

Student Clinical Digest

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Clinical Pharmacist Spotlight: Addiction Pharmacy

What is the role of a pharmacist in addiction pharmacy?

Addiction Pharmacy is the study of three separate distinct, but closely connected areas of pharmacotherapy in a patient that is diagnosed with an addictive disease and the co-occurring disease states of mental illness and/or acute/chronic pain. This patient is particularly difficult to manage due to the vast complexities of the multiple disease states and needs continual evaluation of pharmacotherapies and other treatment modalities (psychotherapy, pain management, etc.).

What types of things do you do at your practice site?

I encounter a variety of disease states in this clinic so I provide evaluation, assessment, intervention and treatment strategies to the patient's treatment team for the following:

- Substance Use Disorders (Chemical and Behavioral) - ambulatory detoxification of alcohol and withdrawal, benzodiazepine withdrawal, and opioid withdrawal;
- Anxiety (assessment and screening);
- Bipolar Disorder (assessment and screening);
- Depression (assessment and screening)
- Tobacco Use Disorder (interventions and pharmacotherapy);
- Acute/chronic pain (assessment and follow-up);
- I also provide ongoing drug information lectures on the neurobiology and pharmacogenomics of addiction, and the appropriate use of medications in recovery to patients and their families. Other disease states that are commonly encountered are metabolic syndrome, insomnia, liver disease, and GERD.

What do you think should change in the field of addiction pharmacy?

Simply to educate all pharmacists to the basics of addiction pharmacy.

I have spent over 25 years of my career as an international clinical pharmacist consultant assisting physicians and psychiatric institutions with drug information about addiction, psychiatric, and pain management medications. Addiction pharmacy requires an understanding of drug information and how to communicate this information to patients, family members, and treatment teams- both of these skill sets are NOT a part of the current Pharm.D. curriculum nationally. My plan is to develop a two year addiction pharmacy residency at the University of Georgia College of Pharmacy.

Why is it important for the student pharmacist to understand addiction?

There are two reasons for student pharmacists to understand addiction: 1.) Over 40-50% of the patients the student pharmacist will treat in their careers will have experienced an addiction or be affected by a loved one's addiction; 2.) The student pharmacist may also be high risk for developing addiction, anxiety, and depression. The pharmacy profession has been somewhat slow in appropriately training the student pharmacist to these risks and outcomes.

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**Dr. Merrill Norton,
PharmD, PhD, ICCDP-D**

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Dangers of Mislabeling: Levaquin Use and the Increased Risk for Peripheral Neuropathy

In 2014, a lawsuit was filed by a woman in California after being diagnosed with peripheral neuropathy caused by her use of Levaquin (levofloxacin), a popular antibiotic and fluoroquinolone¹. Peripheral neuropathy is a serious condition that can be described as damage to the peripheral nervous system resulting in miscommunication between the central nervous system and the remaining parts of the body. Patients who suffer from peripheral neuropathy could experience symptoms such as numbness, burning pain, paresthesia, muscle weakness, and allodynia. Extreme cases can result in complications including rhabdomyolysis, paralysis, and organ dysfunction. The patient complained that the warning label mislead her to believe that peripheral neuropathy associated with Levaquin and other fluoroquinolones was rare. In addition, the lawsuit stated peripheral neuropathy cannot always be avoided by discontinuing the use of Levaquin. The patient also alleged that this debilitating side effect was "buried at a long list of adverse reactions¹".

In 2013, the Federal Food and Drug Administration (FDA) issued a label change for all oral fluoroquinolones based on published case reports and reports from the Adverse Event Reporting System in order to emphasize that peripheral neuropathy can occur rapidly while using Levaquin. According to a study at the University of Washington Seattle, the use of fluoroquinolones, including

Levaquin, can lead to a 30% increased risk of peripheral neuropathy². It was discovered that the risk of peripheral neuropathy development was highest among new users of fluoroquinolones. This case emphasized the necessary change of warning labels by the drug manufacturers to highlight the increased prevalence of peripheral neuropathy occurrence in patients who are taking fluoroquinolones in hopes to increase patient awareness and safety.

By: Ashni Patel, PharmD Candidate & Justin Moore, PharmD Candidate



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2. Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: A pharmacoepidemiologic study. *Neurology* 2014; Epub 2014 Aug. 22.

