P&T Update

Formulary Deletions
1. Codeine injectable solution - deletion – Approved
   Manufacturer discontinued
2. Hemorrhoidal (Anusol®) suppository - deletion – Approved
   Anusol-HC® rectal cream & suppository and preparation H rectal ointment & suppository are available
3. Hydroxypropyl methylcellulose (Tearsol®) - deletion – Approved
   Available formulary alternative: polyvinyl tears (Tears®)
4. Pantoprazole 40mg oral packet - deletion – Approved
   Available formulary alternative: lansoprazole solu-tab
5. Cledivipine 2.5mg/50mL - deletion – Approved
   Proposed deletion due to lack of usage and availability of formulary alternatives (nicardipine)
6. Argatroban 100mg/100mL - deletion – Approved
   Current formulary argatroban product is 50mg/50mL premixed.
7. Benzocaine (Auralgan®) otic drops - deletion – Approved
   Manufacturer discontinued
8. Tromethamine (THAM) solution for injection - deletion – Approved
   Manufacturer discontinued

Policies & Procedures/Floor Stock Update
707-600-103 Automatic Stop Order Policy
Proposed changes to the automatic stop order policy include addition of 72 hour stop time for oral phosphate supplements, extension of enoxaparin and subcutaneous heparin to 30 day stop time, and reduction of albumin automatic stop time to 24 hours – Policy approved

Miscellaneous
Updated UH Antiretroviral dosing guidelines were presented to include newer approved products and revised preferred regimens reflective of recent national guidelines. – Guidelines approved
Introduction

Growing antimicrobial resistance and limited availability has created a need for the reevaluation of treatment protocols. In 1996, an article exploring the connection between antibiotic restriction and resistance first coined the term “Antimicrobial Stewardship”, suggesting it as a solution to growing antimicrobial resistance rates.¹ A year later, the Infectious Diseases Society of America, or IDSA, formally defined Antimicrobial Stewardship, declaring it the prominent way to prevent antimicrobial resistance in hospitals.² The IDSA would later revise these guidelines in 2007, giving proper protocol for Antimicrobial Stewardship and how to establish an institutional program.

Antimicrobial Stewardship Program

Antimicrobial Stewardship, or AMS, is a program dedicated to the appropriate use of antimicrobial agents in order to reduce resistance, improve patient outcomes, reduce excessive costs, and halt the spread of infections and epidemics. This program, headed by an appointed certified pharmacist or physician, focuses on both patient-specific treatment and hospital-wide protocols to optimize medication use. The leader is responsible for forming a multidisciplinary team composed of at least one practitioner, pharmacist, infectious disease physician, and infection preventionist.

Generally, an AMS program will review the practices and analyze the outcomes of its particular institution on a clinical and economic basis. This knowledge is combined with up-to-date national guidelines to form a plan specific to its institution. It is the responsibility of the multidisciplinary team to disseminate this information to staff members at the institution as well as the patients and their families to ensure appropriate antimicrobial medication usage.³ According to Joint Commission standards, antimicrobial stewardship program standards can be set internally by hospital policy, the P&T Committee, and the Infection Control Committee. Changes to these standards may be done without the need of federal consent from the Joint Commission or the IDSA.⁴

Why Should My Institution Start a Program

There are many economic and clinical benefits for founding an AMS program. Just as a financial aspect, AMS programs have shown a 22-36% decrease in antimicrobial usage, translating into an annual savings of $150,000-$900,000, depending on the size of the institution. An additional $500,000 can be saved annually through the use of more appropriate agents through dose optimization, targeted therapy, and redundant therapy elimination.⁵ Clinically, AMS programs can improve patient outcomes and shorten hospital stays. According to several studies, institutions that have initiated an AMS program have shown a statistical decrease in meticillin-resistant Staphylococcus aureus, imipenem-resistant Pseudomonas aeruginosa, and extensive-spectrum beta-lactamase Klebsiella spp. without any associated adverse outcomes or mortality rate changes.⁶

The most pressing motivation for starting an AMS program is a newly proposed regulation change by the Centers for Medicare & Medicaid Services, or CMS. On June 13, 2016, the CMS proposed a new requirement for hospital participation in Medicare and Medicaid programs that would require hospitals to implement antibiotic stewardship programs in order to receive reimbursement.⁷ These requirements for these programs are as follows: Hospitals will need to demonstrate that they use antibiotics appropriately,

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The Role of Antimicrobial Stewardships in Modern Healthcare (Continued from page 2)

will need to put someone in charge of antibiotic oversight, and must show that they have fewer antibiotic-resistant infections under certain guidelines that have not yet been released. To meet these requirements, it is beneficial for institutions to establish a program as soon as it is feasible.

