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- ASHP Midyear Meeting: Las Vegas, NV; Dec 2-6, 2012 *Hope to see you there!*
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NYS ACCP – Fall Clinical Meeting 2012

By: James Schurr, Stephen Argiro, & Michael Cronin, PharmD Candidates c/o 2014

This October, we had the privilege of attending the New York State chapter of the American College of Clinical Pharmacy (ACCP) annual meeting held at the Albany College of Pharmacy and Health Sciences. The purpose of this event was to orient members of ACCP in New York State to the current developments of the organization and the outlook for the future of clinical pharmacy practice. The keynote speakers for the event were Commander Sherri Yoder of the Indian Health services and Dr. Curt Haas, president-elect of ACCP. This was the first time that separate, student-only content was integrated into the program. This included presentations by pharmacy residents on "hot topics" in clinical pharmacy, a primer on pediatric pharmacy practice by Dr. Brian Cowles, and a resident roundtable discussion.

We arrived at Albany College of Pharmacy on Monday, October 8 at 7 AM for registration and breakfast, which offered opportunities for some impromptu networking. Shortly thereafter, we took our seats in the auditorium for the opening session. After a brief welcoming by Dr. Amy Pai, Commander Yoder was introduced to deliver the keynote address. Commander Yoder was a consummate professional, whose current work is serving to restructure pharmaceutical practice (in order to facilitate our progress in the advancement of a rapidly changing health care system). Commander Yoder is a co-author of "Improving Patient Outcomes through Advanced Pharmacy Practice: A Report to the Surgeon General." In her presentation, she brought light to the fact that in New York State, the Collaborative Drug Therapy Management (CDTM) provision has a sunset clause that will expire if not renewed by legislators. This is a challenge to pharmacists who are actively participating in CDTM practice, as they must report their positive outcomes to make a case for continued validation for providing this service. Because most pharmacists who are currently practicing CDTM are doing so in an independent and disparate manner, Dr. Yoder challenged pharmacists in advanced practice to implement a standardized method for documenting clinically beneficial outcomes of CDTM. If we are to make CDTM permanent, we must effectively report evidence-based outcomes communicating the value of a pharmacist in a CDTM role.

After Dr. Yoder gave a very compelling speech for CDTM practice, Dr. Haas, president elect of ACCP, was introduced to give his speech on the positions of the national organization. Dr. Haas addressed the fact that ACCP is officially endors-

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ing the position that pharmacists suited for advanced practice have PharmD degrees, PGY-1 and PGY-2 experience, and board certification. While this may be a controversial position to clinicians who are currently in practice without such credentials, it is adopted with the intention of advancing clinical pharmacy as a profession. A key point of this statement is that more opportunities for clinical pharmacists to obtain residency training must be made available through the expansion of residency programs throughout the country, and an emphasis be placed on obtaining board certification through the Board of Pharmacy Specialties for the individual's career ambitions.

After the keynote speeches were made, student attendees were then ushered to another lecture hall for the student portion of the meeting. The first session of the student programming featured talks by three pharmacy practice residents who gave lectures on "hot topics" in clinical pharmacy. The topics covered included emergency management of patients abusing bath salts, the newly approved prophylactic use of Truvada® to prevent transmission of HIV, and an overview of the newly approved weight loss medications Qsymia® and Belviq®. After these presentations, Dr. Brian Cowles gave an informative primer on pediatric pharmacy practice. He focused on understanding pharmacokinetic principles of neonates and children, as they differ from adults. His talk provided insight for the sensitivity of dosing medications in younger patient populations. Our roundtable discussion was a great opportunity to sit down with current pharmacy practice residents and gain an understanding of their worlds.

Overall, our experiences were both rewarding and inspirational. We were able to connect with other pharmacy students and professionals currently working in the field. Additionally, we gained insight into the current "hot topics" in clinical pharmacy, as well as the official positions of ACCP (as the organization prepared for its annual national convention). We highly recommend that St. John's students interested in a career in clinical pharmacy attend future New York State ACCP meetings.

Fungal Meningitis Outbreak: A Sobering Tragedy

By: Mahdieh Danesh Yazdi, Associate Student Editor

For the past few weeks, we have heard about the terrible breakout of fungal meningitis from contaminated methylprednisolone acetate vials manufactured by the New England Compounding Center (NECC). Approximately 14,000 patients received medication from the contaminated lots. So far, over 400 cases have been reported and over 40 people have tragically lost their lives. Most cases were caused by the fungus *Exserohilum rostarum*, but there has also been one confirmed case of infection due to *Aspergillus fumigatus*.

Since the outbreak, the FDA has visited the compounding site, and Congress has begun to hold hearings on the case. The Centers for Disease Control and Prevention (CDC), state and local health officials, and the Massachusetts Board of Pharmacy are also tracking the case, in order to try to identify potentially infected patients and limit the damage caused by the outbreak.

There were serious problems with proper sterilization at the NECC site. The company voluntarily recalled all of its products on October 6, 2012. Ameridose, a company closely connected with the NECC, also voluntarily withdrew its products on October 31, 2012. The FDA has encouraged health care professionals who administered any product produced by the NECC after May 21, 2012 to reach their patients and follow up with them to rule out any infection.

The drug shortage office of the FDA announced that it did not anticipate any drug shortages to result from the shutdown of the NECC and Ameridose. However, the ramifications could be felt across the nation. Pharmacies have had to scramble to find replacements for the missing NECC and Ameridose products. From gathering information to finding alternate sources of drugs to trying to track down patients who have been potentially infected, this outbreak had a tremendous impact on day-to-day pharmacy operations.

However, no impact is more profound than that of the lesson it teaches us. Many of us take our compounding classes and the details of aseptic techniques for granted. We do not fully realize how something as simple as hand washing could literally mean life or death for a patient. Please remember this the next time you are in the lab and are compounding a preparation: someday this will go into a patient's body. That patient could be your parent, brother, sister, spouse; someone you care for. Treat your patients as if they were members of your family. My father once spent a night at the hospital where I currently work. Each time that I fill a patient's medications, I cannot help but ask myself, "would I have wanted my father to receive this medication?" I assure you, it is the most sobering thought a person could have.

Our hearts go out to those affected by this outbreak. For more information regarding the outbreak, please visit the CDC and FDA websites at http://www.cdc.gov/HAI/outbreaks/currentsituation/ & http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm

Quick Update on the Clinical Efficacies of GLP-1 Receptor Agonists and DPP-4 Inhibitors

By: Mohammad A. Rattu, PharmD [PGY-1 Resident at VA NYHHS]

Type 2 diabetes mellitus (DM) is a chronic medical condition warranting lifestyle changes and eventual initiation of medication.[1,2] The current algorithm from the American Diabetes Association (ADA) includes glucagon-like-peptide-1 (GLP-1) receptor agonists and dipeptidylpeptidase IV (DPP-4, a serine protease) inhibitors as potential, second-line options after incorporating lifestyle changes (e.g. healthy diet, weight loss, exercise) and metformin.[1,2] Although relatively new to the market, both classes of medications offer decreases in hemoglobin A1C levels, fasting plasma glucose, and even body weight (GLP-1 receptor agonists, specifically).[3] There are unique characteristics for each agent, but their underlying mechanisms are related to the effects of incretin.[3]

GLP-1 receptor agonists are incretin mimetics (*i.e.* exogenous sources), while DPP-4 inhibitors prevent the breakdown of incretins (*i.e.* endogenous sources).[4] After oral consumption of carbohydrates (e.g. glucose) or lipids (e.g. cholesterol), gastrointestinal hormones are released from the intestine.[4] These include GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which increase the amount of insulin produced by pancreatic beta cells.[4] Endogenous GLP-1 (and analogs) also inhibit glucagon release from the pancreas and gastric emptying, which minimizes postprandial glucose excursions.[4]

Currently, there are two unique GLP-1 receptor agonists available: exenatide (Byetta® [twice daily], Bydureon® [once weekly]) and liraglutide (Victoza®); and three unique DPP-4 inhibitors: linagliptin (Tradjenta®), saxagliptin (Onglyza®), and sitagliptin (Januvia®).[5-10] Other agents are not currently approved by the Food and Drug Administration (FDA), but have favorable Phase II and III trial results. These include GLP-1 receptor agonists like albiglutide, dulaglutide, and lixisenatide; and DPP-4 inhibitors like alogliptin, gemigliptin, and vildagliptin.[11-16]

A large meta-analysis of GLP-1 receptor agonists and DPP-4 inhibitors revealed key points of interest (efficacies).[3] Examining trials with durations of 12 to 52 weeks, it reported the following data:

Dose comparison between GLP-1 receptor agonists and DPP-4 inhibitors.[3]

Drug	Highest Maintenance Dose	All Doses
GLP-1 receptor agonists		
Exenatide BID	10 mcg SC BID	5, 10 mcg SC BID
Exenatide QW	2 mg SC QW	2 mg SC QW
Liraglutide	1.8 mg SC QD	0.6, 0.9, 1.2, 1.8 mg SC QD
DPP-4 inhibitors		
Alogliptin	25 mg QD	12.5, 25 mg QD
Linagliptin	5 mg QD	5 mg QD
Saxagliptin	5 mg QD	2.5, 5 mg QD
Sitagliptin	100 mg QD	25, 50, 100 mg QD
Vildagliptin	50 mg BID*	50 mg BID*, QD**

Note: BID = twice daily; QW = once weekly; QD = once daily; * = only with sulfonylurea; ** = only with metformin or thiazolidinedione

Mean A1C (%) differences (95% CI) between GLP-1 receptor agonists and DPP-4 inhibitors at highest maintenance doses after 12 to 52 weeks of treatment.[3]

Drug	Mean A1C (%) Differences (95% CI)
GLP-1 receptor agonists	
Exenatide BID	-1.10 (-1.22 to -0.99)
Exenatide QW	**-1.59 (-1.7 to -1.48)**
Liraglutide	-1.27 (-1.41 to -1.13)
DPP-4 inhibitors	
Alogliptin	-0.69 (-0.85 to -0.54)
Linagliptin	-0.6 (-0.75 to -0.46)
Saxagliptin	-0.68 (-0.78 to -0.57)
Sitagliptin	-0.67 (-0.75 to -0.6)
Vildagliptin	**-1.06 (-1.48 to -0.64)**

Note: BID = twice daily; QW = once weekly; mmol/L x 18 = mg/dL.

