

Drug Information News

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Drug Information Center Events

The Texas Southern University College of Pharmacy and Health Sciences Drug Information Center has plans underway for another productive and exciting year! We are looking forward to maintaining our professional relationships as well as establishing new relationships with various health care organizations within our community. In addition, we anticipate great success with our involvement with the first through fourth year professional pharmacy students as we move to expand our resource collection. Our Drug Information Center has several services to offer and is always willing to explore the option of undertaking new projects. We will be hosting our 2nd Annual Open House, as well as preparing and disseminating information for upcoming ACPE approved Continuing Education Programs. We appreciated your interest in our quarterly newsletter, and are always open to suggestions! Feel free to email us @ tsudic@tsu.edu with any topic of interest that you would like to see in future editions.

H1N1 Influenza: An Update

By: Portia N. Davis, Pharm.D., Drug Information Resident

The H1N1 Influenza virus has been at the forefront of media coverage in recent months due to its rapid emergence and rampant spread in various countries. This particular influenza strain mimics symptoms of seasonal flu with nausea, vomiting, and diarrhea reported in some cases. The first confirmed human case of H1N1 flu in the United States was confirmed on April 15, 2009, and by June 19, 2009, all 50 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands all reported confirmed H1N1 infections. The World Health Organization (WHO) officially declared H1N1 a global pandemic on June 11, 2009 due to the fact that over 70 countries had reports of confirmed cases at that time and there were community level outbreaks occurring simultaneously worldwide. The Center for Disease Control and Prevention (CDC) is predicting that the upcoming 2009-2010 influenza season will be marked with sharp increases in the number of cases, hospitalizations, and deaths due to the spread of the H1N1 virus. A novel H1N1 vaccine is currently in production and after receiving fast track approval by the U.S. Food and Drug Administration (FDA). This vaccine is designed to be administered along with the seasonal flu vaccine and it is expected that the United States will receive approximately 120 million doses. The Advisory Committee on Immunization Practices (ACIP) has designated the following groups of people with priority status to receive the vaccine due to their higher risk of severe illness: Pregnant women, household contacts/caregivers for infants 6 months of age or younger, healthcare and emergency medical services (EMS) personnel, all persons aged 6 months through 24 years of age, and those with certain chronic medical conditions. Trends in the number of flu cases to date have shown that persons 65 years and older are at a lower risk of contracting the H1N1 strain, however, current recommendations to vaccinate this population against seasonal flu are still highly encouraged. Antiviral treatment options for H1N1 infection include oseltamivir and zanamivir, and are most effective when therapy is initiated no within 48 hours of onset of symptoms. Although a number of confirmed H1N1 infection have resulted in moderate to severe illness, it is important to note that most cases of H1N1 influenza have produced mild to moderate illness and have resolved without medical treatment. Proactive measures are critical in order to prevent the spread of H1N1 flu. Proper hand hygiene (washing with soap and warm water or using alcohol based hand cleaners), covering coughs and sneezes, avoiding close contact with sick people, and staying home for 24 hours after cessation of fever if stricken with the flu, although seemingly simple, are fundamental in preventing the spread of the flu. These measures are especially important for what the CDC, FDA, and WHO are predicting to be an incredibly active influenza season in the United States.

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1. Center for Disease Control and Prevention Website. Swine Flu: General Information. Available at: http://www.cdc.gov/h1n1flu/general_info.htm

New Drug Approval: Multaq[®] (dronedarone)

