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New Jersey Pharmacists Association

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Mission Statement:

*To advance the profession of pharmacy, enabling our
members to provide optimal care to those they serve.*

President's Letter

Dear NJPhA,

I believe I can hear a collective sigh of relief as the calendar flips to March and the days grow longer. Still not out of the cold, it's time to end any hibernation we've been doing. Exciting news: our new website will be launched in the coming weeks and it will make interacting with NJPhA leadership and each other much easier.

Right now, we need nominations for the role of 2nd VP (4-year leadership role) and Treasurer (2-year term). You know if you have the fire and you know the folks you'd like to see leading NJPhA into the next several years - so start talking and encouraging them

(or yourself!) to take that next Leadership step. All it takes is an email to njpha@njpharma.org expressing interest in the particular role. Soon we'll also be seeking award nominees; if there are folks you want to recognize this year, start jotting down their names and why. The award information will be coming soon, too.

Finally, I know you will appreciate this issue of the NJPhA Journal with focus on Public Health. Our accessibility makes us essential in protecting and improving public health.

May we all have Spring Fever very soon.

Carrie

From The Editors' Desks...

Dear Colleagues,

Welcome to our third peer-reviewed issue of the NJ Journal of Pharmacy - focusing on Public Health, an important topic for all of us as pharmacists and as human beings. According to the American Pharmacists Association Policy Statement, "the pharmacist's centralized placement in the community and clinical expertise are invaluable" in addressing public health issues. Pharmacists perform health screenings, and provide immunizations, and counseling. Health education includes education on self-care, smoking cessation, family planning, and patient-centered disease-specific services, such as diabetes and lipid management.

This issue introduces electronic cigarettes as an alternative to smoking tobacco cigarettes. It is important for pharmacists to become familiar with these products as utilization by the public increases.

We also offer an overview of our role as pharmacists in assessing and managing sports-related concussions. Appropriately recognizing and triaging patients with concussions are crucial to avoid complications.

Dietary recommendations in patients on warfarin therapy are often controversial and contradictory. A current overview is presented to provide an update on available clinical data.

Cardiovascular effects from azithromycin are also under scrutiny as conflicting data have been reported. Here we offer an update on this topic as well.

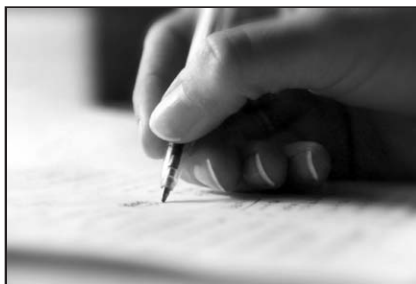
Our Practice Spotlight highlights Dr. Sharon See, who is active in CERT (Community Emergency Response Team) in Hoboken, NJ. She shares with us her experiences that began with Superstorm Sandy.

We hope you enjoy reading the Journal and become inspired to embrace your role as an accessible public health professional in your community!

Regards,

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Writers and Researchers:

Submit an article for a future issue of the
New Jersey Journal of Pharmacy.

The upcoming topics are:

- Infectious Disease • Deadline: June 8, 2014
- Endocrinology • Deadline: September 8, 2014

To submit an article, request submission guidelines or for more information, please email the editors at the addresses above.

Message from the BOT Chairman

The Most Trusted Profession and Public Safety

When you consider all of the various medications that are entering the market for medical treatments, such as, Oncology, HIV, Rheumatoid Arthritis, MS, etc, pharmacists have provided additional patient counseling to encourage patient compliance and to obtain necessary feedback to improve treatment outcomes. The degree of safety in the use of these medications cannot be taken for granted.

Pharmacists have attained public trust and must continue to serve and protect.

Pharmacists are encouraged to be advocates in their communities.

We all have read recent news related articles regarding the abuse of opioids and the consequences resulting from their misuse. The opioid epidemic has led to overuse and addiction. In some instances, this greater dependence has resulted in death, as a result from using hydrocodones, or additional drugs, in excessive combinations. When opioid supplies become limited, there has been a trend towards using the less expensive alternative, heroin. Likewise, this pathway could result in seizures, and/or, death.

Thus, society needs to be made aware of the pitfalls that may occur with the misuse of pain medications. Therefore, pharmacists need to counsel their patients and advise them to carefully follow the prescribed directions. Patients need to understand their therapy and maintain proper adherence.

In addition, the *Prescription Monitoring Program* (PMP) is another tool to discover improper usage. Pharmacists need to be diligent.

Pharmacists need to work in collaboration with the prescribing physician to ensure patient safety.

The profession of pharmacy has always supported public safety and encouraged improved patient health.

Yours truly,
Joseph Tarallo, Jr., RPH
NJPhA, BOT Chairman, 2013-2014

Message from the CEO

Calling All Students—Select an NJPhA Rotation

In 2013, NJPhA reinstated student rotations, and six students participated in IPPE and APPE rotation assignments. They represented Philadelphia College of Pharmacy at USciences, Ernest Mario School of Pharmacy at Rutgers University, and Temple University School of Pharmacy.

The program description, available at each school, outlines the general concepts you learn and the experiences you have during the NJPhA rotation. It, however, is not as predictable as it seems on paper. Yet, each rotation will demand that, by choosing to enter our program, you are ready to utilize your talents in many ways. It is a unique opportunity to hone your research, presentation, and communication skills, while learning the value of a professional, membership organization, and its role in the legislative process. Addressing emerging legislative issues or providing detailed

background data on current disease management topics, exposure to the regulatory and legislative processes and its effect on pharmacy are eye opening, and unforgettable opportunities.

I can assure you that through this experience, your ability to employ knowledge and develop skills will reach new heights. Issues NJPhA addresses today may influence your career. You are the pharmacists we will represent tomorrow—help shape the future—request an NJPhA rotation today!

Hear what students – read firsthand student reflections on pages 8 and 9.

Elise M. Barry

Letters To The Editors'...

Dear Editors and Colleagues,

Dietary supplements are not only vitamins and minerals but also energy bars and liquid food supplements. Like drugs, dietary supplements can have side effects as well as drug interactions. Unlike prescription drugs, supplements are mostly used at the discretion of patients, without the involvement of a health care professional; even for our well-informed patients, reliable and accurate information may be hard to find on Dietary Supplements. In 2009, the US Food and Drug Administration (FDA) reported exposure to supplements accounted for greater than 29,000 calls per month to US poison control centers, in which 500 were considered to have moderate to severe outcome and one resulted in death. Additionally, between October 2010 and March 2011, an average of approximately 120 supplement-related adverse events were reported to the FDA per month.⁽¹⁾

With that said, dietary supplements may help reduce the risk of some diseases and many patients feel strongly about the use of these types of products. As a result, it is our responsibility to ensure our patients are well educated regarding the use of dietary supplements.

There are several ways that supplements may cause problems for patients receiving treatment for cancer. For example, some products may cause sun or skin sensitivity and patients being treated with radiation therapy are also at increased risk for sunburn. The combination of the two sensitizing agents greatly increases the chance of sunburn in these patients. Another problem associated with the use of supplements during cancer treatment relates to drug interactions, which may be missed as supplements are usually purchased over the counter or via online stores. Some cancer experts recommend the discontinuation of supplements for patients who are currently undergoing cancer treatment. Pharmacists, especially in the community setting, have ample opportunity to speak with patients about supplement use and provide counseling.⁽¹⁾

It is important to educate your patients regarding the differences in the FDA regulation of dietary supplements versus the FDA regulation of prescription medication. Many patients believe “the FDA would not let a manufacturer make a claim if it wasn’t true” and/or “if it could hurt me, the FDA would not allow it to be sold” and it is this myth that warrants explanation. It is important to note that dietary supplements are treated as special foods by the FDA thus do not undergo the same safety procedures as prescription drugs. According to current developmental and promotional regulations of dietary supplements, pre-marketing safety research is left to the sole discretion of the manufacturer. Unless a problem arises with a particular supplement the FDA is not permitted to step in.^(1, 2, 3)

Prescription drugs must be proven safe and effective on humans for the marketed indication before being marketing to the public

whereas dietary supplements are available to the public and are considered safe until proven unsafe. Once a prescription drug is approved, it must be manufactured under specific conditions (called Good Manufacturing Processes or GMPs) and packaged with product information (referred to as Labelling), the details of which are all dictated by FDA regulation. Dietary supplements are defined as a category of food according to the Dietary Supplement Health and Education Act (DSHEA), enacted in 1994.^(1, 3)

As of 2010, the Department of Health and Human Services (DHHS) put in place a guidance for industry for producing supplements, covering all supplement makers. The new DHHS rules require that supplements follow standards called Good Manufacturing Practices (GMPs). This means that dietary supplements must:^(1, 2, 4)

- Be produced in a quality manner
- Contain no impurities
- Be labeled with the actual ingredients in the product

These new rules provide guidance on the quality of manufacturing for supplements and the accurate listing of their ingredients on the label. Companies will continue to sell their products the same way they always have but if following these rules it is more likely that the product will contain what is indicated on the labeling. However, the rules do not:^(1, 4)

- Limit consumers’ access to dietary supplements
- Address the safety of the supplements’ ingredients
- Address the supplements’ effects on health (assuming GMPs are followed).