Mean fasting plasma glucose (FPG) differences (95% CI) between GLP-1 receptor agonists and DPP-4 inhibitors at highest maintenance doses after 12 to 52 weeks of treatment.[3]

Drug	Mean FPG (mmol/L) Differences (95% CI)	Mean FPG (mg/dL) Differences (95% CI)
GLP-1 receptor agonists		
Exenatide BID	-1.16 (-1.35 to -0.97)	-20.88 (-24.3 to -17.46)
Exenatide QW	**-2.12 (-2.28 to -1.96)**	**-38.16 (-41.04 to -35.28)**
Liraglutide	-1.82 (-2.07 to -1.57)	-32.76 (-37.26 to -28.26)
DPP-4 inhibitors		
Alogliptin	-0.97 (-1.27 to -0.67)	-17.46 (-22.86 to -12.06)
Linagliptin	-1.04 (-1.59 to -0.49)	-18.72 (-28.62 to -8.82)
Saxagliptin	-0.73 (-0.95 to -0.5)	-13.14 (-17.1 to -9)
Sitagliptin	-0.87 (-0.98 to -0.77)	-15.66 (-17.64 to -13.86)
Vildagliptin	**-1.57 (-2.23 to -0.9)**	**-28.26 (-40.14 to -16.2)**

Note: BID = twice daily; QW = once weekly; conversion: mmol/L x 18 = mg/dL.

Mean weight (kg) differences (95% CI) between GLP-1 receptor agonists and DPP-4 inhibitors at highest maintenance doses after 12 to 52 weeks of treatment.[3]

Drug	Mean Weight (kg) Differences (95% CI)	Mean Weight (lb) Differences (95% CI)
GLP-1 receptor agonists		
Exenatide BID	-2.03 (-2.46 to -1.6)	-4.47 (-5.41 to -3.52)
Exenatide QW	**-2.41 (-2.83 to -1.99)**	**-5.3 (-6.23 to -4.38)**
Liraglutide	-2.29 (-2.99 to -1.59)	-5.038 (-6.58 to -3.5)
DPP-4 inhibitors		
Alogliptin	-0.3 (-0.9 to 0.3); NS	-0.66 (-1.98 to 0.66); NS
Linagliptin	-0.64 (-1.11 to -0.16)	-1.41 (-2.44 to -0.35)
Saxagliptin	-0.29 (-0.61 to 0.03); NS	-0.64 (-1.34 to 0.07); NS
Sitagliptin	-0.16 (-0.92 to 0.6); NS	-0.35 (-2.02 to 1.32); NS
Vildagliptin	**-2.03 (-2.46 to -1.6)**	**-4.47 (-5.41 to -3.52)**

Note: BID = twice daily; QW = once weekly; conversion: kg x 2.2 = lb; NS = not (statistically) significant.

From the meta-analysis, among the GLP-1 receptor agonists, once-weekly exenatide demonstrated the greatest reductions in A1C (~1.6%), FPG (~38 mg/dL), and weight (~5 pounds) [followed by once-daily liraglutide and twice-daily exenatide] after 12 to 52 weeks of treatment.[3] Among the DPP-4 inhibitors, twice-daily vildagliptin (unavailable in the U.S.) also demonstrated the greatest reductions in these parameters.[3] The other DPP-4 inhibitors generally reduced the A1C by 0.6-0.7% and FPG by 13-18 mg/dL, but did not demonstrate statistically significant decreases in mean body weight (except for linagliptin, which did not seem to be clinically significant with a 1.4 pound weight loss).[3]

Among many favorable characteristics highlighted in other reviews, GLP-1 receptor agonists and DPP-4 inhibitors are attractive options because they are associated with decreases in hemoglobin A1C levels, fasting plasma glucose, and weight loss with GLP-1 receptor agonists.[3,4] GLP-1 receptor agonists veritably are more efficacious than DPP-4 inhibitors because they lead to supraphysiologic levels of incretin activity.[4] Before simply initiating this class of medications, prescribers must consider several factors such as the goal A1C reduction, route of administration, and significant gastrointestinal side effects.[4] There are still questionable concerns about pancreatitis with both, medullary thyroid cancer with GLP-1 receptor agonists, and infection with DPP-4 inhibitors; thus, we have yet to determine their long-term safety in humans.[4]

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NOVEMBER IS...

DIABETES AWARENESS MONTH

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OUR EMAIL: **RHOCHIS@GMAIL.COM**

New Drug Review: Tofacitinib (Xeljanz®)

By: Jessica Lee, PharmD Candidate c/o 2013

Rheumatoid arthritis (RA) is an autoimmune disease in which the immune system attacks healthy tissue, causing inflammation of the joints and potential harm to other organs. It affects 0.5-1% of the adult population and is more prevalent in the seventh decade of life. These patients tend to experience joint pain and stiffness; over time, the joints can become deformed and lose their range of motion. Current treatment options for RA consist of nonpharmacological therapy, including physical and occupational therapies, and pharmacological therapy, namely the disease-modifying antirheumatic drugs (DMARDs). DMARDs include nonbiologic agents (e.g. methotrexate) and biologic agents (e.g. adalimumab [Humira®]).[1]

The biologic agents target the proinflammatory cytokines, such as tumor necrosis factor (TNF) and interleukins (IL), which have roles in lymphocyte activation, proliferation, and function. These cytokines can cause inflammation and damage to the joints and surrounding tissue.[1] The current treatment guidelines from the American College of Rheumatology includes eight biologic agents, which are further categorized into anti-TNF agents [etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®)] and non-TNF biologic agents [abatacept (Orencia®), rituximab (Rituxan®), and tocilizumab (Actemra®)].[2]

On November 6, 2012, the FDA approved Pfizer's new agent, tofacitinib (Xeljanz®), for the treatment of moderately to severely active RA in patients who have failed methotrexate.[3] It is approved to be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.[4] It is the first, new oral DMARD to be approved in more than 10 years, which can be advantageous to patients who lack the dexterity to perform self-injections.[5] Unlike the previous biologic agents that act on extracellular targets, tofacitinib takes on a new approach by targeting the intracellular pathways of the inflammatory cytokines. Tofacitinib is a Janus kinase (JAK) inhibitor (specifically at JAK1 and JAK3), which modulates the immune response by interrupting signal-transduction activity for multiple cytokines, including interleukins 2, 4, 6, 7, 9, 15 and 21.[6] The FDA approved tofacitinib to be given twice daily as a 5 milligram dose; the safety of a 10 milligram twice daily dose is still under investigation.[3] Several clinical trials have shown reduction in symptoms and improved physical functioning in patients receiving tofacitinib.[7] One study found tofacitinib monotherapy to be significantly superior to methotrexate in reducing signs / symptoms and inhibiting structural damage.[5]

The most common side effects are upper respiratory infections, headache, diarrhea, and nasopharyngitis. Adverse effects of tofacitinib include serious infections (e.g. tuberculosis and herpes zoster), malignancies (e.g. lymphomas), gastric perforations, decreased neutrophil and lymphocyte counts, and elevated lipid levels. This side effect profile is similar to other anti-TNF agents.[4] Post-marketing surveillance will be conducted in order to study the long term effects of tofacitinib in heart disease, cancer, and serious infections.[3]

Overall, as a JAK inhibitor, tofacitinib has the potential to be helpful in treating other autoimmune diseases. There are clinical trials to assess its use in psoriasis, ulcerative colitis, and Crohn's disease.[8]

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IVACAFTOR (KALYDECO™): TARGETING THE CORE OF CYSTIC FIBROSIS

BY: EUGENE KOLOMIYETS, PHARMD CANDIDATE C/O 2013, AMSCOP AT LIU

Cystic fibrosis (CF) is an autosomal recessive disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7.[1] The disease has been linked to thousands of possible mutations, but only as many as 25-30 are tested for in newborns.[1,2] CFTR is responsible for chloride transport in epithelial cells throughout the body.[1] The defective gene causes increased salt production in sweat, as well as increased mucus production in the lungs and gastrointestinal tract.[1] These changes lead to decreased respiratory function and chronic *Pseudomonal* pneumonia, malnutrition and malabsorption of crucial vitamins, pancreatic dysfunction and insulin-dependent diabetes, hepatobiliary disease, meconium ileus, and reproductive dysfunction.[1,2]

Ivacaftor (Kalydeco™) potentiates CFTR receptor opening in patients six years and older who have a G551D mutation in the CFTR gene.[3,4] Only up to five percent of patients with cystic fibrosis have this G511D missense mutation.[3,4] The drug is not efficacious for patients with the F508del mutation, for which as many as 50% of CF patients are homozygous and 40% are heterozygous.[3-5]

A phase III, randomized, double-blind, placebo-controlled, international study of orally administered ivacaftor, designed by Vertex Pharmaceuticals, looked at the absolute change from baseline through week 24 in predicted FEV_1% as the primary endpoint.[3] It found that there was 10.4% increase from baseline in the predicted FEV_1% in the ivacaftor group, as compared with a decrease of 0.2% in the placebo group; a treatment effect (or absolute difference) of 10.6% ($p < 0.001$).[3] The study also revealed a 55% reduction in the risk of pulmonary exacerbations ($p = 0.001$) and a decrease in the total number of hospitalization days for pulmonary exacerbations with ivacaftor ($p = 0.03$).[3]

Ivacaftor is a 150 mg oral tablet taken every 12 hours with fat-containing food.[4] Patients with moderate and severe hepatic impairment require dose reductions.[4] The drug interacts with moderate or strong CYP 3A4 inhibitors (e.g. azole antifungals), CYP 3A4 inducers (e.g. rifampin, phenytoin, St. John's Wort).[4] It should also be used with caution with P-glycoprotein substrates (e.g. digoxin, cyclosporine, tacrolimus).[4] Although ivacaftor is pregnancy category B, it has not been extensively studied in pregnant or nursing women.[4]

Ivacaftor may also elevate hepatic transaminases.[4] ALT and AST should be assessed prior to initiating the drug, every three months during the first year of treatment, and then annually afterward.[4] Patients who develop increased transaminases should be closely monitored until the abnormalities resolve.[4] Common side effects of ivacaftor include headache, upper respiratory tract infections, nasal congestion, nausea, rash, rhinitis, dizziness, and arthralgia.[4]

Overall, ivacaftor is the first of a new class of medications that could revolutionize the treatment of CF for some patients. It targets the root of the problem by potentiating the CFTR receptor and improving the various qualities of the disease. Although it is limited to a small subset of the CF population, it is a vital first step in researching and developing similar CFTR potentiating drugs for more common CFTR mutations like F508del.