By: Daniel Begnaud, Doctor of Pharmacy Candidate

Dronedarone (Multaq[®]) is a new antiarrhythmic agent indicated for adult patients with atrial fibrillation (AF) or atrial flutter. It is chemically similar to amiodarone, with the major difference in structure being the removal of the iodine groups and addition of a methyl-sulfonamide group. Removal of iodine groups minimizes the risk of iodine-caused toxicities, while addition of the methyl sulfonamide group is believed to lower lipophilicity, thereby reducing the likelihood of experiencing neurotoxic effects. Dronedarone, similar to amiodarone, possesses class I-IV properties which has potential for treatment in various patients with AF. Dronedarone exhibits its antiarrhythmic effects through inhibiting multiple ion channels (Na⁺, K⁺, Ca²⁺ and L-type calcium channels), possesses anti-adrenergic effects through inhibiting α and β receptors, and does not increase action potential duration. Normal dosing for dronedarone is 400 mg by mouth twice a day. Trials measuring various dosing schedules reported no clinical benefits of doses greater than 800 mg/day. Adverse events were reportedly increased at the daily dosage increased above 800 mg/day. Hohnloser, et al compared 800 mg/day of dronedarone to placebo in 4628 patients with AF or flutter to determine its efficacy and safety in reducing the time to hospitalizations or death due to cardiovascular events. Patients were treated for 12 months and had a 12 month follow up period. Hospitalizations or death occurred in 54.5% of the dronedarone group and 71.7% of the placebo group (p<0.001). A separate study aimed to determine appropriate doses of dronedarone for preventing recurrent AF after cardioversion. Patients received either 800, 1200 or 1600 mg/day of dronedarone or a placebo for six months. Patients receiving 800 mg/day had a significantly increased time to AF relapse (median 60 days) versus placebo (median 5.3 days; p=0.001). There were no significant increases in the other two treatment groups. The most common adverse events reported with dronedarone use were gastrointestinal effects; pulmonary toxicity has been reported in animal models, but not in humans. There appears to be no effect on thyroid function through triiodothyronine, thyroxine, or thyroid-stimulating hormone levels, however, documented thyroid dysfunction was seen in rats believed to be through stimulation of thyroid α -1 receptors. Dronedarone may increase the risk of torsades de pointes by causing QTc interval prolongation. Currently, head to head studies comparing amiodarone to dronedarone are being conducted to more completely assess dronedarone therapy in AF. Although the long-term adverse effects of dronedarone have yet to be determined, this new agent shows promise as a treatment option for patients intolerant to amiodarone.

1. Wegener FT, Ehrlich JR, Hohnloser SH, et al. Dronedarone: An emerging agent with rhythm and rate controlling effects. *J Cardiovasc Electrophysiol*. 2006;17(Suppl 2):S17-20.
2. Dale KM, White MC. Dronedarone: An amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother*. 2007;41(4):599-605.
3. Hohnloser SH, Crijns HJGM, Van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668-78.
4. Touboul, P, Brugada J, Capucci A, et al. Dronedarone for prevention of atrial fibrillation: a dose ranging study. *Eur Heart J*. 2003;24(16):1481-7.

Olaparib Use in the Treatment of Breast and Ovarian Cancer

By: Ketal Patel., Doctor of Pharmacy Candidate

Olaparib is a novel, orally active poly ADP-ribose polymerase (PARP) inhibitor with activity in BRCA1 and BRCA2-deficient cells being developed by AstraZeneca. The drug is currently in Phase II clinical trials for treatment of aggressive breast and ovarian cancer. A phase I clinical trial evaluated the use of olaparib in 60 cancer patients. Of the patients enrolled, 22 had BRCA1 or BRCA2 mutations. The initial dose started at 10 mg daily and was gradually increased to a final dose of 600 mg twice daily. Greater than 90% inhibition of PARP was observed in patients treated with 60 mg or more twice daily. Of the BRCA carriers, 19 qualified for evaluation. In phase I trials peak plasma concentrations reached in 1 to 3 hours with a terminal half-life of 5 to 7 hours, volume of distribution of 40.3 liters and a clearance rate of 4.6 l/h. Clinical benefit from treatment was seen in 12 of the 19 (63%). Of the BRCA carriers 9 showed response including 1 patient with sustained response for 76 weeks. In advanced ovarian cancer 8 showed a partial response. In patients with BRCA2 breast cancer, one showed plasma complete remission while another was disease stable for 7 months. In addition, a patient with BRCA2 resistant prostate cancer showed a greater than 50% reduction in PSA level. An additional study was conducted to determine olaparib response rate, while evaluating safety and tolerability at doses of 400 mg bid followed by 100 mg bid in 28 day cycles. The results of this study confirmed safety and efficacy results of phase I trials. Adverse events that have been reported include mild gastrointestinal symptoms such as nausea and vomiting as well as fatigue, anemia, mood alteration, thrombocytopenia and somnolence. So far clinical trials have reported no known significant drug interactions and further studies are warranted. More studies are warranted on dosing, drug interactions, side-effect profiles, and pharmacokinetics and therapeutic effects in the body. AstraZeneca has initiated other clinical trials for the use of olaparib in combination with other medications such as Avastin[®], doxorubicin, paclitaxel and gemcitabine just to name a few chemotherapeutic agents, as well as its potential use in solid, advanced and ovarian cancers. While the verdict is still pending, the results of these additional clinical trials show promise of olaparib as a novel agent with a new site of action in the treatment of aggressive breast and possibly other cancers as well.