All in all, it is up to the FDA and other law enforcement groups to stop criminal manufacturers once they have been uncovered. Manufacturers of supplements are not required by law to follow USP standards, but many of them have chosen to do so and thus present the USP acronym on their label. Others may have the initials NF (National Formulary) on their labels; NF is paired with USP, and has standards that more specifically relate to herb- and plant-based ingredients. On top of following the FDA rules, manufacturers who choose to also use the USP or NF initials indicate that they choose to follow even higher quality standards.^(1, 2, 4)

Patients should be advised that in order to avoid tainted supplements, they should not buy any products that:

- Claim to work like prescription drugs
- Are advertised through mass e-mails
- Are marketed mainly in a foreign language
- Promise weight loss, body-building, or enhanced sexual performance
- Say they are a legal alternative to anabolic steroids

In summary, when advising patients on which supplements to buy, it is important to remind them to focus on the following 3 items:

- Look for supplements with USP or NF on the label; this means they have chosen more stringent requirements for their product.
- Realize that the use of the term “natural” on an herbal product is no guarantee that the product is safe; products can be natural but not safe.
- Take into account the name and reputation of the manufacturer or distributor; if they are a nationally known manufacturer, the products are more likely to have been made under tight quality controls.

Additionally, it may be helpful to research products so that when asked, you can recommend a brand that you feel confident in.

Checklist for your patients:

- Check with your doctor or other health care providers before you try a supplement.
- If you are shopping for an herb- or other plant-based supplement, make sure to find a product that uses only the part of the plant that is thought to be helpful.
- Reputable manufacturers will give contact information on the label or packaging of their products. Ensure the label provides the contact information.
- Avoid products that claim to be “breakthrough” products and those that claim to have benefits but no side effects.
- Try to avoid mixtures of many different supplements; until you understand the way each ingredient affects you.
- Start with only one product at a time. Take note of any side effects you have while taking the product and report any reaction to your doctor, and any serious (causing serious harm, hospitalization or death) events to the FDA. A report can be submitted through:
<https://www.accessdata.fda.gov/scripts/medwatch/>.
- If you have any surgery or procedure planned, including dental surgery, talk with your surgeon about when you should stop taking the supplement (some may require up to 3 weeks prior to surgery).

- During pregnancy or breastfeeding, take only dietary supplements prescribed by your doctor.
- Dietary supplements are not intended for use in place of any prescribed medications unless instructed by your doctor. Speak with your doctor before using supplements and/or stopping your medication.
- Do not depend on any non-prescription product to cure cancer or any other serious disease.
- Follow the dosage limits and recommended duration of treatment on the label.
- Never give a supplement to a baby or a child under the age of 18 years without consulting a healthcare provider or physician.
- Avoid products that claim to treat a wide variety of unrelated illnesses.

Regards,

Kristine Cigna, RPh, PharmD
Community Pharmacist

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Journal Peer Reviewers Needed

Share your expertise as a New Jersey Journal of Pharmacy peer reviewer. Critique articles prior to publication to help ensure the highest standards for our readers. For more information, please contact Maria Leibfried (leibfrim@stjohns.edu) or Rutu Patel (ritu.p.parikh@gmail.com).

Student Intern Reflections:

The New Jersey Pharmacists Association: A Pharmacy Student's World Unknown

By Derrick Ng, 2014 PharmD Candidate, Ernest Mario School of Pharmacy at Rutgers University

"Please describe what you expect to learn from this experience."

That was precisely the question I was asked by my preceptor, CEO Elise Barry, in an email prior to the start of my advanced pharmacy practice experience (APPE) at the New Jersey Pharmacists Association (NJPhA) office in Princeton, NJ. At the time, one can say that I was oblivious, clueless, and unaware as to what NJPhA was or what purpose it served to the state's pharmacy profession. I knew it represented the state in all fields of pharmacy, similar to how the American Pharmacists Association (APhA) operates on a national level- I was more familiar with APhA through participation as a student member in pharmacy school. Beyond that, all I could say was NJPhA advocated for the profession, as most other organizations do for their members; so that was something I expected and hoped to get exposure to.

At the end of the five-plus weeks I spent at NJPhA, I will advocate and recommend this rotation experience with full confidence. I do not believe there are many opportunities for a pharmacy student, or even a practicing pharmacist for that matter, to see the necessity of the diligent efforts of a professional organization. I had the chance to learn and observe first-hand the importance of advocacy, which is especially important in a dynamic profession where impactful laws and regulations are ever-changing and bill proposals and amendments are tossed from left and right on a regular basis. Under

the guidance of Elise and NJPhA legislative counsel Laurie Clark, I frequented the New Jersey State House on an almost weekly basis to attend hearings on current hot topics in the world of pharmacy. I was entrusted to prepare and present background reports on some of the current issues to be relayed to the assemblywoman and other influential parties. I compiled reports that assisted in the scheduling and topic selection for their many continuing education programs. I felt that my professional expertise and perspective as a student and future pharmacist was respected, appreciated, and applied in many projects of the organization. One of the greatest rewards is to know that you were able to effectively contribute just as much as you were able to learn and take away from an experience.

Whether you have an interest in professional advocacy, or you are just looking for a unique experience, the NJPhA rotation will allow you an educational opportunity like no other. Time management, teamwork, and communication skills are just some of the skills that you will apply, practice and develop through the variety of tasks and responsibilities. While it isn't a critical ICU environment, there is just as much for pharmacy students to learn and experience in a field of pharmacy that is relevant and essential to the evolving professional environment in which we are all members. I would like to personally thank Elise Barry, Laurie Clark, and office manager Dorita Allen for the wonderful journey and I wish the best of luck to all future students at NJPhA.

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Student Intern Reflections:

By: Selamawit Teklu, 2014 PharmD Candidate, Temple University School of Pharmacy

A couple of weeks ago I finished a six week rotation at the New Jersey Pharmacists Association (NJPHA). What made my NJPHA rotation different from my other rotations is that, In my other rotations, taking care of my patients was my priority; which I strongly believe is an amazing opportunity and is also one of the main reasons why I chose to become a pharmacist. However, during my NJPHA rotation, I had the opportunity to make the pharmacy profession my priority and work for the different aspects of the pharmacy profession. Before I went to the NJPHA rotation I had taken an elective political advocacy class which gave me a general knowledge of what professional organizations do for their members. My rotation at NJPHA expanded my on political advocacy knowledge and I was also able to learn and be a part of many other tasks that are done in a professional organizations.

During my rotation at the NJPHA, I was able to learn the reason why students and pharmacist should belong to a professional organization. In pharmacy school, pharmacists gain a tremendous amount of knowledge about the medications that are available in the market. Depending on the type of practice, they have the opportunity to dispense medications, administer vaccines, therapeutically manage chronic diseases, participate in collaborative practices, perform MTM, and more. For all of these improvements to come true professional organizations together with members, had to work hard in educating legislators, representing members, supporting bills, networking with key personnel, lobbying at the state and federal levels, and training and informing pharmacists. I feel fortunate to have had the opportunity to see and be a part of some of the above key functions that NJPHA, as a professional organization, does.

One of the most interesting tasks that I did at the NJPHA was help in supporting the "Lowering the influenza immunization age to 7 in NJ" bill. During the first two weeks of my rotation, I had the chance to gather information and help compose a desk letter to educate the legislators and the governor of NJ on why pharmacists should be enabled by the law to administer vaccines to adolescents and children above the age of 7. To do this I had to read the data from the Department of Health and Human Services (DHHS), Centers for Disease Control and Prevention (CDC), APHA, and many other sources. Not only that, but also I had to inform all NJPHA members to contact their legislators and the governor to pass the law. I also had the chance to be present at the New Jersey State House to see the bill pass the Assembly vote. Finally, once the bill was signed by the Governor, I was able to send an e-mail notice to all members of NJPHA informing them that the bill passed. From this experience I learned in practice, how bills pass and become laws. This was amazing.

Before I went on my rotation to NJPHA I always had confusion on the New Jersey (NJ) and Pennsylvania (PA) pharmacy laws. I knew the PA laws because; I work and go to school in PA. However, I didn't have the opportunity to look at the NJ pharmacy laws. One of the things I worked on at the NJPHA was comparing the NJ and PA pharmacy laws, which answered many of the questions I had about the laws. I was also able to learn about how pharmacist can bill for cognitive services, such as ambulatory care pharmacist services, to get paid by the health insurance companies; who don't consider pharmacists as healthcare providers. I had an opportunity to help in the APHA immunization certification live training that NJPHA provides for members. Not only that, but also I was able to attend the NJ Board of Pharmacy meeting, visit a compounding pharmacy, visit a hospital pharmacy, and participate in other interesting things.

My rotation at the NJPHA was an eye opener towards pharmacy politics, healthcare, and many laws that I didn't know about. This rotation has made me more well-rounded and knowledgeable in the pharmacy politics field. I wish my classmates had the chance to do this rotation. My preceptor (Elise Barry) was very knowledgeable, attentive to my educational needs, and a very good role model. Her administrative assistant (Dorita Allen) was very cooperative and helpful too. I am glad that I did this rotation.

Nominations for Second VP and Treasurer Sought

Fire and drive are the attributes of the next individuals who will move into the leadership of NJPhA. Is it you? Do you know a pharmacist who fits the bill? Become a candidate for the NJPhA Second Vice President position, or the Treasurer position.

You can participate in the process in two ways:

- send an email expressing your interest in one of the positions
- nominate a member whom you believe will be a good candidate

All it takes is an email to Permanent Organization Chair, Steve Zlotnick (ccpconsu@aol.com) expressing interest in the particular role. Please add Candidate in the subject line.