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SAFETY AND EFFICACY OF ATROPINE FOR SALIVARY HYPERSECRETION

BY: ELSA THOMAS, PHARMD CANDIDATE C/O 2013

Atropine is an anticholinergic used to treat various conditions, such as bradycardia, neuromuscular blockade, mydriasis, nerve agent poisoning, and salivary hypersecretion.[1,2] Pharmacologically, it inhibits smooth muscle and glands innervated by postganglionic cholinergic nerves.[1,2] It also has functions in the central nervous system (CNS); it could stimulate or depress it based on the administered dose.[1,2] Its utility for treating salivary hypersecretion (*i.e.* sialorrhea) is a result of muscarinic antagonism of acetylcholine, resulting in dry mouth and reduction of salivary, bronchial, gastric, and sweat gland secretions.[1,2] For adults, to reduce salivation and bronchial secretions, an oral dose of 0.4 mg is suggested, which may be repeated every 4 to 6 hours as needed.[1,2] In the form of an injection, 0.4 to 0.6 mg may be administered intramuscularly (IM), intravenously (IV), or subcutaneously (SC) over 30 to 60 minutes, and repeated every 4 to 6 hours as needed.[1,2] Interestingly a 1% ophthalmic solution of atropine has also been widely used, sublingually (SL), for the treatment of the same.[1,2]

SL atropine sulfate appears to have several advantages over the conventional IM route, including better bioavailability, rapid onset of action, and early "atropinization."[3] It is a relatively safe and effective procedure (with the aim of substituting conventional IM injections), and is readily available in the form of ophthalmic drops.[1-3] Yet, there are very few clinical studies on the safety and efficacy of SL delivered atropine for the treatment of sialorrhea.[3-7]

A single randomized controlled trial investigated the efficacy of atropine to reduce salivary hypersecretion with 2 drops of 0.5% SL atropine (0.5 mg total dose).[4] In the 22 adults who were receiving palliative care in the trial, the drug failed to show any benefit versus placebo.[3] The authors of this study suggested that their findings might have been a result of inadequate dosing.[4] In contrast, SL atropine was a simple and inexpensive treatment for sialorrhea, as reported by an open-label pilot study of SL atropine drops for the treatment of sialorrhea in seven patients (six with Parkinson's disease, one with progressive supranuclear palsy).[5] Participants demonstrated statistically significant declines in saliva production, both objectively and subjectively, and the majority of patients did not experience any anticholinergic side effects.[5]

In 2000, there was a case report of a 44 year old female with chronic schizophrenia with hypersalivation secondary to clozapine.[6] It cited resolution of persistent symptoms after administration of atropine 1% eye drops, 1 to 2 drops (0.5 to 1 mg) administered SL in the morning.[6] The patient also reported no adverse effects from the treatment, which appeared to be the benefit of local administration of atropine versus systemic use (e.g. IM, IV).[6] An updated report on the benefit of atropine drops for the treatment of sialorrhea induced by clozapine described that several patients experienced rebound sialorrhea due to the short duration of atropine, which necessitated repeat dosing.[7]

Although atropine does not require any specialized skill for use, unlike surgical removal, and has reversible effects, it is still contraindicated in patients with cognitive impairment, dementia, or hallucinations.[1,2,4] These patients are at higher risks for overdose due to mishandled dropper bottles.[1,2,4] Some patients reported difficulty in manipulating the dropper to ensure proper dosing.[6] In addition, dropper sizes are not standardized; ideally, 1 drop of 1% atropine solution should contain 500 micrograms of atropine (if 20 drops are in 1 mL of solution).[1,2] The potential for accidental overdose with drops is therefore worrisome.[6]

Drug-related adverse effects caused by atropine include dry mouth, blurred vision, urinary hesitancy and retention, tachycardia, palpitation, and constipation.[1,2] It may also produce CNS disturbances, ataxia, hallucinations, and delirium, but these effects are more common with systemic doses of atropine (exceeding 10 mg) and are rare with local administration.[1,2] Therefore, it is necessary that a patient's heart rate, blood pressure, and mental status be monitored closely while on extended and high daily dose therapy with this drug.[1]

Hence, even with limited trial data, it seems that 1-2 drops (0.5 to 1 mg) of 1% ophthalmic atropine sulfate every 4 to 6 hours (not exceeding 10 mg daily) may be both effective and safe in the treatment of sialorrhea.[1-7]

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Word Search Puzzle

BY: Marie Huang, Associate Student Editor

E K I N E R E T Y V A E K
N N B U E N M E A E L N N
L R E R I X R E C E O L R
I A L O C V A N E R N I A
N T E R O L Y V E Y E N T
A V C Y I S D N A R E A V
R O T P I R C S E R R R O
F R E V L I M I D D X F R
A K U X A D O T S I O A K
N J F R V Y V U S A V N J
A I I C L F C I R A R A I
E K I N E R E T Y V A E K
N N B U E N M E A E L N N

FIND THE FOLLOWING WORDS:

ANAFRANIL®
NEXAVAR®
JUVISYNC®
REVLIMID®
ORENCIA®
CELEBI®
RESCRIPTOR®
ISTODAX®
KINERET®
YERVOY®

TRIVIA: **Which one of these brand-name medications… never existed?**

MATCHING CHALLENGE: LOOK-ALIKES, SOUND-ALIKES

BY: ADDOLORATA CICCONE, STUDENT COPY EDITOR

The following medications are easily confused. Try to match each one with its corresponding fun fact.

If you need help, please view the answers on page 13.

1. This over-the-counter antihistamine is used for seasonal and perennial allergic rhinitis or urticarial; best results are seen with continual use. The drug may cause somnolence or fatigue and patients should avoid alcohol while on it.
2. This serotonin agonist used an antimigraine agent is available as both tablet and orally disintegrating tablet dosage forms, as well as a single-dose nasal spray. Cardiovascular adverse effects are more likely with oral dosage forms, whereas tase perversions are associated with the nasal spray.
3. This serotonin agonist used an antimigraine agent is available as a tablet, nasal spray, and subcutaneous solution. Patients should be counseled on proper administration instructions for each dosage form, as misuse or overuse may cause worsening headaches or increased frequency of headaches.
4. This antidepressant is a monoamine oxidase (MAO) inhibitor available in both oral and transdermal dosage forms. Patients should avoid eating foods high in tyramine within 14 days of therapy, as this may cause hypertensive crisis, and to rise slowly from supine positions, as this drug may cause orthostatic hypotension.
5. This antidepressant is a serotonin reuptake inhibitor available in both tablet and solution dosage forms. Patients should not take MAO inhibitors within 14 days of therapy. Serious associated syndromes to counsel patients on are serotonin syndrome and Stevens-Johnson syndrome.
6. This agent is indicated for treatment of rheumatoid arthritis and ulcerative colitis and is used off-label for various other gastrointestinal tract disorders. Patients should be counseled to take the drug after meals, adequately hydrate to prevent renal stone formation, and expect the urine/skin to turn yellow-orange.
7. This cardiovascular agent is a type III antiarrhythmic indicated for atrial and ventricular arrhythmia. Its nonselective beta-blocker properties may mask symptoms of hypoglycemia, which may be concerning for patients with diabetes. Sudden discontinuation may cause serious cardiac events.
8. This antibiotic is available in formulation with erythromycin indicated for acute otitis media. Side effects include photosensitivity, diarrhea, loss of appetite, nausea, stomach cramps, vomiting, and ototoxicity.
9. This antibiotic has a wide range of indications from acute otitis media to meningococcal meningitis to urinary tract infections to congenital toxoplasmosis. Side effects include diarrhea, nausea, and blood dyscrasia. Patients should adequately hydrate to prevent renal stone formation.
10. This dipeptidyl peptidase (DPP)-IV inhibitor is indicated for type 2 diabetes mellitus. Dosage adjustments are not required in elderly patients based on age nor in patients with hepatic insufficiency; however, patients with renal insufficiency with CrCl less than 50 mL/min should take a maximum 50 mg once daily and those with CrCl less than 30 mL/min or on hemodialysis should take a maximum 25 mg once daily.