1. Website: AstraZeneca.
<http://www.astrazenecaclinicaltrials.com/clinicaltrials/products/indevelopment/?itemId=4216233> Accessed on July 16, 2009.
2. Fong P et al. Inhibition of Poly (ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. *NEJM* 2009;261:123-134.
3. Tutt, A; Robson, M; Garber, J et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer [Abstract]. *J Clin Oncol* 2009;27(18S).

Metformin May Decrease Risk of Pancreatic Cancer

By: Te Jung Lin, Doctor of Pharmacy Candidate

Pancreatic cancer is the fourth leading cause of cancer death in the United States with a three-year survival rate of 3-5%. Diabetes has been associated as a risk factor for various cancers, including pancreatic cancer. Dr. Donghui Li of University of Texas M.D. Anderson Cancer Center noted, "It's a very complicated association because pancreatic cancer can cause diabetes, while on the other hand diabetics have a higher risk for pancreatic cancer. So it's been quite controversial, and the question is: What can we do to reduce this risk?" Two recent studies have shown that antidiabetic therapy with metformin can either lower the risk of or inhibit pancreatic cancer growth. These findings are quite significant because of the extremely low survival rates in pancreatic cancer patients and the increasing number of diabetic patients. In a case-controlled study at M.D. Anderson Cancer Center, researchers analyzed data from the past four years that followed 973 pancreatic cancer patients of which 259 were diabetics, and 863 control patients of which 109 were diabetics. Interviews were conducted to obtain pertinent risk factors and antidiabetic medication usage history. An unconditional regression analysis was performed to compare cases versus controls and it was found that diabetic patients who took metformin had a 60% lower risk of pancreatic cancer compared with those who did not take metformin (odds ratio, 0.38; 95% confidence interval, 0.22– 0.69; p=0.001). In contrast, diabetic patients who had taken insulin or insulin secretagogues, such as sulfonylureas, had a significantly higher risk of pancreatic cancer than those who did not take those medications. The authors suggest that a larger trial is needed to confirm their findings. In a separate study, researchers at UCLA identified a novel crosstalk between insulin and G protein-coupled receptor (GPCR) signaling pathways in human pancreatic cancer cells and investigated whether metformin would disrupt it. Insulin is known to enhance GPCR signaling through a rapamycin-sensitive mTOR-dependent pathway, however, metformin activates AMP kinase (AMPK), which negatively regulates mTOR. Treatment of cancer cells with 10 ng/mL of insulin for 5 minutes markedly enhanced the increase in intracellular Ca²⁺ induced by GPCR agonists. Metformin pretreatment of the same cell types completely abolished insulin-induced potentiation of Ca²⁺ signaling, but did not interfere with the effect of GPCR agonists alone. The authors concluded that these results raise the possibility that metformin could be a potential candidate in novel treatment strategies for human pancreatic cancer. The findings of these studies are interesting, but larger trials are warranted to further study the effects of metformin on pancreatic cancer risks.

1. Metformin May Lower Diabetics' Odds for Pancreatic Cancer. Drugs.com Mednews Web site. August 2, 2009. Available at: http://www.drugs.com/news/metformin_may_lower_diabetics_odds_pancreatic_cancer-19130.html. Accessed August 19, 2009.
2. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009 Aug;137(2):482-8.
3. Kisfalvi K, Eibl G, Sinnott-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. *Cancer Res*. August 15, 2009;69(16):6539-45.