The deadline is April 30, 2014.

Cardiovascular Safety Warning for Azithromycin

by Sharon See, Pharm.D., BCPS, FCCP* and David Said

The FDA issued a Drug Safety Communication in the spring of 2013 regarding the risk of cardiovascular adverse events with azithromycin. Specifically, it states that “azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias”.¹ Since that time, the package insert for azithromycin has been updated under “warnings,” citing cardiovascular side effects such as arrhythmias, including ventricular arrhythmias, hypotension, QT prolongation and torsades de pointes.² This article will review the details of the clinical trials that served as the basis for this labeling change.

According to the International Marketing Services (IMS) Institute for Healthcare Informatics, azithromycin was the 11th most prescribed medication and dispensed antibiotic in the United States for 2012.³ Azithromycin belongs to a class of antibiotics known as macrolides, used to treat gram-positive bacterial infections including *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Macrolides bind irreversibly to the 50S subunit of bacterial ribosomes and inhibit translocation of tRNA during translation thereby inhibiting and preventing the growth and reproduction of bacteria.⁴ There are four macrolides currently available for use in the United States: erythromycin, clarithromycin, azithromycin, and telithromycin. The most common side effects of azithromycin include diarrhea, nausea, and abdominal pain.²

Ray and colleagues conducted a retrospective cohort study to determine if patients who took azithromycin, compared to those patients who were either on different antibiotics or no antibiotics at all, would have an increased risk of cardiovascular death.⁵ Cardiovascular death was confirmed by death certificates and defined as death by myocardial infarction, ischemic heart disease, angina and other cardiovascular causes. The cohort study included Tennessee Medicaid patients who were prescribed azithromycin between 1992-2006, were 30 to 74 years of age, had no life-threatening, non-cardiovascular illness, had not received a diagnosis of drug abuse or resided in a nursing home in the previous year, and had not been hospitalized in the prior 30 days. At baseline, participants on azithromycin had a mean cardiovascular disease risk summary score of 9.3. Scores range from 0 (lowest risk) to 19 (highest risk). The antibiotics that were compared with azithromycin were amoxicillin, ciprofloxacin, and levofloxacin. Any person who was at high risk for death from causes unrelated to the possible pro-arrhythmic medication was excluded including, but not limited to, cancer(s), HIV, drug abuse, end-stage illness, organ transplants, and serious neuromuscular disorders.⁵ There

was no indication that this study controlled for patients taking azithromycin for other conditions such as sexually transmitted diseases.

A 5-day course of azithromycin increased the risk of cardiovascular death almost 3 fold compared to patients on no antibiotics (HR 2.88; 95% CI, 1.79 to 4.63; $P<0.001$). Azithromycin did not increase non-cardiac deaths but did increase the risk of death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P=0.002$). In patients with the highest cardiovascular risk scores, azithromycin caused 245 more deaths per 1 million 5-day courses compared to patients on amoxicillin. Cardiovascular disease risk scores take into account baseline cardiovascular disease risk and baseline co-morbidities. When adjusted for propensity scoring, a 5-day course of azithromycin increased the risk of cardiovascular death (HR 2.53; 95% CI, 1.37-4.67) compared to amoxicillin. Azithromycin also showed increased risk of cardiovascular death compared to patients on ciprofloxacin, (HR 3.49; 95% CI, 1.32 to 9.26; $P=0.01$) and a non-significant increase in death from any cause (HR 1.75; 95% CI, 0.91 to 3.37; $P=0.09$). There was no difference in cardiovascular mortality, however, when compared to patients taking levofloxacin (HR, 1.27; 95% CI, 0.66 to 2.47; $P=0.48$). The authors concluded that current use of azithromycin in patients with cardiovascular disease lead to a small increased risk of cardiovascular death in high risk patients.⁵

The results from this study should be interpreted cautiously as this is a retrospective, observational cohort study which cannot prove a causal effect between azithromycin and cardiac death. While the results show an increase in cardiovascular death in the azithromycin group compared to the various groups, the absolute risk is low. For example, while a 5 day course of azithromycin appeared to increase cardiovascular risk almost 3 times compared to no antibiotics, the actual number of deaths was 29 (85 per 1 million courses).

The results of the study conducted by Ray et al,⁵ prompted the initiation of a study funded by the Danish Medical Research Council led by Svanström et al.⁶ They attempted to determine whether or not the use of azithromycin and its increased risk of cardiac death in patients with high baseline risk extended to the general population. Using the Danish National Prescription Registry, investigators compared patients taking azithromycin from 1997-2010 to patients on no antibiotics or penicillin V. This study included Denmark citizens between the ages of 18 and 64 years and excluded those who had been hospitalized or had used any antibiotics within 30 days prior to the study date. The primary outcome was cardiovascular death, and the secondary outcome was death from non-cardiovascular causes. The timing of treatment was defined as current use (1 to 5 days) or recent use (6 to 10 days), similar to the criteria outlined in the aforementioned study lead by Dr. Ray.⁵

The risk of cardiovascular death was significantly increased with current use of azithromycin as compared to no use of antibiotics (defined as a 5-day treatment episode: rate ratio, 2.85; 95% CI, 1.13 to 7.24).⁶ However, when compared with penicillin, azithromycin was not associated with a significantly increased risk (rate ratio, 0.93; 95% CI, 0.56 to 1.55, $P=0.79$). It also did not increase the risk of cardiovascular death with recent (rate ratio 0.75; 95% CI 0.34-1.62) or past use (rate ratio, 0.92; 95% CI, 0.60 to 1.42) of azithromycin compared to penicillin V. The excess number of cardiovascular deaths per 1,000,000 treatment episodes with azithromycin as compared with penicillin V was estimated to -1 (95% CI -9 to 11). Based on these findings, the investigators concluded that azithromycin use was not associated with an increased risk of death from cardiovascular causes in a general population of healthy young and middle-aged adults.⁶

The differences between the two studies are essential to understanding how to extrapolate the results. The patients in the Danish study were younger and healthier compared to the older and more infirm Medicaid population in the initial study by Ray et al, which may make the data more applicable to the general population and may explain why there was an increase risk of cardiovascular deaths in the initial study but not in the latter. Given the evidence in the study by Ray et al, azithromycin may increase the risk of cardiovascular death in older patients with high cardiovascular risk scores but the risk is relatively low. In the younger and generally healthy population, azithromycin should not have the same risk.^{5,6} Before prescribing azithromycin, practitioners should weigh the risk and benefit. When used in appropriate patients, a 5-day treatment with azithromycin should not pose harm.

If patients have cardiac risk factors for cardiac conditions such as arrhythmias, hypokalemia or hypomagnesemia, have current prolonged QT intervals or are on medications that may prolong QT intervals, prescribers may want to reevaluate their antibiotic choice. Pharmacists can make recommendations for alternative antibiotics and can advise patients taking azithromycin that signs and symptoms such as nausea, vomiting, weakness and muscle cramps may indicate an electrolyte abnormality which could increase the risk of cardiac arrhythmias.

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Sports-related Concussions: What Pharmacists Need To Know

by Nicholas A. Favatella, Pharm.D. Candidate and John L. Colaizzi, Ph.D., R.Ph.

It is estimated that 1.6 to 3.8 million sports-related concussions occur annually in the United States.¹ The majority of concussions are self-limiting injuries, but serious and even catastrophic outcomes are possible, and the long-term effects of multiple concussions are unknown.² Medical dictionaries define “concussions” as injuries from impact with an object resulting from a blow or a fall and leading to partial or complete loss of function. The type of concussions that are the focus of major concern in sports are concussions of the brain, also called cerebral concussions, resulting from a violent shock or jar to the head, or a fall that impacts the end of the spine with force sufficient to be transmitted upward.^{3,4} A recent seminal report of the American Academy of Neurology defines concussions as clinical syndromes of biomechanically induced alterations of brain function typically affecting memory and orientation, which may involve loss of consciousness.⁵ A brain with neurological damage is more susceptible to additional injury, which explains the concern and danger associated with prematurely returning to play. Multiple concussions can lead to serious neurological problems, some of which can be permanent and debilitating.