**IDSA Recommended Actions**

There are many actions that members of the AMS multidisciplinary team can take to increase institutional effectiveness. The IDSA has an established set of guidelines that note ways to improve antimicrobial usage through AMS programs. One of the most beneficial outcomes is from education. Simple reminders like proper hand hygiene and environmental cleaning and disinfection help, but active education intervention to employees and patients has shown to drastically increase compliance and in turn provide financial benefits.

Dose optimization is also crucial for organism and patient-specific treatment. Traditional examples such as time-dependent beta-lactams, drug concentration-dependent fluoroquinolone and aminoglycosides, and trough dependent vancomycin show that patient and organism-specific parameters are crucial to drug effectiveness and must be carefully monitored.

Having a systematic plan for proper formulation utilization is an easy way to reduce patient hospital stays and save on medications. Proper conversion from parenteral to oral therapy has shown to do just that; one pharmacist-led program focused on the proper parenteral to oral conversion showed a decreased length of hospital stay by 1.53 days, with cost savings for drug acquisition and reduced length of hospital stay of $15,149 and $161,072, respectively, over 12 months.

Lastly, formulary review and restrictions are a must; for example, both formulary restriction and preauthorization requirements for use of clindamycin during nosocomial epidemics of C. difficile infection have led to prompt cessation of the outbreaks (clindamycin is a well known C. difficile-causing agent). AMS programs should be able to combine national guidelines with local needs. Certain areas and hospitals have different community susceptibilities; the program should have a protocol in place and should be prepared with alternatives when local resistances are a problem.

**References:**
7. Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes To Promote Innovation, Flexibility, and Improvement in Patient Care, 81 Federal Register 39447,(16 June 2016) pp. 39447 -39480

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**Introduction**

QTc prolongation is an important topic for healthcare professionals to be familiar with, although treatment does not have well-defined recommendations. The QT wave is an interval on an electrocardiogram (ECG), which is a tool used by doctors to understand the activity of the heart. A corrected QT interval, the QTc, must be calculated to be useful in a clinical setting. This corrected value accounts for the fact that the interval shortens as heart rate increases. Presently there is no ideal formula that provides the perfect QTc for each and every patient.1

QTc prolongation occurs if there is not enough potassium leaving the cells or too much sodium coming in. Ventricular repolarization is extended, which is pictured on the ECG as a longer QT wave.2 Clinicians are concerned about prolonged QTc intervals because they indicate an increased chance of developing Torsade de Pointes, or TdP. TdP is the “twisting of points” in a patient’s ECG, in which the QRS complex twists around the isoelectric baseline.3 Although most episodes of TdP are transient and terminate on their own, they could lead to ventricular tachycardias. If this happens, a patient can very quickly go into cardiac arrest and even death.

**Causes of QTc Prolongation**

Patients that develop drug-induced TdP have at least one risk factor. About 71% of patients that exhibit a prolonged QTc have two or more risk factors.3 They are most likely female and over 65 years old. It is important to take note of abnormal electrolyte levels, such as hypokalemia, hypomagnesemia, and hypocalcemia. Comorbidities that increase patient risk include alcoholic liver disease, congestive heart failure, and left ventricular hypertrophy. QTc prolongation may also occur when patients have decreased renal function, recent cardiac events, or are currently on digoxin or diuretic therapy. Genetics also play a role in many of these cases, with congenital genes found in 10-15% of patients.1-5

There is a large list of drugs that have the potential side effect of increasing the QT interval. Anti-arrhythmics are the most common offending agents, such as dofetilide, sotalol, procainamide, quinidine, and amiodarone.4 Antipsychotics to look out for are haloperidol and thioridazine. Important antidepressants are amitriptyline, desipramine, sertraline, venlafaxine, and escitalopram. Fluoroquinolones, macrolides, and antimalarials should be noted as well.1-5 These are some of the most common offending agents, but the complete list is much longer. Most drugs that cause QTc prolongation have increased cardiac complications at higher doses. The exception to this generalization is the IA antiarrhythmic class, which can lead to a prolonged QTc interval at even sub-therapeutic doses.5

**Monitoring**

There is no clear guideline for when a drug may induce TdP, but it is generally accepted that a QTc interval greater than 450ms in males and 470ms in females is higher than the normal.1 Arrhythmias are most common when values exceed 500ms.3 However, there is no established low threshold in which a patient is sure to be free from any possible cardiac complications. Healthcare professionals need to be familiar with the risk factors for an increased QTc interval and the common precipitating drugs. Every patient is unique, so the clinician needs to pay close attention to each case to determine important monitoring parameters.

