasma and chlamydia. It is a broad spectrum antibiotic

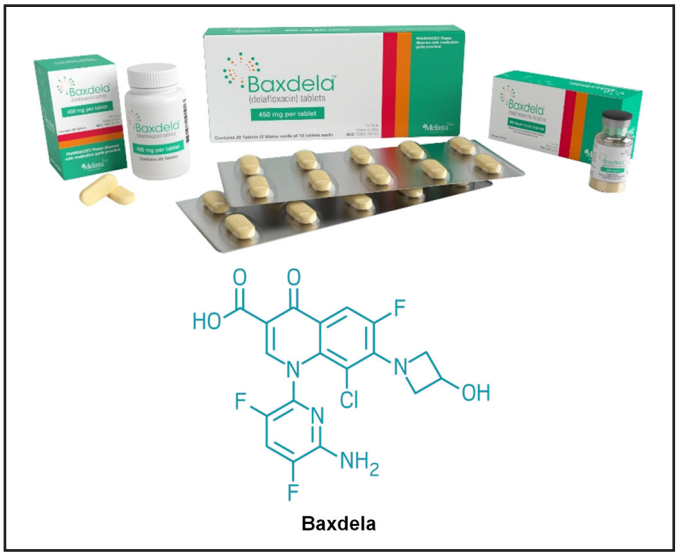

Figure 2. Delafloxacin.

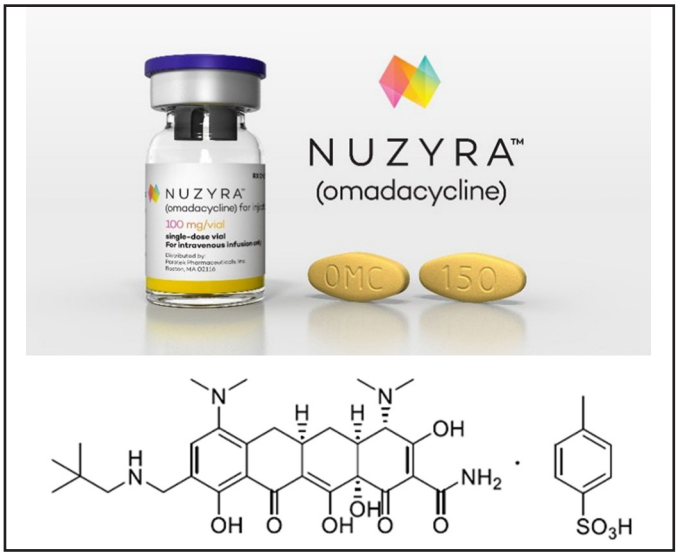

Figure 3. Omadacycline.

effective against gram-positive organisms including MRSA, gram-negative, atypicals, and drug resistant strains (7). It is available in both oral and intravenous forms. Omadacycline was approved by the FDA after three phase III clinical trials. One single phase III trial was conducted on CABP patients and the other 2 studies were conducted in acute bacteria skin and skin structure infections (ABSSSI) patients (8). Adverse reactions are the same as other tetracyclines such as inhibition of bone growth, tooth discoloration in children, and should be avoided in pregnant women. Drug to drug interaction should be considered in patients taking antacids and iron preparations. It also depresses plasma prothrombin activity in patients on anticoagulant therapy.

ANTICOAGULATION

About 2 million Americans are affected by deep vein thrombosis each year (9). It is not uncommon for our patient population to be on some form of long-term anticoagulant. For over half a century, the only chemical anticoagulant available was heparin/warfarin, a Vitamin K antagonist. Heparin, a naturally occurring glycosamine discovered in the 1930s, was the first intravenous anticoagulant. Still in use today, however it has several drawbacks such as weekly monitoring, narrow therapeutic index and requires the need for bridging. Over the past decade, new oral anticoagulants have been introduced into the market that target specific pathways in the clotting cascade, it is important to briefly review the clotting cascade to fully appreciate how these drugs work.

The coagulation cascade begins with a break in the endothelial cells, platelets aggregate to the site to form what is best described as a "soft clot," then recall that the Intrinsic Pathway starts with Factor XII while the Extrinsic pathway begins with Factor III, both pathways activate Factor X, and Factor X activates Factor II (prothrombin to thrombin). It must be noted that thrombin has a positive feedback mechanism that further activates Factor V, VII, VIII, XI, XIII and most importantly thrombin activates Factor I (fibrinogen to fibrin), which is connected together by strands to form a mesh at the injury site. The fibrin strands are held to one another by Factor XIII. Thrombin also helps activate plasmin from plasminogen to break down fibrin clots.

Now that we have reviewed the clotting cascade, we will better appreciate how anticoagulants work. Heparin is a vitamin K antagonist and blocks Factors X, IX, VII & II. However, the new oral anticoagulants have targeted more specific Factors in the cascade system such as dabigatran (Factor II inhibitor), rivaroxaban (Factor Xa inhibitor), apixaban (Factor Xa inhibitor), edoxaban (Factor Xa inhibitor) and darexaban (Factor Xa inhibitor). Next, we will discuss the latest Factor X inhibitor recently approved by the FDA.