A. Cetirizine
B. Selegiline
C. Sertraline
D. Sitagliptan
E. Sotalol
F. Sulfadiazine
G. Sulfasalazine
H. Sulfisoxazole
I. Sumatriptan
J. Zolmitriptan

Utility of Nicotinic Receptor Partial Agonists in Smoking Cessation

By: Mohammad A. Rattu, PharmD [PGY-1 Resident at VA NYHHS]

Each year, cigarette smoking, in one way or another, is responsible for nearly 6 million deaths worldwide.[1] As one could imagine, there is significant economic burden attached to these deaths, which could theoretically be lessened by effective psychological and pharmacological interventions. Focusing on the latter, examples of such interventions include nicotine replacement therapy (NRT), nicotinic receptor partial agonist (NRPA) therapy, and bupropion SR.[2-4] NRPAs, such as varenicline, cytisine, and dianicline, have been studied in various clinical trials.[2-4] Of these three agents, varenicline is similar in efficacy to NRT (the patch, specifically) and more effective than bupropion SR, while dianicline is no longer favorable and cytisine requires more studies.[2-4] Lobeline, another investigational NRPA, has yet to demonstrate any efficacy in abstinence.[5]

Cigarette smoke contains thousands of components, including nicotine, polycyclic aromatic hydrocarbons, and cadmium.[6] Of all of these components, nicotine is responsible for the prevalent addiction (which is also referred to as nicotine dependence).[3,4,7,8] In fact, through various surveys, while 70% of smokers stated that they desired to quit smoking, only up to 7% remained abstinent after one year.[7] To combat this issue, in the general practice setting, the most commonly utilized method to promote smoking cessation is the 5 A's approach (Ask, Advise, Assess, Assist, Arrange).[2,3] All five steps include some elements of psychotherapy, but in the fourth step (Assist), providers recommend pharmacotherapy (which includes NRPAs).[7]

NRPAs specifically act on presynaptic $\alpha4\beta2$ nicotinic acetylcholine receptors (nAChR).[4,8] In mice models, chronic nicotine intake demonstrated various effects on these receptors, including $\alpha4\beta2$ nAChR upregulation, $\beta2$ nAChR downregulation (and subsequent $\alpha7$ nAChR upregulation), and increased glutamate output.[8] Each effect ultimately increased dopamine release, leading to enhanced dopaminergic activity at the nucleus accumbens (*i.e.* brain-reward pathway).[8] This supports the rationale for developing a partial agonist, as opposed to an antagonist (*e.g.* mecamylamine), taking advantage of a dual action.[10] NRPAs sufficiently stimulate nAChR-mediated dopamine release to reduce cravings when quitting and inhibit nicotine reinforcement when smoking.[10,11]

In 2003, Sanofi-Aventis described compound SSR591813 (subsequently known as dianicline) and registered two trials (AMERIDIAN and EURODIAN) in 2006.[4,13,14] Eight years later, results from the only published Phase III trial of dianicline (EURODIAN) did not demonstrate favorable results.[14] Although dianicline seemed to trend toward a 22-24% greater probability of achieving long-term abstinence, there was clearly no statistical difference from placebo.[14] More likely than not, further study of the compound has been halted.[4]

Abstinence rate comparison between dianicline and placebo, with data from the EURODIAN trial.[14]

Variable	Abstinence Rate	Risk Ratio (RR)
[n = 300 (dianicline), 302 (placebo)]		
Weeks 4-7 (7-week intervention period)	24% vs. 20.5% (3.5% absolute)	1.22 (95% CI, 0.83-1.80); p = 0.307; NS
Weeks 4-26 (19-week follow-up, without any drug)	16.7% vs. 13.9% (2.8% absolute)	1.24 (95% CI, 0.79-1.93); p = 0.366; NS
Pooled analysis of aforementioned *(n = 602)*[4]		
Weeks 4-26	2.8% absolute	1.2 (95% CI, 0.82-1.75); p = 0.35; NS

NS = not (statistically) significant.

Produced in 1997, but introduced in 2005, Pfizer's varenicline (Chantix®) has been compared to counseling / behavioral support, placebo, bupropion SR, and NRT.[4,15] A 2012 meta-analysis pooled together data from these comparator trials, supporting the notion that varenicline is more efficacious than most other pharmacotherapy utilized for smoking cessation.[4] Varenicline, regardless of dose, was 109-127% more likely to result in abstinence versus placebo for at least six months.[4] It was 52% more likely to help with abstinence versus bupropion SR at one year, but did not demonstrate a statistical difference in effect versus NRT at 24 weeks.[4] Hence, as per current guidelines, first-line pharma-

cotherapy for smoking cessation is either varenicline or NRT.[2-4] Interestingly, a clinical trial on the addition of NRT to varenicline for smoking cessation (CONVICT Study) was completed in late 2011, and results have yet to be published.[16]

While efficacious for smoking cessation, varenicline is not devoid of side effects (including nausea, which usually subsides over long-term use).[4,17] The drug may increase the chance of severe adverse effects by 36%, including a possible association with serious psychiatric events (e.g. depressed mood, agitation, and suicidal behavior or ideation).[4,17] In 2008, Pfizer updated the package insert for Chantix® with black box warnings, and produced a medication guide.[17]

Pooled abstinence rate comparisons with varenicline.[4]

Variable	Abstinence Rate	Risk Ratio (RR)
Varenicline standard dose vs. placebo *[14 trials; n = 6,166]*		
CAR (≥ 6 months)	30% vs. 12% (18% absolute)	2.27 (95% CI, 2.02-2.55)
Varenicline lower or variable dose vs. placebo *[4 trials; n = 1,272]*		
CAR (≥ 6 months)	20% vs. 10.2% (9.8% absolute)	2.09 (95% CI, 1.56-2.78)
Varenicline vs. bupropion SR *[3 trials; n = 1,622]*		
CAR (at 1 year)	21.1% vs. 13.9% (7.2% absolute)	1.52 (95% CI, 1.22-1.88)
Varenicline vs. NRT *[2 trials; n = 778]*		
Point prevalence abstinence (at 24 weeks)	38.8% vs. 34.5% (4.3% absolute)	1.13 (95% CI, 0.94-1.35); NS

NS = not (statistically) significant; CAR = continuous or sustained abstinence rate

Although developed in the 1960s and utilized as a smoking cessation aid in several parts of Europe, cytisine (Tabex®) is still unapproved in the United States.[4] Trials from 1971, 2008, and 2011 demonstrated significant risk ratios in favor of cytisine versus placebo, but the absolute percentage difference in effect was modest (6-8%).[4,18,19] Before it could be recommended for widespread use, cytisine needs to be studied versus other pharmacotherapies (e.g. NRT, bupropion) and for longer treatment durations.[4]

Abstinence rate comparison between cytisine and placebo.[4,18,19]

Variable	Abstinence Rate	Risk Ratio (RR)
[n = 100 (cytisine), 97 (placebo)][18]		
CAR (at longest follow-up)	9% vs. 1% (8% absolute)	8.73 (95% CI, 1.13-67.61)
[n = 370 (cytisine), 370 (placebo)][19]		
CAR (at longest follow-up)	8.4% vs. 2.4% (6% absolute)	3.44 (95% CI, 1.66-7.13)
CAR (at 1 year)	*same as above*	3.5 (95% CI, 2.7-9.2)
Pooled analysis of aforementioned *(n = 937)*[4]		
CAR (at longest follow-up)	8.5% vs. 2.1% (6.4% absolute)	3.98 (95% CI, 2.01-7.87)
[n = 607 (cytisine), 607 (placebo)][4]		
Point prevalence abstinence (at 2 years)	21% vs. 13% (8% absolute)	1.61 (95% CI, 1.24-2.08)

NS = not (statistically) significant; CAR = continuous or sustained abstinence rate

In 2010, a phase III trial of 750 patients compared sublingual lobeline to placebo, and did not find a statistical difference (p = 0.62).[20] As of 2012, there are no registered studies of lobeline for smoking cessation, a situation similar to dianicline (mentioned earlier; based on data from ClinicalTrials.gov).

Overall, NRPAs like varenicline and cytisine have clinical utility in smoking cessation.[4] Due to the lack of evidence with the latter, varenicline is a first-line agent (as is NRT) for smoking cessation, but patients initiated on this therapy require close monitoring for psychiatric changes.[4,21] Bupropion SR remains a second-line option, based on comparative trials.[2-4,21] Dianicline and lobeline have not demonstrated favorable activity via Phase III trials, and there are no known, ongoing studies with these agents.[4,5]

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MATCHING CHALLENGE: LOOK-ALIKES, SOUND-ALIKES (ANSWERS)

BY: ADDOLORATA CICCONE, STUDENT COPY EDITOR

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1 = A, 2 = J, 3 = I, 4 = B, 5 = C, 6 = G, 7 = E, 8 = H, 9 = F, 10 = D

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SSRI Discontinuation Syndrome

By: Shannon Tellier, PharmD Candidate c/o 2013

Antidepressant discontinuation syndrome has been reported in all categories of antidepressants after abrupt interruption of therapy.[1] Symptoms usually occur within a few days of stopping or reducing the dosage of antidepressant, and rarely occur with therapy of less than five weeks.[1] If left untreated, most symptoms self-resolve within one day to three weeks.[1] It is difficult to determine the incidence of symptoms due to underreporting, but selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome may be as high as 40%.[2]

Many pathological hypotheses exist for this discontinuation syndrome, but a definite explanation remains unknown. Since long-term use of SSRIs results in a down regulation of postsynaptic serotonin receptors, these receptors may remain in their hypoactive state for days to weeks.[3] There is also a concern of a temporary absence of serotonin in the synapse after a sudden withdrawal of an SSRI.[3] A combination of down-regulated receptors and absence of serotonin may be responsible for SSRI discontinuation syndrome.[3] All SSRIs may cause a discontinuation syndrome, but it is more prevalent with paroxetine due to its short half-life (and less likely, if ever, with fluoxetine due to its long half-life).[3]

Recognition of symptoms of antidepressant discontinuation syndrome is important for both the patient and health care provider.[1,3] The FINISH mnemonic (Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory Disturbances, Hyperarousal) is used to remember these symptoms.[3] The most common symptoms for SSRI discontinuation include dizziness, nausea, lethargy and headache.[1]

To prevent the symptoms of discontinuation syndrome, a healthcare provider-supervised tapering over six to eight weeks is recommended.[3] There are no validated recommendations, but SSRIs should be tapered slowly (agent-specifically) due to their varying half-lives and active metabolites.[3] If the patient starts experiencing discontinuation syndrome, the full dose of antidepressant can be restarted and very slowly tapered again.[3] Another option is to provide fluoxetine, which is "self-tapering" due to its long half-life and active metabolite.[2] In mild to moderate cases of discontinuation syndrome, the patient can be treated symptomatically.[1] For example, a patient can be prescribed a short course of benzodiazepines for insomnia.[1] In general, the patient should be reassured that these symptoms are benign and subside in one day to three weeks.[1]

Education about antidepressant discontinuation syndrome for patients and healthcare providers is essential to prevent misdiagnosis (particularly when an antidepressant is discontinued or switched to another agent). Often, discontinuation symptoms, such as fatigue, appetite changes, insomnia, and cognitive problems may be mistaken as a depressive relapse.[3] It should be explained to the patient that relapses occur two to three weeks after stopping an antidepressant, and discontinuation syndrome can occur in little as a few hours after missing a dose.[3] In addition, patients who are nonadherent to their antidepressants may experience discontinuation syndrome, and believe that their treatment regimen is ineffective.[3] Switching antidepressants may also result in discontinuation syndrome from stopping the first agent.[3] Patients may associate these symptoms as adverse effects from the new antidepressant, leading to more therapy changes.[3] Hence, it is important for the health care provider to be aware of antidepressant discontinuation syndrome to prevent misdiagnosis and unnecessary therapy changes.

