



# From the Front Lines

Alixarx Clinical Pharmacists Address Everyday Challenges in Long-Term Care

## The Race to Develop a Zika Vaccine

Since the World Health Organization declared Zika virus a global public health emergency in February 2016, the race has been on to develop a safe and effective vaccine to prevent Zika virus infection. The development of an effective Zika virus vaccine for humans has recently moved one step closer to reality.

Scientists have demonstrated that 2 different formulations of Zika virus vaccine were effective in preventing Zika infection in several different strains of mice. One form of the vaccine contained purified and inactivated Zika virus, similar to conventional vaccines currently used in humans. The other form of vaccine contained DNA from the outer coating and membrane of the Zika virus.

Mice were immunized with either the DNA or inactivated Zika vaccine. Four Mice were immunized with either the DNA or inactivated Zika vaccine. Four weeks after immunization, vaccinated mice were exposed to the Zika strain that is currently active in Brazil. Immunized mice were protected from infection up to 8 weeks after immunization.

Although these results are encouraging, scientists caution that development of a vaccine that would be effective in humans may prove more difficult. Other related studies have shown that previous infection with Dengue fever could make Zika infection worse. If the reverse is true, it is feared that Zika vaccination could unintentionally make Dengue infection worse and even more life-threatening. Additionally, DNA-derived vaccines have not previously been shown to be effective in humans. Historically, trials of DNA derived vaccines for HIV and influenza were not successful in producing adequate immune response in humans, despite promising evidence in animal models.

The Pennsylvania-based pharmaceutical company, Inovio, has received approval from the FDA to start Phase One trials of a DNA- derived Zika vaccine in humans. These trials will focus on safety, effective dosage and the body's immune response to the DNA vaccine. Trials are expected to begin in the coming weeks.

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References: 1. Beth Israel Deaconess Medical Center. (2016, June 28). Vaccine protection against Zika virus achieved. ScienceDaily. Retrieved July 13, 2016 from [www.sciencedaily.com/releases/2016/06/160628114836.htm](http://www.sciencedaily.com/releases/2016/06/160628114836.htm) 2. Larocca, R. A. et al. Vaccine protection against Zika virus from Brazil. Nature <http://dx.doi.org/10.1038/nature18952> (2016). 3. Glenza, Jessica (2016, June 20) Human testing of experimental Zika Vaccine to begin. The Guardian. Retrieved July 13, 2015 from <https://www.theguardian.com/world/2016/jun/20/human-testing-experimental-zika-vaccine-virus>

## New Oral Anticoagulants – Pradaxa® (dabigatran)

In the prior two editions of this newsletter we discussed Xarelto® and Eliquis®, including indications, dosing guidelines, and administration pearls. This month, we will discuss Pradaxa®(dabigatran), which has a slightly different mechanism of action. Pradaxa® is a direct thrombin inhibitor which disrupts the coagulation cascade preventing the development of clots in the blood. Remember Xarelto and Eliquis are Factor Xa inhibitors. Pradaxa® is dosed twice daily, has more complex dosing recommendations than other agents, and also needs to be adjusted for renal function. Pradaxa has all of the advantages of the other new oral anticoagulants compared to that of warfarin and also has a FDA approved reversal agent idarucizumab (reversal agents may be available soon for the other medications in this class).

### **Pradaxa® (dabigatran) Approved Indications and Dosages:**

**Non-valvular A.Fib. – Stroke and embolism prevention:** 150mg PO twice daily.

**DVT or PE Treatment** (in patients treated with parental anticoagulant for 5-10 days): 150 mg PO twice daily.

**DVT or PE Prevention:** 150mg PO BID.

**DVT prevention post hip replacement surgery:** 110mg PO on the first day 1-4 hours after surgery, then 220mg PO daily for 28-35 days.

**DVT prevention post knee replacement surgery:** 150 or 220mg PO once daily with a half dose 1-4 hours after surgery. Guidelines suggest continuing for 10-35 days.

### **Administration:**

May be taken without regard to food. Capsules should not be opened or crushed. Capsules need to be stored in the manufacturer's container and used within four months of opening. Do not repackage or store capsules in any other container due to potential product break down.

### **Dose adjustment for elderly:**

The Beers Criteria lists Pradaxa® as a potentially inappropriate medication in patients 75 years of age and older. Caution is recommended given the lack of evidence for efficacy and safety in patients with a creatinine clearance (CrCl) less than 30 mL/min and a greater risk of bleeding than with other oral anticoagulants including warfarin. According to the manufacturer, the risk-benefit profile is favorable among all age groups.

Dosage adjustments for patients with A.Fib.:

CrCl 15 to 30 mL/min: 75 mg PO twice daily.

CrCl less than 15 mL/min: Dosing recommendations not provided

*With concomitant use of P-glycoprotein (P-gp) inhibitors\*:*

CrCl 30 to 50 mL/min: Dose reduction to 75 mg PO twice daily should be considered when coadministered with the P-gp inhibitors dronedarone or ketoconazole.

CrCl less than 30 mL/min: Avoid coadministration.

Dosage adjustments for patients post hip or knee replacement:

CrCl more than 30 mL/min: No dosage adjustment needed.

CrCl 30 mL/min or less: Dosing recommendations not provided

*With concomitant use of P-glycoprotein (P-gp) inhibitors\*:*

CrCl less than 50 mL/min: Avoid coadministration.