Sports-related concussions are extremely common, and they are not limited to occurrences among professional athletes exclusively, but are also widespread among high school athletes. Athletic activities among elementary school-age children, middle school, high school and college students, and participants in community-based amateur sports programs, often result in concussions that may be brought to the attention of pharmacists, as athletes, parents, family members and coaches approach their pharmacists for advice. The prevalence of concussions in sports increased significantly throughout the 20th and 21st centuries, as has our understanding of their significance. As a result, there has been an increase in safety regulations as various sports have implemented many preventive policies and guidelines. Major League Baseball made batting helmets mandatory in 1971 to prevent being hit by a pitched ball.⁶ Currently, in college and high school baseball, home plate collisions between players are prohibited, forcing the runner to either slide into home plate, or veer away from the play. Due to recent collisions and consequent head injuries, this rule is now being discussed in for implementation into professional baseball as well.⁷ The National Hockey League has required players to wear helmets since 1979, due to serious head injuries and even deaths resulting from such injuries.⁸ Perhaps most indicative of the increased prevalence of concussions in sports are the actions of the National Football League (NFL).⁹ Helmets were first introduced into the NFL in the 1920s, but were not made mandatory until 1943. Improvements were made to the preexisting helmets in subsequent years between 1949 and 2002. Additionally, game-play rule changes have also been implemented, especially in recent years. In 1982, it became prohibited to tackle a defenseless player leading with the tackler’s helmet and striking the player’s neck or helmet. This rule was later expanded to prohibit a tackle to a player’s head or neck when leading with the tackler’s forearm and shoulder. This rule became more strictly enforced in 2010. Beginning in 2011, a play is considered finished as soon as a

player’s helmet comes off. To summarize the importance the NFL is now placing on concussion, “the NFL has allocated more than \$100 million over the next decade to medical research with the vast majority going to concussion-related research.”⁹

Hospital emergency department visits for sports-related injuries, including concussions, among children and adolescents have increased by 60 percent over the past decade.¹⁰ Currently available data for the overall incidence of concussions (concussion rates) in high school and college-level competitions for commonly played sports indicate that football, followed by soccer, produces the highest concussion rates (CRs) among high school male athletes, while soccer, followed by basketball, produces the highest CRs among high school female athletes. Football, followed by ice hockey, followed by soccer, produces the highest CRs among male college-level athletes. Soccer, followed by basketball, followed by baseball/softball produces the highest CRs among female college-level athletes.⁵ A particularly worrisome aspect of the increased prevalence of sports-related concussions is that many individuals experiencing traumatic brain injury (TBI), a term encompassing all head related injuries, are not aware of it. This leads to concussed players returning to the field of play too soon, and experiencing more serious injuries.

Symptoms of Concussion

The symptoms of concussion vary with location and extent of injury, whether the injury was the result of a direct blow to the head or to another part of the body, and whether the concussion is mild or severe. The most common symptoms of concussions are (1) symptoms affecting cognition and thinking, such as loss of consciousness, slurred speech, or difficulty in thinking clearly, concentrating or remembering new information; (2) physical symptoms such as headache, blurry vision, dizziness, nausea and vomiting, sensitivity to noise or light, and fatigue; (3) symptoms affecting emotional state, such as anxiety, depression and irritability; and (4) altered sleep patterns including insomnia or hypersomnia.¹¹ Some of these symptoms may be evident immediately after the concussion occurs. Others may not appear for days or even months after the injury, or until the patient resumes practice or a full schedule of normal activities. Symptoms of post-concussion syndrome (PCS), one of the long-term effects of multiple concussions usually appear within seven to ten days of the injury. Most PCS patients experience symptoms for three months, but in some patients symptoms may persist for over a year. These symptoms mainly include depression, memory loss, migraine, dizziness, malaise, and mood swings. The danger for players with PCS is that an additional TBI can cause cerebral swelling and even death.¹² PCS sidelines players for extended periods, and may even force an athlete’s early retirement.¹³

The Centers for Disease Control and Prevention (CDC) points out that there are certain danger signs associated with the symptoms of concussions that should prompt a visit to a hospital emergency department right away which include a headache that gets worse and does not go away, repeated vomiting, slurred speech, seizures,

altered pupil size, and loss of consciousness, even if brief.¹¹ The CDC reports that a substantial number of deaths and cases of permanent disability result each year from TBI, but the severity of such injuries ranges from mild TBI to life-threatening injuries. Mild TBIs usually cause a brief onset of symptoms, whereas severe TBIs result in extended periods of unconsciousness or other symptoms.¹¹ Rest and avoidance of physically demanding activities promote brain healing following a TBI, and patients who have experienced a TBI should return to normal levels of activity only gradually, and upon the advice of a qualified health care professional. Recovering patients must avoid any alcohol, and should only take medications, whether prescription or OTC, as advised by qualified health care professionals.

Concussion Guidelines

In 1997 The American Academy of Neurology (AAN) published guidelines for the management of concussions in sports; however, knowledge related to the best practices for the diagnosis and treatment of sports-related concussions has expanded significantly since 1997.^{14,15} “Sports Neurology” has emerged as a subspecialty, and the involvement of neurology-specialist physicians in professional sports such as the National Football League (NFL) and the National Hockey League has become routine. In 2009, the National Football League Players Association (NFLPA) urged the NFL to develop concussion guidelines designed to protect players. In 2013, the AAN published an extensive updating of guidelines, described as evidence-based guidelines, for the evaluation and management of sports-related concussions.⁵ The 2013 updated guidelines are focused on four areas of concern:

- Factors that increase or decrease the risk of sports-related concussions.
- Diagnosis techniques to ascertain the seriousness of concussion injuries.
- Clinical factors identifying players who are at risk for post-concussion impairments and recurrent concussions.
- Interventions that enhance recovery and avoid long-term adverse effects.

The new guidelines have been endorsed by the National Association of Emergency Medical Service Physicians, the American Football Coaches Association, the National Association of School Psychologists, the National Athletic Trainers Association, and many other groups. Christopher Giza, M.D., one of the authors of the new guidelines, summarized its importance in the following statement:¹⁶

“We’ve moved away from the concussion grading systems we first established in 1997 and are now recommending that concussion and return to play be assessed in each athlete individually.

There is no set timeline for safe return to play.”

The new guidelines emphasize several key points. Any athlete experiencing concussive symptoms should be immediately removed from play, and should not be allowed to return to play that day, and until seen by a qualified licensed health care professional (LHCP). According to the 2013 guidelines, the return to play timeline must be individualized based on the symptoms and

cognition level of the athlete. Another recommendation is that post-concussive return to play must be gradual, and that there is no specific set time, since each individual is a unique case. High school athletes have a greater susceptibility for multiple TBIs;⁵ therefore the guidelines have included recommendations which distinguish between high school and professional athlete-type concussions. Concussions occurring in high school athletes and younger athletes in general require a slower return to play due to a slower neurological recovery. The new guidelines also state that while an athlete should be removed from play immediately after a concussion, little evidence exists to indicate that absolute rest is required. Activities that do not worsen and do not create potential for recurrent concussion may become a part of post-concussion management.¹⁶

Concussion Risks⁵

Athletes and their family members should be made aware of risk factors and how to minimize them. There is insufficient evidence to determine if age and level of competition affect risk. Since there are more male players than female players, the total number of concussions for all combined sports is greater for males, but a relationship between concussion risks and gender has not been clearly demonstrated for many sports.⁵ However, concussion risk appears to be greater for female athletes in soccer and basketball. There is considerable evidence to indicate that football, rugby, hockey and soccer pose greater risk of concussion than other sports. The use of well-fitted headgear of approved design has a protective effect especially in rugby. Although protective headgear seems to reduce the risk of concussion in sports like football, hockey and rugby, there is no strong evidence to indicate that mouth guards reduce the risk of concussions, or that one type of football helmet is superior to another. There is no general agreement that concussion risk is greater for one specific position compared to another in most major team sports, although in college football, linebackers, offensive linemen and defensive backs appear to be at greater risk. Increased body mass and decreased training time (per week) are also risk factors known to increase risk.⁵ Any athlete who has a confirmed or suspected concussion must be immediately removed from play in order to minimize the risk of additional injury.

Diagnosing and Assessing Suspected Concussion⁵

No single test should be the sole basis of a concussion diagnosis. Several standardized symptom checklists are recommended as part of the evidence-based guidelines. In general, physicians with expertise in concussion are not available at most sports events where an injury is sustained, and the initial assessment may be made by an athletic trainer or school nurse. In amateur sports, the coach or other available non-physicians make the initial assessment. Specific concussion assessment tools can be implemented by non-physicians, including pharmacists who have been properly trained in the utilization of the various assessment methodologies. Any athlete who is suspected of having sustained a concussion should be immediately removed from play in order to minimize the risk of further injury, and the athlete must not be allowed to return to play until an experienced and properly qualified licensed health care provider (LHCP) with training in the diagnosis and management of concussion has examined the athlete. A LHCP is defined as an individual who has acquired

knowledge and skills relevant to evaluation and management of sports concussions and is practicing within the scope of his or her training and expertise. The examination should include a competent determination as to whether a more-severe traumatic brain injury has occurred.

Computed tomography (C-T) scanning is not generally useful to diagnose sports-related concussion, but might help to rule out more serious traumatic brain injuries including intracranial hemorrhage that could lead to a subarachnoid hematoma, particularly in cases where the athlete has lost consciousness or experienced a persistently altered mental status. Some of the diagnostic tools or checklists described in the evidence-based guidelines include the following approaches: (a) simple checklists of symptoms; (b) assessment of orientation, individual memory concentration, and delayed recall; (c) neuropsychological testing of memory, reaction time, and speed of cognitive processing; (d) balance assessment for postural stability. Once there has been confirmation of the presence of a concussion, it is important to attempt to identify athletes who are at increased risk of severe or prolonged early impairments, neurological catastrophe (*e.g.*, subarachnoid hemorrhage), or chronic neurobehavioral impairment. Some patient characteristics that are helpful in determining if an athlete who has sustained a concussion is possibly at risk for one of these more serious outcomes include: (a) a history of prior concussions; (b) early post-traumatic headache; (c) early amnesia; (d) younger age; (e) dizziness; and (f) ongoing (prolonged) clinical symptoms.