Ache No More! New Drug Therapy for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system mistakenly attacks the joints, causing inflammation and joint damage. RA typically affects women ages 30 to 60. Patients experience symptoms such as pain, fatigue, morning joint stiffness, and red swollen joints.¹ Based on the guidelines by the American College of Rheumatology, there are different treatment options contingent upon disease activity and features of poor prognosis, such as functional limitations or rheumatoid nodules. If a patient does not have features of poor prognosis, a typical starting regimen is DMARD (disease-modifying antirheumatic drug) monotherapy, such as methotrexate. If features of poor prognosis appear, an option is to start the patient on a biologic agent in combination with the DMARD. An example of this regimen would be the addition of Humira to methotrexate.²

In June 2014, Sanofi announced positive phase 3 trial results of sarilumab for the treatment of RA in combination with methotrexate.³ The study was randomized, double-blinded, and placebo controlled. The sample size consisted of Japanese patients ages 20 to 65 with moderate to severe RA, already taking methotrexate as

monotherapy.^{4,5} Sarilumab is the first fully human monoclonal antibody targeting IL-6 receptors, thereby inhibiting the cytokine-mediated inflammatory pathway.³ Historically, non-human antibodies, which typically come from mouse cells, have elicited immune responses since the mouse cells are seen as foreign. Therefore, the advantage of administering fully human monoclonal antibodies is having a decreased risk of patient rejection of the drug both short and long term.⁶

Based on the original study, patients receiving a dose of sarilumab 150 mg or 200 mg subcutaneously every two weeks proved to have the most favorable safety and efficacy profiles after 12 weeks of therapy.⁴ The most common side effect seen thus far is infection. However, further studies are underway to determine additional adverse effects. Although this is the first fully human antibody, there are other IL-6 receptor inhibitors on the market for treatment in RA. Side effects for these medications, such as tocilizumab, include increased cholesterol and LFTs, neutropenia, and hypersensitivity reactions. Therefore, these are some adverse effects researchers might expect to see in future studies.⁷ Transitioning from mouse cell to

fully human antibodies is a revolutionary concept that is expected to continue throughout future drug developments for RA and other autoimmune disease treatments.

By: Allyson Cox, PharmD Candidate

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- ³Sanofi and Regeneron Announce New, Detailed Data from Positive Sarilumab Phase 3 Rheumatoid Arthritis Trial at EULAR. Regeneron. <http://investor.regeneron.com/releasedetail.cfm?releaseid=854328>. Published June 12, 2014. Accessed April 2, 2015.
- ⁴Huizinga, T.W., et al. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis* 2014; 73: 1626-34.

Reversal Agent for Direct Factor Xa Inhibitors

In the scope of anti-coagulation therapy, warfarin has historically been the drug of choice for oral therapy. However, due to its high drug interaction profile and high demand for blood monitoring there has been a push to see new drugs for anti-coagulation therapy. In recent years, the market has been introduced to agents such as rivaroxaban (Xarelto®) as a safer alternative to warfarin for anti-coagulation therapy. Rivaroxaban is a direct factor Xa inhibitor and has been approved for the prevention and treatment of DVT, pulmonary embolism, and prevention of cerebrovascular accident due to atrial fibrillation. Rivaroxaban (Xarelto®) has fewer drug-drug interactions compared to warfarin, thereby decreasing the complexity of prescribing to patients on many different chronic medications. Also, rivaroxaban does not require constant INR monitoring, unlike warfarin. Additional factor Xa inhibitors include apixaban (Eliquis®) and edoxaban (Savaysa®). The major disadvantage to using direct factor Xa inhibitors is the lack of an antidote. However, this disadvantage may soon be eliminated based on the results of the first part of the Phase 3 trials by Portola Pharmaceuticals.

On March 2, 2015, Portola Pharmaceuticals announced the success of the safety and efficacy study for andexanet alfa in reversing the anticoagulation effects of rivaroxaban. Based on the success of the drug, John T. Curnutte, executive vice president for research and development stated, "Andexanet alfa has the potential to become the first approved universal antidote for direct Factor Xa inhibitors and the standard of care to manage bleeding associated with these novel anticoagulants. [It] is the only antidote in development shown to directly and significantly impact definitive markers for coagulation in clinical studies¹."