As mentioned previously, increased professional awareness allows for the early recognition of antidepressant discontinuation syndrome, and can prevent misdiagnosis or unnecessary therapy changes. Patients should not to abruptly stop an antidepressant, and ought to taper slowly (under supervision of their health care provider). The patient should also be reassured that antidepressants are not addictive, and that these symptoms are not life threatening and will resolve in a couple of weeks.[1,3]

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Low-dose SSRIs for the Overly Sensitive Esophagus

By Sunhae Chang, PharmD Candidate c/o 2013

When patients complain of heartburn, the blame usually shifts to gastroesophageal reflux disease (GERD). Therefore, patients receive the "standard therapies for GERD": antacids, histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), or prokinetics.[1,2] Luckily, most patients respond well to these agents.[1,2] Unfortunately, the not-as-lucky ones, despite PPI use, continue to suffer from the classic symptoms of GERD.[2]

GERD involves mucosal damage from gastric content reflux into the esophagus, causing heartburn and symptoms like burning in the throat, difficulty swallowing, or chest pain.[2] The medications prescribed for GERD target acid in the stomach, including counteracting the acidity or reducing the production / release of gastric acid.[2] Yet, what if the culprit is not just the acid? Interestingly, less than 5% of all acid reflux events (pH < 4) are responsible for symptoms like heartburn.[3] Upon pH testing, patients and healthy volunteers demonstrate multiple acid reflux events, but report very few complaints of heartburn episodes, if any.[3] For patients not responding to conventional drugs that combat acidity, another cause for their symptoms may exist: esophageal hypersensitivity.[1] In such patients, the esophagus is hypersensitive to even normal physiological amounts of acid, inducing a feeling of heartburn.[1]

The "-hydroxides", "-tidiness", and "-prazoles" (*i.e.* antacids, H2RAs, and PPIs) only work for acid reduction, but not for an overly sensitive esophagus.[1] So, what is the alternate solution to GERD? Antidepressants![1] Previously published studies described strange patterns in esophageal responses with antidepressants, such as tricyclic antidepressants (TCAs) and selective serotonin receptor inhibitors (SSRIs).[1] In a study by Peghini, imipramine, a TCA, raised the esophageal pain threshold (*i.e.* decreased esophageal pain perception).[4] In this double-blind, placebo-controlled crossover study, esophageal perception for first sensation and pain was measured with intraesophageal balloon distension in 15 healthy male volunteers who received imipramine in increasing doses (25 mg on days 1–3, 50 mg on days 4–6, 75 mg on days 7–12).[4] The results showed that the balloon inflation volume at pain threshold was higher for the imipramine group ($p = 0.015$) compared to the placebo group.[4] The authors concluded that increased pain thresholds for the imipramine group in the absence of changes in esophageal tone implied the presence of a visceral analgesic effect.[4]

There is more! In another study, citalopram, an SSRI, was shown to lower chemical stimulation (discomfort during < 15 min of esophageal acid perfusion) and mechanical hypersensitivity (discomfort during < 10 mL esophageal balloon distention) without changing esophageal motility.[1] On two separate occasions, 10 healthy volunteers with established esophageal hypersensitivity received placebo or citalopram 20 mg intravenously in a randomized, crossover, double-blind trial.[2] Citalopram significantly increased the threshold inducing first perception (4.6 ± 0.3 vs. 6.7 ± 0.4 mL, $P < 0.005$) and discomfort (8.6 ± 0.4 vs. 9.9 ± 0.6 mL, $P < 0.01$) during balloon distention.[1] It also significantly prolonged the acid perfusion time to induce perception of heartburn (6.0 ± 0.9 vs. 10.7 ± 0.6 min, $P < 0.005$) and discomfort (12.2 ± 0.8 vs. 16.7 ± 0.7 mL, $P < 0.001$).[1] Seven subjects (70%) experienced a retrosternal sensation during edrophonium provocation with placebo, which was reduced to two out of ten (20%) after citalopram ($P = 0.02$).[1]

Encouraged with such results, researchers are looking into SSRIs for the treatment of hypersensitive esophagus.[5] In a recent study, 252 patients with normal endoscopy and typical reflux symptoms (*e.g.* heartburn, chest pain, and regurgitation), despite twice daily PPI therapy, underwent ambulatory 24-hour pH impedance monitoring.[5] Through this pH monitoring, 75 out of 252 (29.8%) patients had normal distal esophageal acid exposure time, but had positive symptom indices (SI) for either acid and/or nonacid reflux.[5] These patients had hypersensitive esophagus, and randomly received citalopram 20 mg or placebo once daily for 6 months, while PPIs were discontinued.[5] At the end of the follow-up period, 15 of the citalopram arm (38.5%) continued to report reflux symptoms, which was significantly less than the 66.7% proportion seen in the placebo arm ($p = 0.021$).[5]

It is without question that more studies in this area are necessary, but SSRIs do seem promising in treating hypersensitive esophagus. However, antidepressants will, certainly not be a "magic bullet" for everyone with heartburn. In addition to having a more serious side effect profile than antacids, H2 antagonists, PPIs, and prokinetics, antidepressants have sociopsychological impacts. The side effects of traditional GERD therapies are relatively limited to headaches, dizziness, constipation, and diarrhea, while the side effects of SSRIs include suicidal ideation, somnolence, and insomnia.[5] Thorough education is required for patients to overcome the stigma associated with being on a psychiatric medication.

If we consider similar circumstances, bupropion is an antidepressant frequently used for smoking cessation, and citalopram may soon become the antidepressant frequently used for esophageal hypersensitivity.

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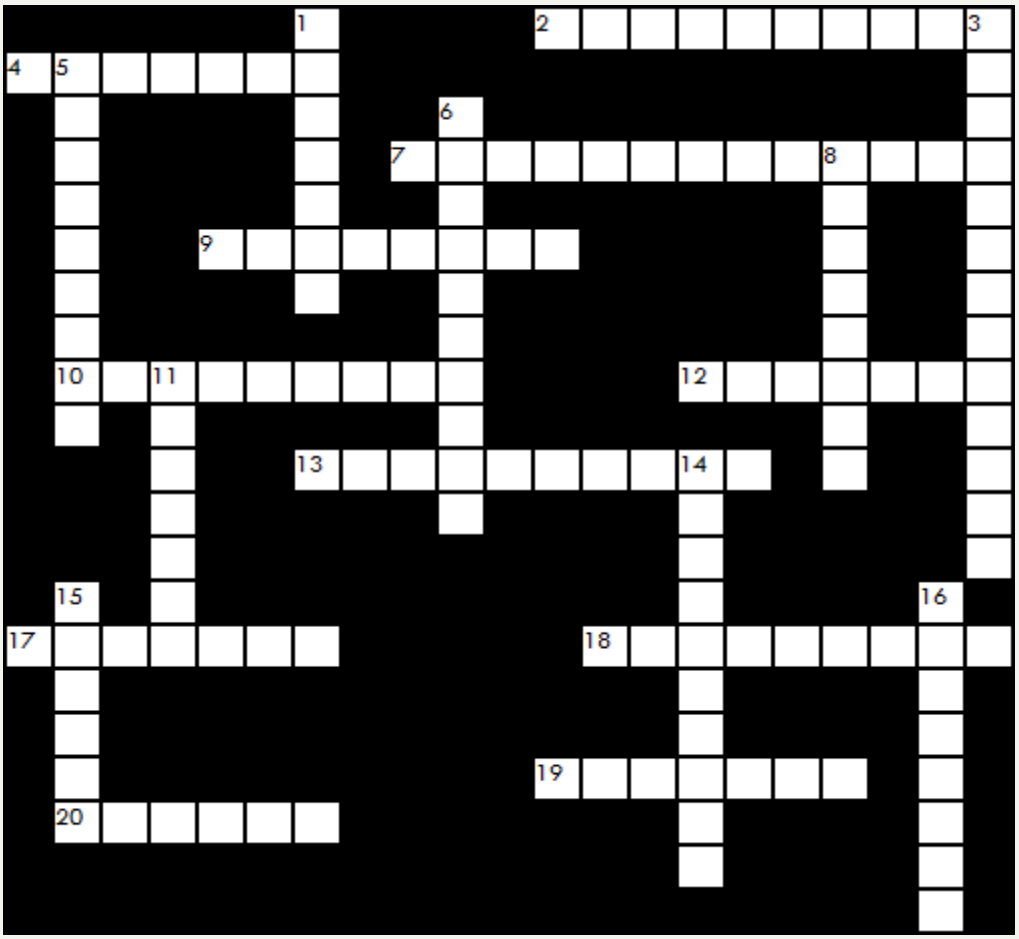
Image Source: http://www.samaritanspurse.org/index.php/occ/

WISH TO SEND A CHILD A GIFT THIS HOLIDAY SEASON?