\*Common P-gp inhibitors include ketoconazole, itraconazole, dronedarone, verapamil, quinidine, amiodarone, clarithromycin, and erythromycin. Your AlixaRx Pharmacists screen for drug interactions prior to dispensing all medications.

Challenge yourself to know the names and dosages of these new oral anticoagulants. Ensure an accurate indication (diagnosis) is entered into your electronic health record. Utilize drug information resources to double check that the dose and duration are appropriate. Ask your AlixaRx Clinical Pharmacist for additional guidance on the use of these agents.

Don't miss a review of Savaysa® (edoxaban) in the next addition of From the Front Lines.

References: Clinical Pharmacology accessed 6/28/16. Available at: <http://www.clinicalpharmacology.com/>

## Use of Psychopharmacological Medications for Behavior Control

As we reported last month, CMS has issued six new quality measures including:

- Percentage of long-stay residents who received an antianxiety or hypnotic medication (MDS-based)

Psychopharmacological medications are defined as “any medication used for managing behavior, stabilizing mood, or treating psychiatric disorders”. These medications may include antipsychotics (i.e., Risperdal), antidepressants (i.e., Lexapro), anxiolytics (i.e., Ativan), sedative-hypnotics (i.e., Restoril), anticonvulsants (i.e., Depakote), antimanic (i.e., lithium), and cognitive enhancers (i.e., Aricept).

These medications are typically indicated to treat a medical condition (i.e., seizures) or a psychiatric condition (i.e., bipolar disorder, depression). Indication for use must be documented in the medical record and monitoring must be in place for both efficacy and side effects. If any of these medications are used to control behavior, other causes for the behavior must be considered and non-drug interventions must be documented to not have been effective.

Psychiatric disorders or distressed behavior – As with all symptoms, it is important to seek the underlying cause of distressed behavior, either before or while treating the symptom. Examples of potential causes include:

- Delirium (medications, infection, electrolyte imbalance, metabolic disorders)
- Pain
- Chronic psychiatric illness such as schizophrenia or schizoaffective disorder;
- Acute psychotic illness such as brief reactive psychosis;
- Substance intoxication or withdrawal;
- Environmental stressors (e.g., excessive heat, noise, overcrowding);
- Psychological stressors (e.g., disruption of the resident's customary daily routine, grief over nursing home admission or health status, abuse, taunting, intimidation);
- Neurological illnesses such as Huntington's disease or Tourette's syndrome; or
- Medical illnesses such as Alzheimer's disease, Lewy body disease, vascular dementia, or frontotemporal dementia.

When a resident is experiencing an acute medical problem or psychiatric emergency (e.g., the resident's behavior poses an immediate risk to the resident or others), medications may be required. In these situations, it is important to identify and address the underlying causes of the problem or symptoms. Once the acute phase has stabilized, the staff and prescriber consider whether medications are still relevant. Subsequently, the

medication is reduced or discontinued as soon as possible or the clinical rationale for continuing the medication is documented.

When psychopharmacological medications are used as an emergency measure, adjunctive approaches, such as behavioral interventions and techniques should be considered and implemented as appropriate. Longer term management options should be discussed with the resident and/or representative(s).

References: Revised Surveyor Guidance for Unnecessary Medications (F329) 9-15-06

## FDA Warns of Serious Cardiac Events with High Doses of Loperamide

Taking higher than recommended doses of Loperamide (Imodium) can cause serious heart problems that can lead to death. The risk of serious cardiac events is increased when loperamide is taken with medications that interact with loperamide.

Loperamide (Imodium) is commonly used to treat diarrhea. The maximum recommended dosage for loperamide is 8mg/day for OTC use, 16mg/day for prescription use.

Exceeding the maximum recommended dosage can result in QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope or cardiac arrest.

The majority of problems have occurred in patients intentionally misusing or abusing loperamide. Loperamide is a mu-opioid agonist, chemically related to opioid pain medications. Taking higher doses of loperamide can cause a feeling of euphoria. Patients going through opioid withdrawal will frequently use high doses of loperamide to lessen withdrawal symptoms.

Cardiac events have also been observed in patients taking recommended dosages along with medications that interact with loperamide, increasing levels of loperamide in the bloodstream. Examples of interacting medications include: clarithromycin, erythromycin, gemfibrozil, itraconazole, ketoconazole, quinidine, quinine, ranitidine and ritonavir. Other CYP3A4 inhibitors, CYP 2C8 inhibitors and P-glycoprotein inhibitors can also have this effect.

The FDA recommends using caution when prescribing loperamide in patients who are predisposed to QT interval prolongation, Torsades de Pointes and other serious arrhythmias or who are on medications that interact with loperamide (CYP3A4, CYP 2C8 or P-Glycoprotein inhibitors). Adverse cardiac events should be reported to the FDA via the MedWatch Safety Information and Adverse Event Reporting Program at [www.fda.gov/Medwatch/report](http://www.fda.gov/Medwatch/report).

References: 1. US Food and Drug Administration (2016, June 7). FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse. Retrieved July 13, 2016 from <http://www.fda.gov/Drugs/DrugSafety/ucm504617.htm> 2. Llamas, Michelle (2016, June 15). Overdose of Imodium Linked to Heart Problems. Drug Watch. Retrieved July 13, 2016 from <https://www.drugwatch.com/2016/06/15/imodium-overdose-and-heart-problems/>.

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