Post-concussion Interventions to Enhance Recovery⁵

For athletes who have suffered a documented or suspected concussion, interventions and treatment options designed to minimize the risks of recurrent concussion or long term post-concussion sequelae (especially headache and persistent confusion) and complications must be considered and implemented whenever appropriate. LHCPs should provide counseling and health-related information to athletes and, where appropriate, to athletes' families, regarding concussion risks and post-concussion management. Athletes who have sustained a concussion must not return to play until the athlete has been examined by a qualified LHCP who is able to recognize more severe traumatic brain injuries, and who has determined that the concussion has been resolved. Before being permitted to return to play, athletes who have sustained a confirmed concussion should be asymptomatic when off medication. Decisions about how soon athletes should be permitted to return to play should be made more conservatively for younger athletes such as those of high school age or younger.

The first ten days after a concussion appear to be the period of greatest risk of sustaining another concussion, so decisions about returning to play sooner than ten days post-concussion should be made cautiously. An approach that is thought to benefit some athletes who are recovering from a concussion injury is "cognitive restructuring." This approach involves education, reassurance and a determination of whether symptoms are definitely related to the concussion injury or due to some unrelated reason. Cognitive restructuring is thought to offer some benefits in reducing post-concussion complications. Athletes who have a history

of multiple concussions should be counseled about the risk for developing permanent or long-term neurobehavioral or cognitive impairments.

Pharmacists and the New Concussion Guidelines

It has been well documented that pharmacists are among the most accessible and most trusted health care providers.¹⁷ Community pharmacists are in a position to counsel and educate parents and others concerning the important and relevant points highlighted in the most recent guidelines concerning sports-related concussion injuries that occur in elementary, middle school or high school athletics, community-based athletic competitions, and college-based sports. The Code of Ethics for pharmacists states that "a pharmacist serves individual, community, and societal needs," so providing counseling in the important area of prevention and treatment of concussion injuries in sports is an appropriate service for pharmacists to perform. It is also increasingly common for a pharmacist to be stationed in the emergency department of hospitals where athletes who have suffered a traumatic brain injury are likely to be taken for urgent care. Pharmacists are also increasingly involved as part of a health care delivery team in various out-patient ambulatory care clinics that might be called upon to treat athletic injuries. Pharmacists are qualified to counsel patients and caregivers on the optimal use of medications to treat athletes who have suffered a concussion. The use of drugs to treat athletes with such injuries is mostly limited to symptom management.¹⁸ Pharmacists can offer guidance on the selection of NSAIDs or acetaminophen or other analgesic-type treatments to alleviate pain and discomfort associated with athletic injuries in general. Pharmacists should advise patients who have suffered a traumatic brain injury to avoid alcohol, and also to avoid the use of narcotic analgesics since they pose the risk of addiction. Patients experiencing short term nausea, vomiting or vertigo can be counseled on the availability of prescription or non-prescription medications to alleviate such symptoms. Pharmacists can advise physicians about drugs like methylphenidate or donepezil in cases of memory or concentration problems. Drugs that act as anxiolytics and antidepressants may be helpful in dealing with symptoms affecting emotional state, such as anxiety and depression, and pharmacists are aware of effective drugs in these categories, as well as the various new drugs for treating insomnia.

Legislation recently passed in California gives pharmacists "provider status," and this trend is likely to spread to other states.¹⁹ Provider status represents a major advancement and opportunity for pharmacists and may eventually enable pharmacists to become more involved in concussion intervention. This will give pharmacists the opportunity to evaluate patients such as concussed high school athletes, and potentially increase the role of pharmacists in concussion management. Pharmacists have an important role to play in serving the needs of patients who may have experienced a sports-related concussion. An awareness of the information contained in the new guidelines will be helpful to pharmacists at a time when the incidence of sports-related injuries is widespread, and when society is increasingly aware of and concerned about the dangers such injuries present.

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Practice Spotlight:

Journal: What is CERT?

Sharon: CERT stands for Community Emergency Response Team. Many cities and towns across the United States have CERTs which are made up of local community members who volunteer to help their neighbors during major disasters, floods, or other emergencies. Because CERT volunteers live in the community, when an event occurs, they are often the first people on the scene, even before first responders arrive. We educate the community on disaster preparedness, and are trained in basic disaster response skills, such as fire safety, light search and rescue, team organization, and disaster medical operations.

Journal: How did you become involved in CERT?

Sharon: I learned about CERT after volunteering during Hurricane Sandy in Hoboken. Hoboken CERT mobilized their members during Sandy.

Journal: What are the roles of a pharmacist in CERT?

Sharon: Pharmacists can use their expertise to help determine the medication needs of the community in distress. I helped organize a pharmacy command center after the hurricane. We mobilized volunteers to go to senior citizen apart-

ment buildings to determine if they had any medical or medication needs. I created a process that included a list of specific information volunteers needed to obtain from patients to fill 3 day emergency prescriptions and a plan to deliver medications to them. We filled 206 prescriptions in 2 days!

Journal: How can pharmacists or other community members find out about participating in CERT in their community?

Sharon: You can go to <http://www.fema.gov/community-emergency-response-teams> and find a nearby CERT program.

About the Author:

Sharon See, Pharm.D., is an Associate Clinical Professor at St. John's University College of Pharmacy & Health Sciences and Clinical Faculty with the Beth Israel Residency in Urban Family Practice in New York City. She is also involved in her community CERT. Although she initially volunteered as a lay person, she quickly identified the need for her pharmacy expertise during SuperStorm Sandy in 2012. Her participation has been highlighted in The Annals of Family Medicine (<http://annfam.org/content/11/6/571.full>) and AOL news (<http://jobs.aol.com/articles/2013/10/28/heroes-of-superstorm-sandy-prescriptions-filled-lives-saved/>). The NJ Journal of Pharmacy interviewed Sharon about her experience as a CERT member in Hoboken, NJ.

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Warfarin and Dietary Interactions: Where is the Evidence?

by Carmela M. Silvestri RP, CCP

Introduction

Warfarin is a vitamin K antagonist used for anticoagulation in the prevention and treatment of venous thromboembolism. Although there are other oral anticoagulants available in the United States, warfarin remains the mainstay of chronic anticoagulation therapy.¹ Reports of drug-nutrient interactions with warfarin make it difficult to predict the effects of diet and supplements on international normalized ratio (INR).

Warfarin has the dose dependent capacity to decrease the thrombotic activity of hepatic vitamin K dependent coagulation factors (including factors II, VII, IX, and X) by 30%-50%.² Because of the narrow therapeutic window, warfarin's pharmacokinetic and pharmacodynamic properties can be affected by ingestion of food and herbal products which interfere with warfarin hepatic metabolism, absorption and bioavailability, or which have their own propensity to affect coagulation. The following are some potential mechanisms by which these interactions may take place:

- Alterations in warfarin metabolism by induction or inhibition of CYP metabolic enzymes
- Competitive alterations in protein binding
- Increased vitamin K intake
- Synergistic potentiation of bleeding by inhibition of platelet aggregation.

Metabolism

Warfarin is metabolized by hepatic CYP enzymes primarily by 2C9, 1A2 and 3A4, and, to a lesser extent, 2C19, 2C8, 2C18.³ Food products, including herbs and vitamins which actively induce or inhibit these enzymes can alter the clearance of warfarin and result in corresponding changes in INR. Oral warfarin doses supply a racemic mix of the R-isomer and S-isomer which inhibits vitamin K epoxide reductase. R-warfarin is metabolized primarily by the CYP 1A2 and 3A4 enzymes. S-warfarin, which is absorbed and cleared more rapidly than the R isomer, has the greater biological activity (reported to be about 5 times more active than the R counterpart³) and is metabolized primarily by CYP 2C9.

St John's wort (*Hypericum perforatum*) has been linked to induction of all three of these metabolic enzymes⁴. The induction of these enzymes results in an increased warfarin requirement in order to achieve a therapeutic INR. Initiation of St. John's wort by a person who has a stable INR can cause an increase in metabolism, decrease in INR and elevated risk of clot formation⁵. Conversely, the INR should be monitored closely when a person stabilized on the combination stops St. John's wort, as it may increase².

In two in vitro studies, garlic was shown to inhibit CYP2C9, CYP2C19 and CYP3A4.⁶ The effect varied with the handling and preparation of the herb. Garlic is also suspected of possessing antiplatelet properties.³ A double-blind, randomized, placebo controlled trial of AGE (Aged Garlic Extract) was completed by 48 patients stabilized on warfarin. Results did not show a statistically significant increase in potential bleeding or thrombotic events.⁷

An in vitro/vivo study was conducted using 5 brands of cranberry juice.⁸ Inhibition of CYP2C9 enzyme activity in human hepatocytes was found to be dependent on the strength and brand of cranberry juice used. Only one of the five brands tested showed significant concentration dependent inhibitory activity.⁸ This juice was then used in an open label, prospective, randomized cross-over trial of 16 healthy subjects who received three 240mL glasses of water or double strength cranberry juice followed by 10mg of warfarin. Results, however, did not show a difference in warfarin levels.