VIST OPERATION CHRISTMAS CHILD FOR MORE INFORMATION

Crossword Puzzle: HIV/AIDS

By: Mahdieh Danesh Yazdi, Associate Student Editor



Across

2. NRTI with greater risk of bone marrow suppression
4. Efavirenz + Emtricitabine + Tenofovir
7. Protease inhibitor that should not be given with oral contraceptives as its levels are decreased by these drugs
9. Drug recently approved for use in HIV; the "quad" pill
10. First integrase inhibitor approved for use in HIV
12. Only drug currently approved for the prevention of HIV
13. NRTI which should not be used with stavudine as it may increase the risk of toxicities such as pancreatitis
17. NNRTI commonly associated with side effects such as abnormal and vivid dreams
18. Only drug currently on the market which works as a CCR5 entry inhibitor
19. Protease inhibitor which should be stored in the refrigerator
20. Drug often used as a booster for protease inhibitors

Down

1. Lopinavir + Ritonavir
3. Drug with similar resistance pattern to lamivudine; do not use concomitantly
5. Only NRTI that does not require intracellular phosphorylation
6. Drug with no antiretroviral activity which is used in order to increase levels of other ARV drugs
8. HLA-B*5701 gene testing should be done prior to prescribing this product
11. NNRTI given with a high fat meal in order to ensure proper absorption
14. NNRTI that requires lead-in dosing prior to maintenance dose; should not be given to treatment-naive patients
15. Fusion inhibitor given as a subcutaneous injection
16. Rilpivirine + Emtricitabine + Tenofovir

ARE YOU PREPARED FOR RSV SEASON?

BY: MAHDIEH DANESH YAZDI, ASSOCIATE STUDENT EDITOR

Many of us have prepared for influenza season by receiving the flu vaccine. (If you have not, please speak to your doctor or pharmacist soon! Remember: even if you do not need it for your protection, get it for your patients' well-being). However, for the youngest members of our population, there is also another threat this season: respiratory syncytial virus (RSV). RSV is a single-stranded RNA virus that causes symptoms of the common cold such as fever, runny nose, coughing, and wheezing.[1] For older children and adults, it causes self-limiting sickness that resolves within a couple of weeks.[1] However, in younger children and infants, infection with this virus may cause a much more serious illness. In fact, it is a major cause of pediatric pneumonia and bronchiolitis.[1] This is especially true in infants and young children who have comborbidities such as congenital heart disease or immunosuppression.[1] There is currently no treatment specifically indicated for use against RSV and therapy usually involves supportive care.[1]

As with many other diseases of viral etiology, the best medical option is prevention. Non-pharmacologic prevention methods include minimizing sharing personal items and utensils between children, frequent hand washing, and avoiding contact with those who are sick. Currently, there is only one medication indicated for the prevention of RSV: palivizumab (Synagis®), a monoclonal antibody that works by preventing viral membrane fusion and blocking its entry to host cells.[2]

The American Academy of Pediatrics (AAP) has published guidelines for palivizumab in RSV prevention.[3] They recommend a 15 mg/kg once monthly intramuscular injection for[3]

- Infants < 24 months of age with chronic lung disease requiring therapy in the past six months
- Infants < 24 months of age with congenital heart disease +
  - Therapy OR
  - Moderate to severe pulmonary hypertension OR
  - Cyanotic heart disease
- Infants < 12 months of age with airway abnormality or neuromuscular disease that would decrease one's ability to manage airway secretions
- Infants < 12 months of age who were born at a gestational age ≤ 28 weeks
- Infants < 6 months of age who were born at a gestational age of 29 to 31 weeks and 6 days
- Infants < 3 months of age who were born at a gestational age of 32 to 34 weeks and 6 days +
  - Attends daycare
  - Has one or more siblings < 5 years of age in the same household (excluding multiple birth babies)

The AAP recommends that infants receive these monthly injections during RSV season with a maximum of five injections.[3] The exception is in the case of infants < 3 months of age who were born at a gestational age of 32 to 34 weeks (and 6 days) and either attend daycare or have one or more siblings who are < 5 years of age in the same household.[3] These patients should receive a maximum of three injections.[3]

The common side effects of this drug include erythema and swelling at the injection site, fever, and rash.[4] It is important to keep in mind that injections of this drug may cause anaphylactic reactions in those with hypersensitivity to palivizumab or any component of the drug.[4]

RSV season varies yearly and based on region, but usually begins around November and ends in March or April.[5] Palivizumab is recommended to be given the month before or during RSV season; therefore, the first dose is usually provided between September and November.[5]

If you have a new baby in your household and he/she meets the criteria above, speak to the pediatrician about RSV prevention for the infant. Since this virus is highly contagious and is of special concern in infants with other comorbidities, those working in a hospital setting must be wary of the threat RSV poses. Of course, if you are on rotations (within a pediatric or neonatal unit), be sure to screen patients to determine their eligibility for palivizumab.

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Mechanisms of NSAID-Induced Functional Renal Toxicity

By: James W. Schurr & Stephen Argiro, PharmD Candidates c/o 2014

Patients frequently utilize non-steroidal anti-inflammatory drugs (NSAIDs) for a wide variety of conditions, including but not limited to arthritis, headaches, and generalized pain. Despite an excellent safety profile, NSAIDs are associated with certain toxicities, including renal complications (particularly among at risk populations).[1] Acute and chronic interstitial nephritis, glomerulopathy, and altered intraglomerular hemodynamics have been established as mechanisms by which NSAIDs induce nephrotoxicity.[1] Patients at risk for these problems include those with age-related declines in glomerular filtration rate (GFR), hypovolemia, those concurrently on loop diuretic therapy (e.g. furosemide, torsemide), congestive heart failure (CHF), cirrhosis of the liver, underlying renal disease, and concurrent use of angiotensin converting enzyme inhibitors (ACEIs) (e.g. enalapril, ramipril) or angiotensin receptor blockers (ARBs) (e.g. valsartan, losartan).[2]

The renal mechanisms of toxicity include two overall categories of functional and inflammatory renal impairment. Functional renal impairment involves the decrease of glomerular ultrafiltrate production or intraglomerular hydrostatic pressure, while inflammatory renal impairment involves an underlying hypersensitivity response with interstitial nephritis and glomerulopathy.[1,3] Functional renal failure is a product of inadequate glomerular hydrostatic pressure caused by changes in the hemodynamics of the afferent and efferent arterioles.[3] In abnormal renal physiology, the blood flow through these arterioles is altered, causing an imbalance in the normal pressure and leading to an ischemic state.[3] Interstitial nephritits can be acute or chronic with NSAID use, and occurs as an idiosyncratic, non-dose-dependent, allergic response.[1] Inflammation is noted by the presence of leukocytes found in the urine upon presentation.[1,4] Interstitial nephritis leads to minimal change glomerulopathy (often manifesting as nephrotic syndrome), and is characterized by heavy proteinuria, hypoalbuminemia, edema, hyperlipidemia, and lipiduria.[4]

NSAIDs inhibit the cyclooxygenase (COX) enzymes, which are part of the arachidonic acid pathway.[2] COX has two variant forms (*i.e.* COX-1, COX -2), each with its own particular inflammatory effect.[2] COX-1 and COX-2 have anatomical and physiological overlap within the kidney, evidenced by their presence at the afferent arterioles, glomerulus, and efferent arterioles as denoted in Figure 1.[2] However, their distributive differences dictate their varying functional roles in renal hematologic homeostasis.[2] COX-2, unlike COX-1, can also be found in the Macula densa, the thick ascending limb of the Loop of Henle, and podocytes, leading to effects that vary from those caused by COX-1.[2] COX-1 mainly works by controlling hemodynamics and GFR, while COX-2 exerts its effects on the excretion of salt and water.[2] NSAIDs are classified into two groups, notably COX-2 selective (e.g. celecoxib) and non-selective (e.g. ibuprofen, naproxen, diclofenac).[2] Because of the differences in the roles of COX-1 and COX-2 in the kidneys, non-selective and COX-2 selective inhibitors would theoretically have varying consequences related to renal function.[2]

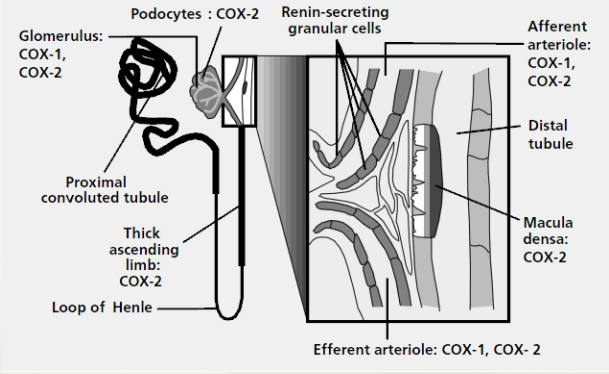

Figure 1.[2]

In individuals with normal renal function and no predisposing hemodynamic insults to the kidney, glomerular filtration is not prostaglandin (PG) dependent.[5] Therefore, NSAID use does not generally lead to functional renal toxicity in these individuals.[5] The primary PG involved in renal hemodynamic homeostasis is prostacyclin (PGI_2).[6] PGI_2 is necessary for maintaining normal renal homeostasis mechanisms, while PGE_2 and PGD_2 dilate the renal vascular bed, lower renal vascular resistance, and increase renal perfusion.[2] Inhibition of PGI_2 synthesis in the kidney specifically produces acute renal fail-

ure and hyperkalemia.[2] Inhibition of PGE_2 can lead to peripheral edema, blood pressure increases, weight gain, and CHF (rarely).[2] COX-2 is located specifically on the thick ascending limb of the Loop of Henle (Figure 1) where it produces PGE_2 and promotes diuresis and natriuresis by blocking reabsorption of water and sodium, respectively.[2] Inhibition of COX-2 in this region is, therefore, a likely mechanism by which edema-related problems may occur from both, COX-2 selective and non-selective, NSAIDs.[2]

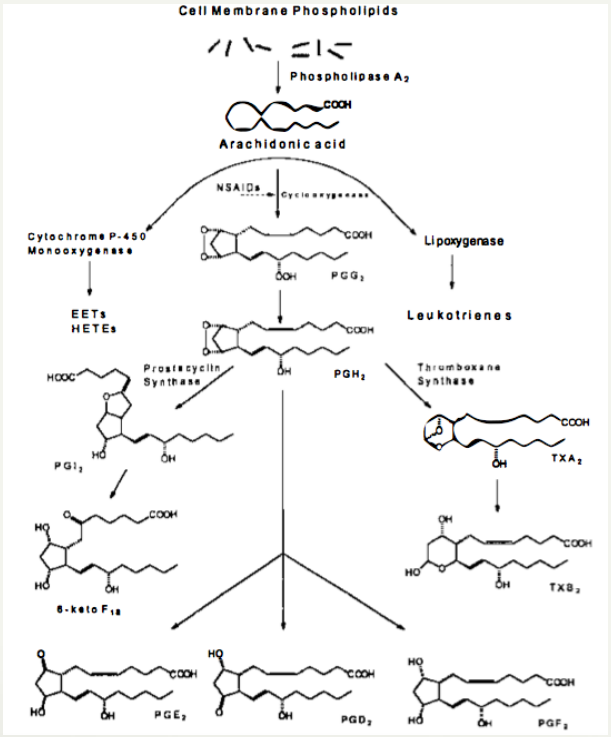

Figure 2.[6]