Pharmacists screen drugs to evaluate the necessity of dose adjustment for drug-drug interactions. Many of these QTc prolonging drugs are metabolized by the CYP3A4 enzyme, so there will be enhanced plasma concentrations if administered with other CYP metabolized drugs. Concentrations also accumulate in the body if renal or liver function is impaired, so dose adjustments will be needed depending on excretion mechanism.1-5

Patients with underlying risk factors should be monitored when receiving medications that commonly

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QTc Prolongation
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cause QTc prolongation. An ECG should be taken before and after drug administration. If a QTc interval is higher than 60ms from the baseline, physicians should investigate alternative therapy. When administering these drugs, doctors should use the lowest effective dose and discontinue the drug as soon as possible. The prescriber needs to make sure that these drugs have a proven salutary effect on the patient's survival or that the medication will lead to a significant improvement in morbidity relative to other treatment options.

Treatment
If a long QTc is observed, the administration of magnesium is probably not necessary. ECG monitoring should be continuous if possible, or taken more frequently. The doctor must examine the patient case and decide if the agent can be discontinued. If there are any problems with oxygen, calcium, potassium, or magnesium, then these levels should be corrected.

In the case that TdP precipitates, the offending drug should be discontinued right away. Then magnesium sulfate should be administered, regardless of the serum levels. If the patient is experiencing continuous TdP with severe hypotension or cardiac arrest, the doctor needs to initiate electrical cardioversion immediately. Asynchronous defibrillation should be used in patients that are hemodynamically unstable; therefore, in cases of low systolic blood pressure, high heart rate, unconscious, or chest pain.

In special cases or in patients that do not respond to magnesium, there are various other solutions. Isoproterenol and transvenous pacing are considered second line. There are other possible pharmacologic therapies, although they carry more complications and are not commonly recommended. These include atropine, phenytoin, and lidocaine. Patients that have previously experienced TdP should not be prescribed QTc prolonging drugs. Long term therapy is rarely required since TdP usually self-limits, but if sick sinus syndrome or atrial ventricular block combined with bradycardia is present, then permanent pacing may be considered.

Conclusion
QTc prolongation is recognized by the FDA as a serious problem. They have requirements for the pharmaceutical industry regarding drug development to ensure that a new molecule does not have potentially devastating cardiac effects. QTc prolongation is the number one reason that drugs are either restricted or discontinued from the U.S. market. Healthcare professionals need to stay vigilant when dealing with possible QTc prolongation, especially because there are no clear guidelines. Physicians must be familiar with risk factors and the common drugs that may induce a long QTc interval, so they can monitor properly and change therapy if necessary.

References

Contributed by: Catherine Vu, Rutgers University, Pharm. D. Candidate Class of 2018
Diabetes and Prediabetes

Every year in the United States, 1.4 million Americans are newly diagnosed with type II diabetes, joining the 21 million diagnosed and estimated 8.1 million additional undiagnosed diabetics. In 2015, diabetes killed 76,488 Americans, making it the 7th leading cause of death in the US, and killing more Americans than breast cancer and AIDS, combined. In addition, diabetes cost the US health system a total of $245 billion in 2012, and is associated with increased risk of cardiovascular disease, retinopathy, kidney disease, and non-traumatic lower limb amputations. Despite these known complications the prevalence of diabetes has increased by 382% from 1988 to 2014 and continues to move in a positive trend. Because diabetes remains a chronic disease a key step even before treatment is prevention.

Know your risk factors for type II diabetes

Being overweight, physically inactive, having a family history of diabetes, a medical history of gestational diabetes, and belonging to certain ethnic groups can all increase the risk of being diagnosed with type II diabetes. In addition, the Finnish Type 2 Diabetes Risk Assessment Form can estimate a person’s probability of developing type II diabetes in the following 10 years and whether a person should seek medical advice or undergo a clinical examination. Knowing the risk factors for diabetes and using assessments together can aid patients in decreasing their preventable risk factors and seeking medical attention before they are diagnosed with diabetes.

Prediabetes

In addition to the millions of Americans already diagnosed with type II diabetes, 86 million Americans are prediabetic. Prediabetes not only increases a person’s risk for developing type II diabetes, but also for heart disease and stroke. If lifestyle modifications, such as modest weight loss or increased physical activity, are not practiced, 15 to 30% of prediabetics will develop type II diabetes within 5 years. Although prediabetes can be treated, 90% of prediabetics are unaware of their status, and therefore unknowingly live at an increased risk for diabetes. Because of this, the American Diabetes Association recommends that people with certain risk factors such as being older than 45 years old, overweight, and of certain ethnicities talk to their doctors about testing for diabetes and prediabetes.

As shown by the Diabetes Prevention Program (DPP), modest weight loss and physical activity can prevent or delay the development of diabetes. Patient vigilance and awareness of risk factors can enable patients to make lifestyle modifications before and even during the prediabetic stage, preventing the multitude of medical conditions and costs associated with diabetes.