Andexanet alfa is a recombinant protein of the human Factor Xa molecule and acts as a decoy for direct factor Xa inhibitors. Drugs, like rivaroxaban, bind to andexanet alfa with high specificity and are sequestered from factor Xa in the blood. In the Phase 3 trial, a randomized, double-blind, placebo controlled study was

performed on healthy volunteers ages 50 to 75. The patients were given Xarelto® 20mg for four days to reach steady state then randomly divided into two treatment groups. One treatment group received 800mg IV bolus of andexanet alfa and the other treatment group received a placebo. The results showed 26 of the 27 patients receiving andexanet alfa "[had] a 90% or greater reduction in anti-Factor Xa activity, [and] the free Xarelto® concentration was reduced significantly²." Based on these results, andexanet alfa appears to be a successful agent in reversing the effects of rivaroxaban.

Currently, the FDA has granted andexanet alfa with orphan drug status for patients experiencing an uncontrolled bleeding event or requiring urgent surgery. Portola Pharmaceuticals is currently planning to submit their preclinical and clinical data to the FDA for approval by the end of 2015.



By: Rachel Stephens, PharmD Candidate

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¹ (March 2, 2015) "Protola Announces Full Results from Positive Phase 3 ANNEXA™-R Study Demonstrating that Andexanet Alfa Rapidly and Significantly Reversed Anticoagulant Effect of Factor Xa Inhibitor Xarelto®" Retrieved From: <http://www.globenewswire.com/news-release/2015/03/02/711337/10122590/en/Portola-Announces-Full-Results-From-Positive-Phase-3-ANNEXA-TM-R-Study-Demonstrating-That-Andexanet-Alfa-Rapidly-and-Significantly-Reversed-Anticoagulant-Effect-of-Factor-Xa-Inhibi.html>

² Center Watch (1995-2015) Retrieved from: <http://www.centerwatch.com/clinical-trials/results/new-therapies/nmt-details.aspx?CatID=772>



Technology Update: FDA Launches New App

On March 4, 2015 the FDA took the next step in keeping the public informed of drug shortages by launching its new Drug Shortages mobile app. This app is designed to provide real-time information regarding "current drug shortages, resolved shortages, and discontinuations of drug products" (APhA 2015). The app is available for free download from the Apple App Store or from Google play on Android devices. Within the app, you can browse for a current drug shortage, resolved drug shortage, or discontinuation by drug name or therapeutic category. Additionally, the app contains information on how to report a drug shortage. By increasing the ease of availability of drug shortage information, the FDA hopes to aid health care professionals in making the most appropriate and timely treatment decisions.

By: Alyssa K. Elrod, PharmD Candidate

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¹ "FDA launches drug shortages mobile app." March 5, 2015. APhA News.

³ www.fda.gov

² FDA Drug Shortages. (2015). Food and Drug Administration (Version 1) [Mobile application software]. Retrieved from <http://play.google.com>

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What advice do you have for students who are interested in pursuing a career in this field?

My best advice to the student pharmacist is to learn as much as they can about the disease state of addiction (Substance Use Disorders), the treatments required, and that no one plans to become addicted to any drug. The profession of pharmacy is truly the profession that is integrated in our communities and institutions in the US. My suggestion is to attend the APhA Institute on Alcoholism and Drug Dependence. As I recently told the American Association for Treatment of Opioid Dependence, 100,000 pharmacists would make a tremendous impact on the treatment of addicted disease if appropriately trained as referral agents and interventionists.

By: Lindsey Sellers, PharmD Candidate

Don't Stay Out for Too Long, Kids: Topicals Effective for Sunburn



Summer is quickly approaching, which means that we can enjoy longer days, sunlight, and tanning breaks at the beach. However, too much sun exposure can result in sunburn, a condition in which skin becomes inflamed due to excess UV radiation. While most sunburn symptoms are easy to manage, severe sunburn may require a visit to the doctor's office.