It is also worth noting that during times of renal stress from poor perfusion, such as in hypovolemic states (dehydration, hemorrhage), CHF, or excessive diuresis, a greater emphasis is placed on PG mechanisms to maintain adequate renal blood flow.[6] Angiotensin II, catecholamines, and vasopressin will be released to support glomerular filtration via vasoconstriction of the efferent arterioles, and PGI_2 and PGE_2 will be produced to dilate the afferent arterioles to support perfusion.[6] In these circumstances, or when a patient is already renal impaired (creatinine clearance < 70mL/min/1.73m^2), PG synthesis becomes a dependent mechanism for renal homeostatic maintenance.[6]

Additional concerns exist in patients who are concurrently taking ACEIs or ARBs. Angiotensin II receptors are primarily located on efferent arterioles, and, when activated, will cause vasoconstriction and increase the pressure inside of the glomerulus.[6] When this mechanism is blocked by ACEIs or ARBs the intraglomerular pressure will decrease.[6] If NSAIDs are added to this therapy, and the patient has PG dependent renal function, the afferent arterioles will be prohibited from dilating, causing further decreases in intraglomerular pressure and precipitating ischemia / acute renal failure.

Despite being considered safe medications and available to the public over-the-counter, NSAIDs have risks associated with use, especially in particular patient populations. Age-related declines in renal function, conditions that develop PG dependent renal perfusion, anti-angiotensin therapy, and comorbid renal diseases are important considerations when initiating NSAID therapy. Pharmacists are able to make excellent recommendations to patients and their physicians regarding NSAIDs, particularly considering patients' comorbidities and concomitant therapies.

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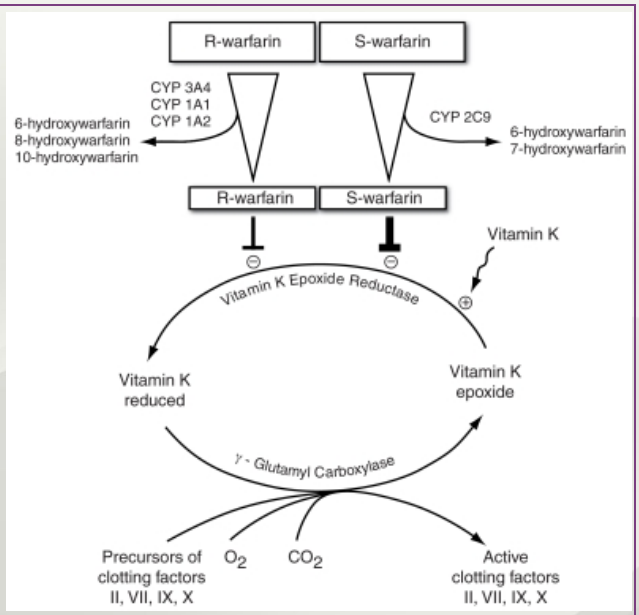
Challenging the Clinical Interactions between Levothyroxine and Warfarin

By: Mohammad A. Rattu, PharmD [PGY-1 Resident at VA NYHHS]

One of the major tasks that pharmacists undertake on a daily basis is drug interaction checking. Although most interactions are minor or not clinically relevant, drugs with narrow therapeutic indices are always of concern. Since the 1970s, several reports in the literature have indicated that the concurrent utilization of oral anticoagulants (e.g. warfarin) and thyroid hormones (e.g. levothyroxine) increases the risk of bleeding, but is of lesser concern if warfarin is added to levothyroxine in a euthyroid patient.[1-4] Alternatively, a recent observational study found that the converse was also true – initiation of levothyroxine in patients stabilized on warfarin did not lead to clinically relevant bleeding events.[5]

Originally approved for medicinal use in 1954, warfarin is a widely prescribed anticoagulant used for the prevention and treatment of various thrombotic / thromboembolic disorders.[6] Through inhibition of the C1 subunit of vitamin K epoxide reductase (VKORC1) enzyme complex, warfarin reduces the regeneration rate of vitamin K1 epoxide.[6] This translates into inhibiting the synthesis of vitamin K-dependent clotting factors (e.g. Factors II, VII, IX, X).[6] Warfarin also inhibits anticoagulant proteins (e.g. C, S), which, in high risk patients, usually necessitates initial "bridged" or overlap of therapy with concomitant unfractionated heparin (UFH) or low molecular weight heparin (LMWH).[6]



Mechanism and metabolism of warfarin.[7]

Major adverse effects revolve around bleeding, and the risk for clinically significant bleeding events increases with the concomitant administration of medications that may decrease warfarin metabolism, increase vitamin K-dependent clotting factor metabolism, or displace warfarin from albumin.[5,6] The international normalized ratio (INR), which is based on prothrombin time, assists in identifying the safety and efficacy of warfarin, and most indications for its use require an INR target of 2 to 3.[5,6]

Warfarin has also been of great interest in the field of pharmacogenomics. The S-isomer yields most its aforementioned activity, and is metabolized by CYP2C9.[5,6] Patients with single-nucleotide polymorphisms (SNPs) in genes encoding for CYP2C9 and VKORC1 require warfarin dose reductions to decrease the risk of bleeding.[6] With these SNPs, there is decreased metabolism of warfarin in patients with 2C9*2 or 2C9*3 alleles and decreased production of VKORC1 in patients with the VKORC1 A haplotype.[6]

On the other hand, levothyroxine (L-thyroxine, T4) appeared in medical literature in 1926, and since its discovery, has often been prescribed as replacement or supplemental therapy in patients with hypothyroidism.[8,9] Thyroid hormones (triiodothyronine [T3] more than T4), are involved in the regulation of multiple metabolic processes.[9] Examples of such processes include increasing cellular respiration / thermogenesis, as well as metabolizing proteins, carbohydrates, and lipids.[9] These hormones are essential in normal human growth / development and maturation of the central nervous system / bones.[9]

As per the package insert, levothyroxine (and subsequent conversions to T3) "increases the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants," such as warfarin.[9] It continues to state that "concomitant use of these agents impairs the compensatory increases in clotting factor synthesis" and "prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants, and the dose of anticoagulant therapy adjusted accordingly."[9] Unfortunately, these statements do not indicate the potential severity (e.g.

quantification of INR changes) of the interaction.

Challenging the clinical relevance of this interaction, a case-control ("trohoc") study examined the associative risk of hospitalization for hemorrhage (*i.e.* a serious bleeding event) in patients who were initiated on levothyroxine while on long-term warfarin therapy.[5] All patients were older than 66 and received warfarin for at least three months.[5] Those with hemorrhagic events often had hypertension, alcohol-use disorders, and utilized other medications that increased the risk of bleeding (e.g. aspirin, other antiplatelets, and COX-2 inhibitors).[5] Results indicated no statistical differences between levothyroxine and other circumstances that led to hospitalization for hemorrhage, implying that there is no "major" interaction between levothyroxine and warfarin – and that such an interaction should be classified, at the very most, as "moderate."[5]

Risk of hospitalization for hemorrhage (event) in patients on warfarin for three months and recently initiated on levothyroxine (T4)

Variable (T4 initiation)	Event Rate	Odds Ratio (OR) Unadjusted	Odds Ratio (OR) Adjusted*
[n = 10,532 (cases) vs. 40,693 (controls)]			
0-30 days prior to event	0.2% vs. 0.15% (0.05% absolute)	1.26 (95% CI, 0.76-2.07); NS	1.11 (95% CI, 0.67-1.86); NS
31-60 days prior to event	0.05% vs. 0.054% (0.004% absolute)	0.73 (95% CI, 0.251-2.11); NS	0.76 (95% CI, 0.26-2.25); NS
61-90 days prior to event	0.05% vs. 0.032% (0.018% absolute)	0.62 (95% CI, 0.14-2.73); NS	0.67 (95% CI, 0.15-3.01); NS

*Adjusted for income quintile, long-term care residence status, history of atrial fibrillation and chronic kidney disease, number of drugs prescribed during the past year, and recent medication use. NS = not (statistically) significant

While in agreement with classifying this interaction as anything less than "major," it is noteworthy to explore clinical experience. Anecdotally, from working in an anticoagulation clinic for several months, patients who presented with supratherapeutic INR levels had *not* recently received levothyroxine. In fact, the most common causes for considerably elevated INRs (*i.e.* greater than 4) often have been decreased vitamin K-rich food intake, concomitant use of high-protein-binding medications (e.g. sulfamethoxazole / trimethoprim, any NSAID, or high-dose corticosteroids), and acute alcohol consumption (not chronic). The major presentations associated with elevated INR levels have been bruising (not painful), intermittent epistaxis, and lightheadedness. At each visit, among other information, patients receive comprehensive instructions for seeking emergency medical attention, and are immediately taken to the emergency room via wheelchair should there be concerns for major bleeding.

This large analysis sought to challenge a theoretical notion, but it only identified one specific type of event (*i.e.* hospitalization for hemorrhage) – and it is at the extreme of an interaction. Current, online drug interaction checking databases (such as Micromedex and LexiComp) already classify the interaction as "moderate," but do not offer expected changes in INR.[10,11] Although statistically demanding, for a quantitative analysis, the investigators could redefine their "event" as simply the initiation of levothyroxine in patients who received warfarin for three months, and then report any documented INR values. Otherwise, on the side of caution, each time that patients receive *any* new medication while on warfarin therapy (stabilized or not), healthcare providers must monitor INR at appropriate intervals.