A prospective, double blind trial of 30 patients stabilized on warfarin, who were randomized to receive 8oz of cranberry juice or placebo each day for 14 days, did not show consistently elevated INRs or warfarin levels in the treatment group.⁹ In contrast, a case study reported that a woman stabilized on warfarin with an average INR of 2.0(1.6-2.2), consumed 1.5 quarts of cranberry juice for 2 days prior to an elevated INR of 4.6. After 14 days without cranberry juice her INR decreased to 2.3. Several months later, after maintaining an average stable INR of 2.1(1.4-2.5), she returned for follow-up, having consumed 2 quarts of cranberry juice cocktail for 3-4 consecutive days. Her subsequent INR had risen to 6.5 showing an elevation in INR with high consumption cranberry juice on re-challenge.¹⁰

Protein Binding

Warfarin is approximately 99% bound to plasma proteins.³ Substances which have a greater affinity for these protein binding sites may reduce the percentage of warfarin bound. An in vitro study on plant derived Quercetin found the bioflavonoid to compete with warfarin for the same binding site on human serum albumin, suggesting that it may have the potential for displacement.¹¹ Sources of this substance, which is described as having antioxidant and anti-inflammatory properties, include dietary supplements, red wine, apples, berries, green tea, ginkgo biloba, St. John's wort and American Elder.¹²

An 85 year old man using warfarin started taking St. John's wort on his own.¹³ Within one month he presented to the ER with an active gastrointestinal bleed and INR of 6.2. The authors of the report commented on the unusual increase in INR with this combination and considered it a result of protein displacement.¹³ St. John's wort is usually associated with greater warfarin needs attributed to increased metabolism.

A case report was presented linking a high protein, low carbohydrate diet to a 22.2% increase in warfarin requirement in order to maintain previously stable INRs.¹⁴ A second patient required a 30% increase in dose to maintain anticoagulation. Both patients required titration back down to the original dose when they returned to a more balanced diet. It is postulated that the increase in dietary protein may have increased the protein binding potential, requiring a higher dose in order to maintain free warfarin levels.

Vitamin K

Some multivitamin, herbal and dietary supplements contain vitamin K. A case series of 3 patients who were vitamin K depleted,

showed that there was a change in INR with and without multivitamin supplementation with Centrum Plus containing 25mcg of Vitamin K₁.¹⁵ The first patient, stabilized with a mean INR of 2.9 discontinued her multivitamin with no other dietary changes. In 2 weeks, she presented with flank pain, hematuria and an INR of 13.2. A second patient with an INR stabilized at mean of 2.8 started the same supplement. In 2.5 weeks the INR had decreased to 1.7 without other dietary changes. The third patient was also stabilized with mean INRs of 2.54. Two weeks after starting multivitamins his INR had dropped to 1.64. In their conclusion, the authors of this case series mention that the patients were advised to limit the daily intake of vitamin K to less than 250mcg in order to prevent fluctuations in INR during warfarin therapy. Although the dose contained in these multivitamin supplements was low, 25mcg/day, the authors considered that this represented a significant portion of their daily intake which may have been the reason why it had a measurable effect on anticoagulation. Patients who are vitamin K depleted, possibly because they are trying to avoid interaction, may be more susceptible to minor changes in intake.

Unsuspected dietary and herbal sources of Vitamin K can also impact warfarin therapy. A case report described a 44 year old man who had an INR of 3.2 and 3.79 one month later. Twenty-two days after the second assessment he presented to clinic with an INR of 1.37. It was later discovered that he had been drinking one half to one gallon of green tea each day for one week prior to the detected drop in INR.¹⁶ His INR was 2.55 following discontinuation of the tea.

Additive Effects

A 2012 review of anticoagulant activity of dietary supplements by Stanger et. al. reported evidence linking garlic, ginko biloba, ginseng, fish oil, feverfew, dong quai, glucosamine, and vitamin E to antiplatelet activity which could provide an additive effect when combined with warfarin.¹⁷ The authors also mention ginger, garlic, policosanol, magnesium, coenzyme Q10, lycopene, L-arginine, taurine and selenium, as dietary supplements which may affect platelets and represent a risk for bleeding. Passion flower and chamomile contain coumarin derivatives. Although the review included both in vitro and in vivo studies, the authors conclude that, "there is no clinical data demonstrating that any unadulterated dietary supplement adversely affects hemostasis when taken alone or in combination with blood-thinning medications". They acknowledge that further research is needed to investigate case reports.

A 67 year old patient with a previously stable INR presented with an increase from 2.8 to 4.3 after increasing her fish oil supplement from 1,000mg to 2,000mg/day for 1 month.¹⁸ In another case, a 70 year old patient was admitted to the ER with an upper respiratory infection and discharged home without antibiotics. Her INR in the ER was 3.6. Five days later she returned with an INR of 7.9. After the first visit to the ER, she had increased both her consumption of chamomile tea and application of a chamomile-based skin lotion from 1-2 to 4-5 times each day.¹⁹

In 2013, a retrospective, single center, observational cohort study was reported on 556 warfarin patients who were included in an on-going prospective study involving oral anticoagulation and vitamin E levels. The analysis found a corresponding increased risk of bleeding events with each increasing quartile of vitamin E blood levels. The quartile with the highest serum levels of vitamin E experienced

the greatest number of bleeding incidents (HR=2.689;95% CI,1.351 -5.251; p=0.005) as compared to the lowest quartile.²⁰ Until more data is available, the researchers suggest caution in Vitamin E supplementations for persons treated with warfarin.

Various or Unknown Mechanisms

A recent study of 250 patients with atrial fibrillation treated with warfarin reported that those patients who consumed dietary herbs (including garlic, ginger and Chinese wolfberry) or alcohol more than 4 times per week spent less time in their targeted INR range than patients whose consumption was less frequent.²¹ This study did not account for volume consumed or analyze response to specific agents. Case reports involving the consuming of large quantities of a single dietary component have also been reported. Thirteen patients in Puerto Rico, where backyard mango trees are frequently found, with a daily mango intake of 1-6 mangoes/day for 2 days to one month prior to INR assessment at anticoagulation clinic, were found to have a 38% increase in INRs on average.²² A reassessment of INRs 2 weeks after mango ingestion ceased showed INRs that had returned to the target range. Large amounts of avocado are considered highly likely to decrease the effects of warfarin.^{1,23}

Quality of the Evidence

Databases often disagree on the clinical relevance of the available data. A comparison of warfarin interactions in commonly used drug references was conducted.²³ Clinical Pharmacology, Micromedex, ePocrates and the FDA approved 2007 update of the Coumadin prescribing information from Bristol-Meyers Squibb Company, were searched for interactions. The investigators found considerable discrepancies in documentation and rating of clinical significance of interactions. Among the four sources, 91 dietary supplements and 16 food items were listed as having interaction potential. The variations ranged from only 7 dietary supplement/food entries in ePocrates to 64 entries in Micromedex.

Most data is not from controlled studies but rather is derived from case reports. In 2005, Holbrook et al published a systematic overview of warfarin drug and food interactions.²⁴ The authors concluded that high quality studies correlate to reports of weak or absent interactions as compared to case reports which are linked to significant interactions. The low frequency with which these interactions are witnessed and reported make it difficult to determine relevance and may be the cause of disagreement among published reviews and references.

Patient Education

Patients starting on warfarin therapy have access to healthcare provider and web-based information which encourage dietary moderation and consistency, such as Mayo Clinic, National Institutes of Health Clinical Center (Medline). The US Department of Agriculture has posted a 23 page listing of dietary items and their approximate Vitamin K₁ (phylloquinone) content which can be accessed by a link provided on the Medline Plus web-page on Vitamin K.²⁵ This can help patients to identify high content foods and portion sizes to make it easier to maintain a relatively consistent daily Vitamin K intake.

The message, however, of dietary awareness may not always reach the patient. A survey on self-reported knowledge about non-vitamin dietary supplements, was offered to patients treated with warfarin in one of 4 geographically diverse anticoagulant clin-

ics in the US. Of the 1203 patients completing the survey, 35% ($p < 0.001$) stated that no one had talked to them about supplements. Use of non-vitamin dietary supplements was reported by 31%.²⁶ A single center survey of 100 patients with atrial fibrillation who were receiving warfarin reported similar results. Smith, et. al found in their study, that only 48% of patients surveyed reported being aware of the potential interactions of herbal supplements with their treatment.²⁷ In a single center survey 44% of 314 patients treated with warfarin reported use of a complementary and alternative medication (CAM) at least weekly.²⁸

Discussion

Complementary and alternative medications in the form of traditional and non-traditional dietary vitamin and herbal supplements are frequently used by those suffering from heart disease. Dietary products are not subject to the FDA scrutiny of testing, approvals, and quality control procedures which ensure potency of approved drug products. Chemical composition of herbs and food products may vary. Few available clinical trials take into account differences such as product variability and there are not enough quality studies to determine safe dosing of supplements in combination with warfarin therapy. Without detailed analysis, including concentration/dose of the chemical entity which provides the interaction or synergistic properties, it is hard to draw conclusions from these studies. There is also the consideration of combined dietary agents which may confound results.

Most of the case studies discussed here involve a lack of moderation in dietary intake. Cases such as those of patients who ingested 1.5 quarts of cranberry juice, 1/2-1 gallon of green tea, 5 cups of chamomile tea, or 5-6 mangoes each day illustrate that interactions seem to be reported when dietary components are ingested in excess. Other reports are the result of dietary changes made without anticipated follow-up. The FDA approved medication guide mentions changes in diet or supplements as something which patients need to communicate to the practitioner monitoring their therapy.³ With the healthcare professional's knowledge, a new routine dietary supplement could be started safely by monitoring the INR to allow for warfarin adjustments as needed.