Mild-to-moderate sunburn can be typically self-treated. Mild-to-moderate sunburn results in symptoms that we are familiar with, such as red skin, tenderness, pain, and peeling of the skin. Moisturizing cream, topical steroids like hydrocortisone cream, and aloe vera gel can be applied to the affected area to relieve discomfort. Topicals that contain benzocaine or lidocaine are to be used with caution, as they can cause allergic reactions in some individuals. Oil-based moisturizer, such as petroleum jelly, is not recommended as it can block pores and lead to infection.

For more severe sunburns, patients may develop painful blisters, which should be left alone to promote faster healing and avoid risk of infection. Silver sulfadiazine cream is a commonly prescribed topically for second- or third-degree burns and can be used for severe sunburns as well. Open erosions should be covered with petroleum jelly and dry gauze to decrease risk of infection. When experiencing fever, chills, extreme thirst, and other signs of shock, heat exhaustion, and dehydration, a healthcare provider should be contacted.

While symptoms of sunburn are typically easy to manage, patients may develop skin cancer in the long run. It is important for people to use a broad-spectrum sunscreen of SPF 30 or higher on exposed skin, which should be reapplied periodically, and wear protective clothing to minimize damage from UV radiation.

By: Joanna Lee, PharmD Candidate

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Comparison of New Treatments for Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is an uncommon but serious disease of the lungs. It is characterized by progressive fibrosis and scarring of the lung tissue, resulting in hypoxemia and significantly impaired lung function. Prior to 2014, there were no FDA-approved medications to treat IPF. Treatment was primarily symptomatic and centered on the use of supplemental oxygen, pulmonary rehabilitation, and corticosteroids. On October 15, 2014, two new drugs gained FDA approval for treatment of IPF: Ofev® (nintedanib), manufactured by Boehringer Ingelheim; and Esbriet® (pirfenidone), manufactured by InterMune. These drugs have shown similar efficacy in their respective clinical trials and are available at comparable costs.

By: Marisa Fortunato, PharmD Candidate

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3. Red Book Online [database online]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed February 21, 2015.

	Ofev®	Esbriet®
Mechanism of Action:	Tyrosine kinase inhibitor	Not fully known, but is involved with decreasing inflammation and decreasing fibroblast proliferation.
Price:	\$8,000 / month	\$7,800 / month
Dosage Form:	Oral capsule	Oral capsule
Daily Dose:	150 mg twice daily	2403 mg / day in 3 divided doses
Pill Burden:	2 pills / day	9 pills / day
Clinical Outcomes:	Demonstrated a slowing of pulmonary decline and reduced disease progression when compared to placebo over a 1-year period	Demonstrated a slowing of pulmonary decline and reduced disease progression when compared to placebo over a 1-year period
Adverse Events:	Most common ADEs were GI-related. 62% of study subjects experienced diarrhea, which was severe in 6% of cases. A small number of subjects also experienced AST and ALT elevations.	Most common ADEs were GI and skin related. 36% of study subjects experienced nausea and 28% developed a rash.

Vaccinations for Traveling Abroad: How Necessary Are They?

There is no place like home. World travelers probably find it true more than anyone else, especially when it comes to health conditions, sanitation, or clean water as they venture in less developed countries. Many contagious diseases are still prevalent in many parts of the world although they are rare in the United States and other industrialized nations due to advanced medicine. To protect your health, meet travel requirements, and fully enjoy your trip, the Center for Diseases Control and Prevention (CDC) recommends you obtain necessary immunizations before departing.

The World Health Organization (WHO) classifies travel immunization requirements into three types: routine, selective and required vaccines. Some vaccines are required for traveling to specific countries; others are simply recommended.

According to the CDC, those who travel abroad should stay up-to-date on routine vaccines and obtain booster doses if necessary. Routine vaccines include:



<u>Routine childhood vaccines:</u>	<u>Routine adult vaccines:</u>
Diphtheria/tetanus/pertussis (DTaP)	Diphtheria/tetanus/pertussis (Td/Tdap)
Hepatitis A (Hep A)	Hepatitis A (Hep A)
Hepatitis B (Hep B)	Hepatitis B (Hep B)
Haemophilus influenza type b (Hib)	Herpes zoster (Shingles)
Human papillomavirus (HPV)	Human papillomavirus (HPV)
Influenza (Flu)	Influenza (Flu)
Measles, mumps, and rubella (MMR)	Meningococcal
Meningococcal	Pneumococcal
Pneumococcal	
Polio	
Rotavirus	
Varicella (Chicken pox)	

Selective vaccines are recommended if there is a higher risk of contracting a disease based on your country of destination, your length of stay, and your work in that foreign country. Those vaccines include cholera, Hep A, Japanese encephalitis, meningococcal, rabies, tick-borne encephalitis, typhoid fever, and yellow fever.