Renal and Retinal Effects of ACE and ARB Therapy in Type 1 Diabetics

By: Brenda Namara, Doctor of Pharmacy Candidate

According to 2007 statistics, 23.6 million people in the United States, about 7.8 percent of the population, have diabetes. Two of the major complications of diabetes are nephropathy and retinopathy. Studies have shown that the progression of these complications is decelerated by early administration of drugs that inhibit the renin-angiotensin system (RAS) by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). The *New England Journal of Medicine* published a five-year, multi-centered, placebo-controlled study conducted by Michael Mauer, MD and colleagues. The objective of the study was to compare the renal and retinal effects of an ARB (losartan), an ACEI (enalapril), and a placebo in patients recently diagnosed with type 1 diabetes. The study population was limited to patients that were normotensive and who had not yet developed renal and retinal complications. The primary endpoint of the study was to assess the effects of "early" RAS blockade by measuring retinopathy progression. Study subjects were randomized to receive 100 mg of losartan, 20 mg of enalapril, or placebo daily. Based on the study results, it was concluded that early inhibition of the RAS in type 1 diabetes did not slow down the progression of nephropathy, but did slow down that of retinopathy. Other studies that have assessed the effect of the RAS blockade with data from enrolled patients that had already progressed to diabetic nephropathy. The results of such studies have shown that in patients with diabetic neuropathy, administration of an ACEI or an ARB slows down the progression of renal function deterioration. This study raises some debate among topic experts indicating that there is still much more research to be done before the debate could be considered settled. Other studies have suggested that the combination of **both** an ACEI and an ARB achieves more complete inhibition of the RAS. This might be of a greater benefit since the proportion of diabetes patients who progress to end-stage renal disease (ESRD) is still quite high, despite the administration of either an ACEI or an ARB as monotherapy. More research is needed to establish whether inhibition of the RAS slows the progression of retinopathy, whether the effects continue beyond five years, and whether or not these effects can be seen in patients with advanced retinopathy. Hopefully this study is the beginning of many to come that will shine more light to the methods of prevention of the different complications of diabetes.

1. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009; 2;361(1):40-51.
2. Rossing K, Jacobsen P, Pietraszek L, et al. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomized double-blind crossover trial. *Diabetes Care*. 2003; 26(8):2268-74.
3. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of antiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993; 329:1456-62.
4. Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int*. 2000;57:601-06.

ADHD Stimulant Drugs Linked to Sudden Cardiac Death

By: B. Inez Sanderson, Doctor of Pharmacy Candidate

A recent study has shown a possible link between sudden cardiac death and stimulants used to treat Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD). The heightened alert is specifically focused on sudden cardiac death of patients taking stimulants with undiagnosed heart conditions. Sudden cardiac death from stimulants creates a great concern considering that stimulants, such as amphetamines and methylphenidate, are first line agents in ADD/ADHD therapy in adolescents. Although both amphetamines and methylphenidate have a known association of unrestricted stimulation of the heart, and an increase of blood pressure, methylphenidate is less likely to increase blood pressure due to its dopamine onset time. In 2006, the FDA documented 11 sudden cardiac deaths in children taking stimulants with methylphenidate and 13 sudden cardiac deaths in children taking stimulants with amphetamines. These statistics were measured against the three sudden cardiac deaths reported in children taking atomoxetine, a nonstimulant drug. With the increased prevalence of unjustified sudden deaths in patients on stimulants, in 2008, the American Heart Association (AHA) enforced recommendation of heart screening for undiagnosed heart conditions prior to stimulant use for treatment of ADD/ADHD. The heightened risks, in addition to AHA recommendations, are two reasons that support the joint US Food and Drug Administration (FDA) and National Institute of Health (NIH) funded research on dopamine stimulants such as the study by M.S. Gould, MD, Dr. Gould's research concluded that there may be an association of adolescent sudden cardiac death risk and stimulant use. This study compared stimulant medication use in 564 healthy children within the United States, and 564 children on stimulant medication who died of motor vehicle accidents. Out of 564 healthy children whom died suddenly, ten were reported to be taking a stimulant medication at the time of death. Of 564 healthy children who died in a motor vehicle accident, two were reported to be taking a stimulant medication. An FDA spokesperson cited that this single, very specific study, only proves a very loose correlation given the "limitations of the methodology used". The FDA confirmed its commitment to a continued review of these studies limitations as well as other studies. The FDA warns that this study should not be used as the basis for discontinuation of ADD/ADHD stimulant medications. Manufactures of these drugs will still be required to affix a label warning of possible sudden cardiac death risks.