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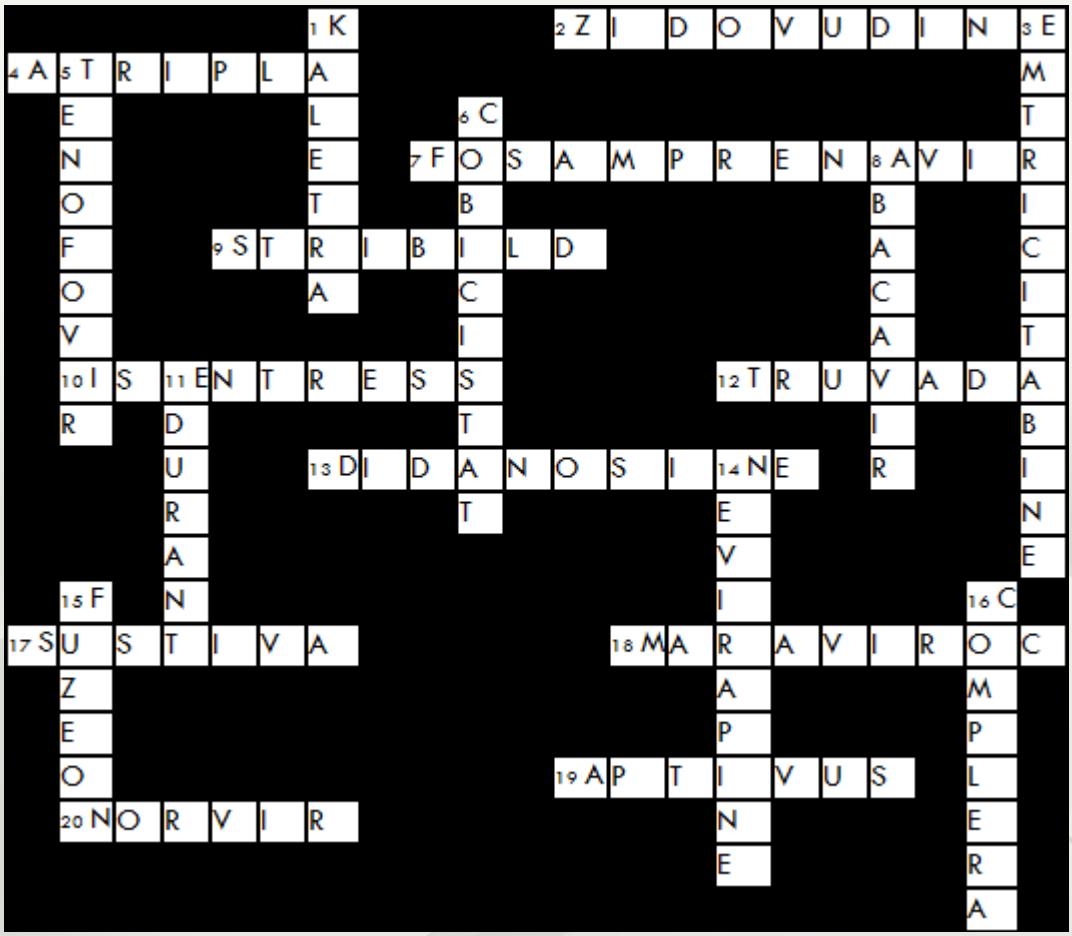
Word Search Puzzle (Trivia Answer)

BY: Marie Huang, Associate Student Editor

TRIVIA: **Which one of these brand-name medications… never existed?**
ANSWER: **CELEBI®**

Crossword Puzzle: HIV/AIDS (Solution)

By: Mahdieh Danesh Yazdi, Associate Student Editor



LETTER FROM THE EDITORS: WE NEED YOU!

Dear Reader,

We are always looking to engage with each of you. If you are a talented cartoonist or have a passion for art, feel free to contact one of the editors. It is a great way to express yourself and earn a spotlight for your artistic skills while drawing attention to an aspect of the pharmacy profession.

Can't draw? No problem, take pictures instead! We need photographers who can attend campus events and seminars that are related to healthcare or the pharmacy profession. Please feel free to send us the pictures with one or two paragraphs explaining the event. Perhaps you have a passion for writing; if so, feel free to write to us in response to an article you read. Even if it is just a question or a few comments on an article, email us!

Don't like what you see in the newsletter? Then let us know! Tell us what you would like to see in the newsletter, what topics you are interested in, and/or if you wish to read more about a specific topic. The newsletter is for you; so, your feedback is very important to us.

Do you have some clinical knowledge or experiences to share? Feel free to send us interesting drug information questions you have answered or share what you have learned throughout your rotations.

This is a commitment-free way to stay involved with the pharmacy profession. Contributing to our newsletter does not obligate you to contribute to every issue. We are more than happy to have guest authors and talented students work with us whenever they are available or free to do so. If you have any questions, comments, and/or concerns, please do not hesitate to email us at: **rhochis@gmail.com**.

With much gratitude,

The RCP Editorial Team

Image Source: easyvectors.com

Always a popular destination, 2012 ASHP Midyear Meeting and Exhibition is heading to Las Vegas and is set to be a record breaking meeting! This year's meeting will be held at the Mandalay Bay Hotel with many affiliate events also taking place at the MGM Grand, the co-headquarter hotel. Not only does this new venue offer more to our attendees, but as the "entertainment capital of the world", Vegas offers something for everyone and we are sure after sessions conclude there will be lots of thrilling activities.

The conference is for pharmacy students of all years to make connections and learn more about the unique opportunities within the pharmacy world. Discover the path for your future today, book now at:

http://connect.ashp.org/midyear2012/Home/

Image Credit: Presbyterian College of Pharmacy

http://pharmacy.presby.edu/organizations/the-midyear-meeting/

RHO CHI POST: EDITORIAL TEAM

CO-EDITORS-IN-CHIEF

@ Steve P. Soman *(6th Year, STJ)*

Previously known as Ebey P. Soman, I really enjoy writing very opinionated articles. I strongly encourage all readers of our newsletter to respond with their own literary pieces. I look forward to hearing from you, and welcome your comments and constructive criticisms!

@ Neal Shah *(6th Year, STJ)*

I frequently assist several professors on campus with their research. My goal is to provide my fellow students with research-based information that correlates with clinical pharmacotherapy. If you have any topics of interest or comments on currently-published articles, please do not hesitate to email me!

STUDENT EDITORS

@ Mahdieh D. Yazdi *(6th Year, STJ)*

I like to stay current with all the changes in our profession, both legal and clinical. I hope to keep you informed with all that I learn. Please enjoy Rho Chi Post, and provide us detailed feedback so that we may improve our newsletter.

@ Mohamed J. Dungersi *(6th Year, STJ)*

I am enthusiastic about promoting the pharmacy profession, and what better way to do this than by being a part of the Rho Chi Post? Should you have any comments or concerns, feel free to contact me!

@ Marie Huang *(6th Year, STJ)*

I am in a continuous process of self-definition, and constantly testing the boundaries of this world. I enjoy channeling my inspiration through words and photographs. As a witness to an evolving profession, I look forward to keeping you updated! Who knows where we will be tomorrow?

@ Shannon Tellier *(6th Year, STJ)*

I believe it is important for students and everyone else in the profession to stay informed about current pharmacy events. Rho Chi Post is a great way to continue learning information about what is happening on our campus and in the nation.

@ Addolorata Ciccone *(6th Year, STJ)*

I am thrilled to serve as a Co-Copy Editor of Rho Chi Post. Whether you are brand new to the world of pharmacy, a seasoned veteran of this profession, or anywhere in between, I hope you find our work engaging, relatable, and informative. I look forward to reading your comments and feedback.

@ Aleena Cherian *(5th Year, STJ)*

The Rho Chi Post has been a source of current information and great advice to students and professionals in this evolving profession. After years of experience in media and graphics-related work, it is now my privilege to be a part of this endeavor as a Co-Copy Editor. I hope you learn as much from future editions of the newsletter as I have, and I welcome your feedback!

CO-COPY EDITORS

RHO CHI Rx post

RHO CHI

The Rho Chi Society encourages and recognizes excellence in intellectual achievement and advocates critical inquiry in all aspects of Pharmacy.

The Society further encourages high standards of conduct and character and fosters fellowship among its members.

The Society seeks universal recognition of its members as lifelong intellectual leaders in Pharmacy, and as a community of scholars, to instill the desire to pursue intellectual excellence and critical inquiry to advance the profession.

CURRENT EXECUTIVE BOARD

Bethsy, Albana, Yining, Elizabeth, and Aleena at the 2012 Induction Ceremony

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THE RHO CHI POST

MISSION

The Rho Chi Post aims to promote the Pharmacy profession through creativity and effective communication. Our publication is a profound platform for integrating ideas, opinions, and innovations from students, faculty, and administrators.

VISION

The Rho Chi Post is the most exciting and creative student-operated newsletter within the St. John's University College of Pharmacy and Health Sciences. Our newsletter is known for its relatable and useful content. Our editorial team members are recognized for their excellence and professionalism. The Rho Chi Post sets the stage for the future of student-run publications in Pharmacy.

VALUES

Opportunity, Teamwork, Respect, Excellence

GOALS

1. To provide the highest quality student-operated newsletter with accurate information
2. To maintain a healthy, respectful, challenging, and rewarding environment for student editors
3. To cultivate sound relationships with other organizations and individuals who are like-minded and involved in like pursuits
4. To have a strong, positive impact on fellow students, faculty, and administrators
5. To contribute ideas and innovations to the Pharmacy profession

UPCOMING EVENTS

Sept 6 – Dec 6: FREE Speech and Hearing Screenings

St. John's University, Seton Complex

152-11 Union Turnpike, Flushing, NY

Nov 12: 2012 Doctoral Seminar Series

D'Angelo Center Room 206

St. John's University, Queens, NY

Nov 26: 11th Annual World Drug Manufacturing Summit

Streamlining Pharmaceutical Manufacturing Operations

Swissôtel, Düsseldorf, Germany

Nov 28-29: Diabetes, Cardiovascular

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