Currently, the WHO's International Health Regulations Committee identifies three mandatory vaccines. Yellow fever vaccines are required for traveling to several countries in Africa and South America. The country list can be obtained at www.who.int/ith/vaccines. Meningococcal and polio vaccines are required by Saudi Arabia for pilgrims visiting Mecca and/or Medina for the annual or at any time. To decide which vaccines to obtain, you need to consider the following factors:

- Your risk of exposure to the disease
- Your age, health status, vaccination history
- Your reactions to previous vaccine doses, allergies including medication allergies
- Your risk of infecting others
- Immunization cost

You can start your travel immunization plan by visiting www.cdc.gov/travel. However, it is recommended that you contact a health care provider or a local travel immunizations clinic 4 – 6 weeks before departure. It usually takes a few weeks obtain vaccine's protective effects and some vaccines might require multiple doses. Moreover, several vaccines might not be readily in stock and require a few days ordering notice.

By: Huong Pham, PharmD Candidate

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Avycaz (ceftazidime/avibactam)

Background

Ceftazidime is a third-generation cephalosporin that demonstrates broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli. Avibactam is a semi-synthetic, non- β -lactam, β -lactamase inhibitor. Together, avibactam enhances the activity of ceftazidime, decreasing resistance and increasing the minimum inhibitory concentration. It was FDA approved for the treatment of complicated intraabdominal infections (cIAI) and complicated urinary tract infections (cUTI).



Mechanism of Action

Ceftazidime binds to penicillin-binding protein 3, inhibiting cell wall synthesis. Therefore, it is considered to be a bactericidal antimicrobial. Avibactam protects ceftazidime from degradation by inactivating beta lactamases allowing the ceftazidime concentration to increase over the minimum inhibitory concentration of microorganisms.

Pharmacokinetics

Ceftazidime is renally excreted unchanged with a half-life ranging from 2 to 3 hours. Avibactam is metabolized by OAT transporters and primarily excreted unchanged via the renal route. Its half-life ranges from 2.22 to 2.71 hours.

Dosing and Administration

Dose = 2.5 grams IV every 8 hours; renal adjustment required for CrCl < 50 mL/min
Infusion time = 2 hours

Adverse Effects

Most common adverse effects are abdominal pain, anxiety, constipation, dizziness, nausea, vomiting, and increased liver enzymes

Efficacy and Safety

The approval process for this new drug relied on ceftazidime's historical data as well as data from Phase I and II trials only. There is limited safety data available; hence the FDA label carries a statement to reserve ceftazidime/avibactam for patients with little or no other treatment options. The combination product has broad Gram-negative activity including *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In a phase II trial, ceftazidime/avibactam PLUS metronidazole was compared with meropenem in 203 patients with cIAI. The primary endpoint was clinical cure in two weeks after the last drug dose. Cure rates were similar between the two: 91.2% for ceftazidime/avibactam plus metronidazole and 93.4% for meropenem. In the second phase II trial, ceftazidime/avibactam was compared with imipenem/cilastatin in 135 patients with cUTI. The primary endpoint was clinical cure at five to nine days after the last drug dose. Cure rates between the two groups were similar: 70.4% for ceftazidime/avibactam and 71.4% for imipenem/cilastatin. Additional phase III trials have been completed in adults with cUTI and cIAI as well as nosocomial and ventilator pneumonia

Future Use

The new combination agent will play a role in the empiric treatment of complicated urinary tract infection as monotherapy and complicated intraabdominal infections in combination with metronidazole (for anaerobe coverage) caused or suspected to be caused by antimicrobial-resistant pathogens. Potential future uses also include hospital-acquired pneumonia and treatment of skin and soft tissue infections caused by antimicrobial-resistant Gram-negative pathogens.

By: Payal Kakadiya, PharmD Candidate

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