References:

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Implantable Probuphine® for Opioid Abuse

During the past few years, there has been a steady rise in opioid abuse, addiction, and dependence. Opioids, known for their pain relieving properties, have been around for many decades, but the steady rise in opioid prescriptions and their diversion for nonmedical purposes has resulted in many deaths. Almost 80 people fatally overdose on opioids each day in the United States, making drug overdose the leading cause of accidental death in the country. In 2014, approximately 47,055 lethal drug overdoses were reported and 18,893 of those deaths were related to opioids. Addiction is characterized as intense drug craving as well as compulsive use, while dependence is characterized as the need to keep using the opioids to avoid withdrawal symptoms. While many different factors produce addiction in an individual, such as stress, psychological conditioning, and a genetic predisposition in the brain pathways, they can produce a craving that can last many years after the patient has been treated and is no longer opioid dependent.¹

The complexity of opioid dependence and the limitations of existing treatments, such as low adherence, medication diversion, and recurring withdrawal symptoms, have made it difficult to treat.⁶,⁷ A new product, Probuphine®, by Titan Pharmaceuticals was created to combat these limitations. Probuphine® is an implant that provides an initial pulse release and then a low and steady level of buprenorphine over the course of 6 months.⁶ This constant level of buprenorphine combats the issues of sublingual administration, such as plasma peaks and troughs, which lead to increased cravings and the risk of relapse. Buprenorphine is a partial agonist, which is less likely to be abused compared to methadone, a full agonist. However, the current available formulations of buprenorphine (sublingual and tablets) pose many problems of drug diversion, nonmedical use, and poor treatment adherence resulting in withdrawal symptoms and eventually relapse.²,⁴

Although the implant seems promising in helping to combat opioid abuse and the problems associated with oral buprenorphine therapy, the approval of the implant has sparked several debates. Supporters argue that the implant helps to eliminate the biggest problem in eliminating withdrawal—patient adherence. David Pickar, a psychiatrist in Maryland and a member of the FDA advisory committee, says that depending on addicts to remember to take their medication daily is one of the biggest hindrances to overcome opioid abuse. In addition, the implant is a safer option for treating patients because it is “a drug that can’t be abused” so accidental ingestions and illegal resale are no longer an issue. However, critics have argued that the implant’s clinical trial data was not sufficient enough to prove that the implant was

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Fentanyl Patches: A Concealed Killer

Although approved by the FDA, many drugs can actually cause an incredible amounts of harm when they are not used properly. Fentanyl is an opioid analgesic, used to treat chronic and severe pain. It is usually used over a longer period of time, especially for those who are opioid-tolerant, or already taking an opioid. Fentanyl is about 100 times more potent than morphine. The Institute for Safe Medication Practices states that patients who are using these fentanyl patches must be extra cautious when dealing with them and discarding them. It was proven that even after the 72 hours of use per patch, there is still active drug left over in the patch. A study shows that about 28-84.4% of the patches original contents was remaining after 72 hours. Using PK values and an average volume distribution of 4L/kg, we can calculate the lethal dose of 3.7 mcg/kg of fentanyl. With almost 85% of the drug remaining, a potentially lethal dose can be received even after the drug has been used for 3

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It is clearly stated to remove the old patch before applying a new one, however the issue is more prevalent in how the medication is discarded. Manufacturing companies as well as FDA state to fold sticky sides together and flush down the toilet. This prevents anyone from retrieving the patch and perhaps potentially receiving a fatal dose. Do not discard in trash can because it can be retrieved and used again. These patches are incredibly small ranging in sizes from 5.35 cm² to 42.8 cm² (2-16 in²). They are also relatively transparent and hard to see on the skin.

There have been many cases of accidental exposure to fentanyl, some tragic. One case, a reversal agent, Naloxone was administered twice, and the baby lived. Not every case is caught early enough, or has the same outcome. A 2-year-old boy swallowed a patch while visiting a family member in the nursing home where they were not being disposed of properly, and died. Another child sat on a patch without realizing. This patch had fallen off a family member. One child removed a patch from his sleeping grandmother and applied it to his own skin. According to Janssen, a patch was transferred from an adult to a child while hugging. A 4-year-old boy was found next to a garbage can with old patches and wrappers on the floor. These are just a few of the many reported cases of accidental fentanyl use.

The most important thing when dealing with the use and disposal of these patches is to properly educate the patients who are using them. Store the medication in a cabinet away from children’s access. Avoid applying the patches in front of children and do not let children call the patches tattoos, band aids, or stickers. Dispose of the patches safely, and not when children are watching. Properly fold the two sticky sides together, and flush the old patch down the toilet. Make sure to keep track of the patches on your body throughout the day.

In the case of accidental exposure make sure to quickly remove the patch and seek medical attention. Signs and symptoms of fentanyl overexposure include slow and shallow breathing, dizziness, confusion, chest pain, rapid heartbeat, sweating, headache, fever, vomiting, and constipation. It is important to remember that with proper handling of the medication, we can prevent negative outcomes.

References:

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