Summary

Case study reports indicate that *some forms* of the dietary supplement in *some doses* will interact with warfarin in *some patients*. One factor that many of these case reports share is a change from a consistent diet or moderation in intake. On starting warfarin therapy, all patients should be counseled about the importance of a **consistent diet**,³ and advised to speak to their healthcare practitioner prior to making any changes to their diet or CAM.² For now, frequent monitoring of INR (at least every 4 weeks) with warfarin dose adjustments as necessary continues to be recommended.¹

Further studies, focused on dose and chemical content, are needed in order to fully understand the scope of dietary products which have the ability to upset the delicate balance needed for consistently safe and effective anticoagulation with warfarin.

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Electronic Cigarettes: Evaluating the Risks vs Benefits

by Asha Gupta, PharmD, RPh

Learning Objectives:

After participating in this continuing education activity, pharmacists and pharmacy technicians shall be able to

- list options for tobacco harm reduction
- describe the procedure for utilizing e-cigarettes
- list FDA concerns with the use of e-cigarettes
- compare and contrast advantages and disadvantages of e-cigarette use and conventional cigarette use

Lately, consumers of all ages have been inundated with radio and television commercials, celebrity advertisements, and we have even seen them being used indoors, in public areas – why are e-cigarettes gaining popularity? This article aims to shed light on these battery-operated nicotine delivery devices, commonly known as “e-cigs.”

I. Background

Cigarette smoking and exposure to secondhand smoke cause more than 440,000 deaths (one out of five Americans) each year.¹ In 2004, the World Health Organization estimated that 5 million adults over the age of 30 died from direct tobacco use (smoking and smokeless) which amounts to one death every six seconds.²

Tobacco consumption is the single most avoidable cause of premature mortality in the world.³ Smoking-related diseases include cancer, cardiovascular diseases, and respiratory diseases.² These illnesses develop due to combustion from the burning of tobacco which results in noxious smoke disseminating throughout one’s body with each inhalation of a cigarette. This smoke is not only harmful to the primary user but also to people and objects around the smoker, referred to as secondhand and thirdhand smoke. Despite knowing the facts, consumers continue to contribute to this \$90 U.S. billion tobacco market⁴ most likely attributable to nicotine addiction and bio-behavioral habit.

To help kick this habit, there are now a few options that fall under the category, tobacco harm reduction (THR): smoking cessation pharmaceuticals, smokeless tobacco (known as “snus” in Sweden) or electronic nicotine delivery devices (ENDD).⁵ **Table 1** displays some of the smoking cessation agents that are currently available in the United States, which include nicotine replacement therapy (NRT) and prescription drugs that are approved by the United States Food and Drug Administration (FDA). The use of NRT and smoking cessation medication use have shown to double quit rates⁶, but nearly 93% of smokers relapse within 6 months of NRT alone.⁷ The advent of “e-cigs” may help defeat the bio-

Table 1

Smoking Cessation Agents Currently Available in the United States				
FDA-approved indications	Smoking Cessation	Depression	Withdrawal Symptoms (ie, nicotine craving)	Recommended Adjunct for Behavioral Smoking Cessation Program
Behind-the-Counter				
nicotine polacrilex gum	X		X	
nicotine polacrilex lozenge	X		X	
nicotine patch	X		X	
Prescription				
nicotine inhaler	X		X	X
nicotine nasal spray				X
bupropion	X	X		
varenicline tartrate	X			
nortriptyline	X	X		
FDA = United States Food and Drug Administration. *This chart is not all-inclusive. Source: Resource Guide: 2013 – Top Drugs for Smoking Cessation. ⁸				

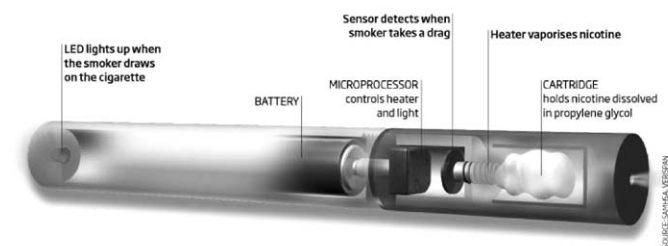
chemical and behavioral aspects of smoking because they deliver vaporized nicotine through a device that looks and feels like a cigarette.⁵ However, THR opponents are concerned that non-tobacco interventions and alternative tobacco products will deter smokers from quitting smoking.

A major concern for the FDA is not only the lack of substantial data to support the safety and efficacy of e-cigarette use, but also the susceptibility of the youth to use tobacco. The National Youth Tobacco Survey (NYTS), conducted in a sample of students in grades 6-12 from all 50 states and the District of Columbia, brought forth some shocking revelations. Among middle school students, ever e-cigarette use increased from 1.4% to 2.7% during 2011–2012 ($p<0.05$); current e-cigarette use increased from 0.6% to 1.1% ($p<0.05$), and current use of both e-cigarettes and conventional cigarettes increased from 0.3% to 0.7% ($p<0.05$). Among high school students, ever e-cigarette use increased from 4.7% to 10.0% during 2011–2012 ($p<0.05$); current e-cigarette use increased from 1.5% to 2.8% ($p<0.05$), and current use of both e-cigarettes and conventional cigarettes increased from 1.2% to 2.2% ($p<0.05$).⁹ Although e-cigarettes are marketed for adults ages 18 and older, flavors such as “chocolate” and “milkshake” could easily entice minors to try and use e-cigarettes.

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) became law under the Obama administration on June 22, 2009. Since then, the FDA gained authority to regulate manufacturing, distribution, and marketing of tobacco products for adults 18 years and older. The FDA, however, cannot: ban certain specified classes of tobacco products, require the reduction of nicotine yields to zero, require prescriptions to purchase tobacco products, or ban face-to-face tobacco sales in any particular category of retail outlet.¹⁰ The FDA is currently in the process of expanding its jurisdiction over e-cigarettes, which would incur restrictions on production, advertising, flavorings and online sales.⁴ In addition, as of 2013, the e-cigarette industry also has to abide by the American e-liquid Manufacturing Standards Association (AESMA) to ensure quality, safety and transparency in the manufacturing of e-liquids.¹¹ Until further notice from the FDA, the state of New Jersey prohibits e-cigarette use in 100% smoke-free venues such as non-hospitality workplaces, restaurants and bars.¹²

II. An Introduction to the “Vaping” Phenomenon

E-cigarettes are rapidly increasing in use and are perceived to be safer than conventional cigarettes. However, “vaping” with e-cigarettes also bring impending risks.



Components of an e-cigarette: Inhaler (mouthpiece) contains a disposable and refillable cartridge full of liquid nicotine; Atomizer (microprocessor) which heats and vaporizes the liquid nicotine;

LED light to simulate “lighting up” and to signal battery power of rechargeable lithium battery.⁵

Potential Uses: Marketed as an alternative to smoking cigarettes for adults 18 years and older. Tobacco harm reduction, smoking cessation and preventing relapse, medical treatment, recreation. *Currently, e-cigarettes are not FDA-regulated.*⁵

E-liquid Ingredients: nicotine dissolved in propylene glycol or vegetable glycerol, along with water and flavoring excipients.⁵ Some brands contain propylene glycol-free and FCC^{1*}¹³ grade vegetable glycerin.¹⁴

E-liquid Testing

It is important to understand that upon heating of an e-liquid by the atomizer, the oxidation of propylene glycol or glycerol can form potentially toxic compounds. An FDA-sponsored testing of 18 e-cigarette cartridges detected diethylene glycol, formaldehyde, acetaldehyde, and acrolein, but the levels in the e-cigarette vapors were substantially lower than in cigarette smoke.¹⁵ E-cigarette vapor also contains various levels of carcinogenic tobacco-specific nitrosamines (TSNAs). A series of analyses by Cahn and Siegel determined that the TSNA levels found in e-cigarettes were similar to nicotine patches, but were only 0.07-0.2% of the TSNAs present in cigarettes (500-fold to 1400-fold lower levels),¹⁶ TSNA levels may be linked to the burning of tobacco; since NRT, snus (which is smokeless tobacco administered sublingually), and e-cigarettes have lower nitrosamine levels than the various types of cigarettes listed in **Table 2**. In addition, elements such as cadmium, lead, nickel have been found in e-cigarette vapor, comparable to levels found in a nicotine inhaler.¹⁷

Table 2

Summary data of maximum tobacco-specific nitrosamine levels in various cigarettes and nicotine-delivery products*				
Product	NNN	NNK	NAT	NAB
Nicorette gum (4 mg)	2.00	ND	ND	ND
NicoDerm CQ patch (4 mg)	ND	8.00	ND	ND
Swedish snus	980.00	180.00	790.00	60.00
Winston (full)	2200.00	580.00	560.00	25.00
Marlboro (full)	2900.00	960.00	2300.00	100.00
Camel (full)	2500.00	900.00	1700.00	91.00
Marlboro (ultra-light)	2900.00	750.00	1100.00	58.00

*Including electronic cigarettes (ng/g, except for nicotine gum and patch that are ng/gum piece and ng/patch).
 NAT, N'-nitrosoanatabine; NAB, N'-nitrosoanabasine; ND, Not detected; NNK, N'-nitrosornicotine; NNN, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
 Modified by: Kahn Z et al. J Public Health Policy 2011.
 Source: Polosa et al. *Harm Reduction Journal* 2013.⁵

*FCC stands for Food Chemicals Codex. The FCC is a compendium of internationally recognized standards for the purity and identity of food ingredients, compiled by the United States Pharmacopeia and The National Formulary (USP–NF).