Betrixaban (Bevyxxa)

Betrixaban is the newly approved Factor X inhibitor (Figure 4). It was approved in June 2017 (10). It is approved by the FDA as an anticoagulant drug indicated as prophylaxis for venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complication due to moderate or severe restricted mobility and other risk factors for VTE e.g., heart failure, stroke, pulmonary disease, and infection (10). It must be stated that betrixaban has not been recommended in patients with prosthetic heart valves because this population was not studied. Platelet aggregation is not affected by betrixaban. It is available in 40 mg and 80 mg capsules. The recommended dose is an initial single dose of 160 mg, followed by 80 mg once daily taken at the same time with food. The dose should be reduced in patients with severe kidney problems and patients on P-glycoprotein (P-gp) inhibitors. This is because betrixaban is mostly excreted through the liver (biliary secretion) via P-gp efflux pumps. clarithromycin, erythromycin, ketoconazole, and amiadarone are examples of drugs that are P-gp inhibitors. The recommended duration of treatment is 35 to 42 days (10).

The approval of betrixaban was based on a randomized, double-blind clinical trial consisting of 7,513 randomized patients receiving either betroxaban or enoxaparin treatment. The multinational clinical trial compared extended duration betrixaban (35 to 42 days) to enoxaparin (6 to 14 days) in acutely medically-ill hospitalized patients (11). The result showed fewer events in patients receiving betrixaban (4.4%) compared to those taking enoxaparin (6%) (11). As with any anticoagulant, there is risk of bleeding associated with betrixaban.

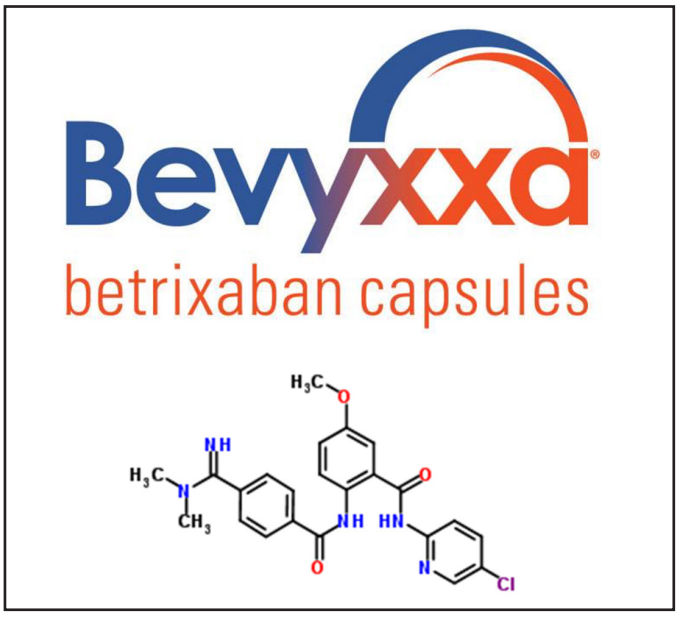

Figure 4. Betrixaban.

Figure 5. Andexanet Alfa.

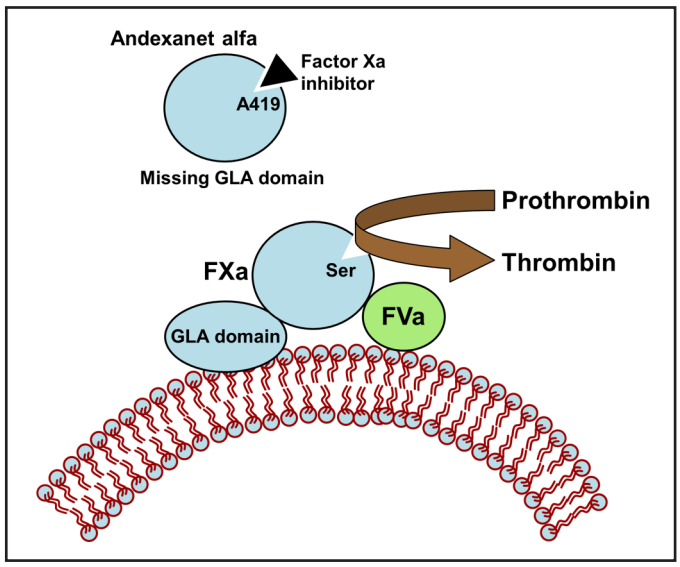

Figure 6. Andexanet alfa mechanism of action.

REVERSAL OF ANTICOAGULANTS

Until 2018, there was no established way to reverse Factor X inhibitiors such as rivaroxaban (Xarelto), apixaban (Eliquis), and newly approved betrixaban (Bevyxxa). Protamine sulfate, Vitamin K, and tranexanic acid are not expected to reverse the anticoagulant activity of Factor X inhibitors. Supportive therapies such as intravenous fluids or blood transfusion were often the last resort for uncontrolled bleeding. On May 3, 2018, the FDA granted accelerated approval for andexanet alfa (Andexxa).

Andexanet Alfa (Andexxa)

Andexanet alfa is the first universal reversal agent for uncontrolled bleeding in patients anticoagulated with an oral or injectable Factor X inhibitor (Figure 5)(12). It was approved on May 3, 2018. Andexanet alfa (Anderxxa) is an inactivated-zhzo, a recombinant Factor Xa Protein (12). It binds and sequesters Factor Xa inhibitor and inhibits tissue factor pathway inhibitor (TFPI) therefore reversing anti-Factor Xa activity and restoring thrombin generation (Figure 6) (13). It is not uncommon for our patient population to be anticoagulated on Factor X inhibitors requiring emergent surgery such as an incision and drainage or an ankle fracture, these surgical patients are at risk of uncontrolled bleeding. Andexanet alfa was approved after two Phase III studies on reversing the anticoagulant effects on healthy volunteers taking rivaroxaban (Xarelto) and apixaban (Eliquis). The study showed that andexanet alfa reversed anticoagulant activity within minutes after administration and through the duration of infusion (14). There is warning of thromboembolic risks, ischemic risks including myocardial infarction and ischemic stroke associated with using andexanet alfa (Anderxxa).

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