1. Chavez B, Sopko MA, Ehret MJ, et al. An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/ hyperactivity disorder. *Ann Pharmacother.* 2009;43:1084-1095.
2. American Academy of Pediatrics. Clinical practice guideline: treatment of the school-aged child with attention deficit/ hyperactivity disorder. *Pediatrics.* 2001;108:1033-44.
3. Wilens TE, Hammerness PG, Biederman J, et al. Blood pressure changes associated with medication treatment of adults with attention deficit hyperactivity disorder. *J Clin Psychiatry.* 2005;66(2):253-259.
4. FDA/CEDR resources page. Food and Drug Administration Web site. <http://www.fda.gov/Safety/MedWatch/default.htm>. Accessed August 20, 2009.
5. Gould MS, Walsh T, Munfakh JL, et al. Sudden death and use of stimulant medications in youth. *American Journal of Psychiatry.* 2009;AIA:1-10.

The Fight for Propoxyphene Removal

By: Tuyen Pham, Doctor of Pharmacy Candidate

Since its approval in 1957, propoxyphene or Darvon[®], has been a widely used analgesic in the United States. More than 20 million prescriptions were written for propoxyphene-containing products in 2007 alone; with Darvocet[®] being the most popular. Darvocet[®] possesses a better analgesic profile than Darvon[®] and contains the generic equivalent combination of propoxyphene and acetaminophen. Propoxyphene became controversial when the nonprofit consumer advocacy organization, Public Citizen, petitioned for its removal in 1978 due to high number of accidental deaths related to the drug. The petition was denied the following year, but the issue reemerged when Public Citizen petitioned for the removal of propoxyphene once again in 2008. The issue took center stage when opponents of propoxyphene and Xanodyne Pharmaceuticals, Inc., manufacturer of Darvon[®] and Darvocet[®], presented their findings about the safety of propoxyphene during a joint committee meeting with the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee of the Food and Drug Administration (FDA) on January 30, 2009. The efforts of Public Citizen once again were deemed futile with the FDA deciding to keep propoxyphene on the market, despite a 14-12 vote to remove the drug by its advisory panel. To the victor goes the spoil. To add insult to injury, Xanodyne Pharmaceuticals, Inc. immediately posted the decision by the FDA, which was announced on July 7, 2009, on its website. The FDA also began to require the addition of black box warnings to the drugs that addressed the risk of overdose when using these products. The FDA has mandated that manufacturers of propoxyphene-containing products conduct studies regarding higher than recommended doses so that the results of these studies can be utilized to determine further regulatory actions. In the mean time, the FDA is working with Centers for Medicare and Medicaid Services and the Veterans Health Administration to study the use of propoxyphene among elderly patients.

1. Press Release. U.S. Food and Drug Administration. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm170769.htm>. Accessed August 24, 2009.
2. History and Overview of the Safety and Efficacy of Propoxyphene Products. U.S. Food and Drug Administration. Available at: <http://www.fda.gov>. Accessed August 24, 2009.
3. Propoxyphene Questions and Answers. U.S. Food and Drug Administration Website. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm170268.htm>. Accessed 8/24/09.
4. Press Releases. Xanodyne Pharmaceuticals, Inc. Available at: http://www.xanodyne.com/newsroom_details.asp?NewsId=5
6. Accessed 8/24/09.

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