Mechanism of Action:

A sensor in the e-cigarette detects when a user inhales on the mouthpiece, and this triggers the liquid nicotine to be heated, and the atomizer turns the liquid into a vapor. The hand-to-mouth motion, inhalation of the vapor and the illumination of the LED light at the end of the e-cigarette, all give the user a physical sensation akin to smoking a real cigarette.⁵

Dosing and Administration: A typical cartridge contains 250 puffs in 4 mL of e-liquid. The nicotine concentration can range from 0 mg/mL to greater than 20 mg/mL.¹⁸ Unlike nicotine replacement therapy pharmaceuticals, e-cigarettes can be used at the consumer's discretion. There is no guidance on the maximum daily dose until e-cigarettes become FDA-regulated.

Clinical Efficacy: More substantial data is needed to evaluate the safety and efficacy of e-cigarette use. Information about e-cigarette trials in progress can be accessed at www.Clinicaltrials.gov.¹⁹

Farsalinos *et al.*, studied 111 former smokers (ages 20-55) who successfully substituted smoking cigarettes with e-cigarettes for at least one month. Volunteers were excluded from the study if they had a whole blood carboxyhemoglobin level greater than 2%, which indicated that they did use tobacco cigarettes before enrolling in the study. The study revealed that 54% of the volunteers used >20 mg/mL of nicotine at initiation of e-cigarette use, while 18 participants (16.2%) had to increase their starting nicotine concentration, for example from 18 to 24 mg/mL. In total, 81% of e-cigarette users used liquids that contained at least 15 mg/mL of nicotine and they did not decrease nicotine levels before smoking cessation was attained. At the time of the interview, 72% of participants significantly lowered their nicotine intake (<20 mg/mL) compared to the time of initiation of e-cigarette use or smoking cessation ($p < 0.001$). In addition, this study also highlighted that participants were more likely to quit smoking and abstain using a second or third generation e-cigarette device. First-generation devices may not deliver nicotine as effectively as later generation devices, which is why some participants enrolled in the study using >20 mg/mL nicotine liquids. Overall, this study demonstrates that it may be possible for cigarette smokers to successfully replace cigarettes with e-cigarettes.¹⁸

Published in June 2013, the EffiCiency and Safety of an eLectronic cigareTte (ECLAT) study demonstrated that e-cigarette use, with or without nicotine, helped decrease cigarette consumption and elicited tobacco abstinence even in smokers who did not intend to quit. In this prospective, 12-month control study, 300 regular smokers were randomized to receive e-cigarettes containing either 7.2 mg, 5.4 mg or no nicotine cartridges. The overall results showed a combined $\geq 50\%$ smoking reduction and complete abstinence from smoking in 99/300 (33.0%) at week-12 and 57/300 (19.0%) at week-52. The mean overall consumption of cigarettes was 21.4 cig/day at baseline and was decreased to a mean of 13.9 cig/day at week-52 ($p < 0.0001$). The results of this study support that e-cigarettes could potentially be used for the indication of smoking cessation.²⁰

Adverse Effects: Generally mild and temporary. Voluntary participants of the Farsalinos *et al.* study, reported

the following adverse effects after using e-cigarettes for a few months¹⁸:

Respiratory: cough (resolves shortly after initiation of e-cigarette use).

Gastrointestinal: throat irritation, gastrointestinal discomfort/epigastric pain.

Oral/Nasal: Gum and nose bleeding. "Dry puff phenomenon" occurs when insufficient liquid is supplied to the wick of the atomizer, leading to temperature elevation and unpleasant burning taste.²⁰

Neurological: headache, sleeplessness.

Metabolic: weight gain (possibly due to smoking cessation or low nicotine delivery).

Cardiovascular: atypical chest pain, palpitations (which resolved spontaneously).

Possible Benefits: Improved olfactory and gustatory senses, less morning cough, better sleep, improved exercise capacity.¹⁸

Cardiotoxicity:

Published in October 2013 by Farsalinos *et al.*, a study evaluated the cytotoxic potential of electronic cigarette vapor extract compared to cigarette smoke on cultured myocardial cells. As expected, tobacco-produced samples had more cytotoxic effects and therefore had lower cell viability. For electronic cigarettes, 4 out of 20 samples of the flavored nicotine e-liquid cartridges were cytotoxic. The results of this study brought attention to high voltage e-cigarette devices, which may result in greater loss of cell viability and to the potential cytotoxicity of flavorings used in e-liquids.²¹

Warnings and Precautions:

Table 3. Positive and Negative Considerations for E-cigarette Use

Positive	Negative
Beneficial effects on health (improved exercise tolerance and less cough)	Small percent of the population is sensitive to propylene glycol (dry mouth and throat)
No tobacco smoke odor or bad breath	Some flavors (e.g. piña colada) have a lingering smell
Much less toxic than conventional cigarettes	Trace amounts of contaminants and metals present in some products
Mimics the "throat hit" sensation of inhaling smoke	"Throat hit" sensation dependent on hardware used and liquid composition
Replicates gestures or actions associated with smoking behavior	Equipment is heavier than traditional cigarette and puffing technique requires some training
Facilitates smoking abstinence	Not all users manage to quit smoking or reduce consumption of conventional cigarettes
Relieves withdrawal symptoms and craving for conventional cigarettes	Relief of withdrawal symptoms varies, affected by quality of equipment and nicotine strength of liquid
No risk to bystanders	
No ash, dirt, or burned clothes	
Accessible prices (in the long run cheaper than conventional cigarettes)	Due to few studies on potential risk to bystanders, some communities are outlawing indoor use
Much improved self-regulatory framework by e-cigarettes industry	Environmental concern about safe disposal of cartridges and batteries
	The intricacies of their use and maintenance may hinder widespread adoption
	Impending medicinal regulation in many countries

Source: Polosa *et al.* *Harm Reduction Journal* 2013.⁵

Availability: E-cigarettes are currently not FDA-regulated therefore they are not available in pharmacy chain stores. Based on individual state laws, e-cigarettes are sold in gas stations, liquor stores, convenience stores and on the Internet.

Cost Comparison:

E-Cigarette Starter Kit	Pack of E-cigarette	Nicotine Gum, Lozenge, Patches	Cigarette Pack (At least 20 cigarettes)
\$79.95 (includes 5 cartridges, spare battery, USB car and wall battery chargers)	\$12.95 (includes an assembled e-cigarette plus 4 cartridges (total 5 cartridges and battery charger)	~\$35.00 (varies depending on strength, quantity, brand vs. generic)	New Jersey (\$8.00 + tax): \$8.55
<p>*For general comparison only. Websites: http://www.walgreens.com/search/results.jsp?Ns=Omniture_Relevance&N=2000011240+2000010717+2000010403+2000013341&Nso=1&Ntt=nicotine; http://www.blucigs.com/; http://www.theawl.com/2013/07/what-a-pack-of-cigarettes-costs-now-state-by-state.</p>			

III. Conclusion:

E-cigarettes are battery-operated devices that provide low-risk delivery of nicotine. E-cigarettes have the potential of becoming substitutes for conventional cigarettes since they are closely related to cigarettes, but without the combustion process. Ten years down the road, will we be discussing “vaping cessation?” These devices are quickly becoming a new phenomenon, however they come with risks which pharmacists should counsel curious consumers about. Some of the concerns surrounding e-cigarettes are the unknown long-term safety and efficacy, easy accessibility to minors, and the potentially toxic composition of e-liquids. Until there is further guidance from the FDA, New Jersey pharmacists should not encourage the use of e-cigarettes for smoking cessation as these devices are prohibited within the state. Pharmacists should continue to assess a consumer’s willingness to quit smoking and counsel them on the health risks from smoking cigarettes and e-cigarettes.

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UAN: 0136-0000-13-059-H04-P Prescription Drug Abuse

Continuing Education Quiz:

Questions

- In addition to smoking cessation pharmaceuticals, which of the following offer tobacco harm reduction (THR) options in the United States?
 - smokeless tobacco and electronic nicotine delivery systems
 - smoking tobacco and nicotine patches
 - conventional cigarettes and bupropion
- Electronic cigarettes and conventional cigarettes are similar in that both:
 - are lit with a match
 - result in the inhalation of nicotine
 - contain atomizers to heat and vaporize the liquid nicotine
- The FDA is concerned about the use of e-cigarettes because
 - they are expensive alternatives to conventional cigarettes
 - there is a lack of substantial data to support their safety and efficacy
 - they are associated with multiple drug interactions
- Electronic cigarettes work by:
 - the smoker lights the e-cigarette and smokes it like a traditional cigarette
 - the smoker rolls the tobacco into the e-cigarette and attaches it to a device for inhalation
 - a sensor in the e-cigarette detects when a user inhales on the mouthpiece, and this triggers the liquid nicotine to be heated, and the atomizer turns the liquid into a vapor
- According to Cahn and Siegel, carcinogenic tobacco-specific nitrosamines (TSNAs) are:
 - not present in e-cigarettes
 - are present in e-cigarettes at lower levels when compared to conventional cigarettes
 - are present in e-cigarettes at similar levels when compared to conventional cigarettes

CE Assessment Answers

Passing Score is 70% or above

Please circle your answers (one answer per question)

- | | |
|----------|----------|
| 1. A B C | 4. A B C |
| 2. A B C | 5. A B C |
| 3. A B C | |

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Please rate the following items on a scale from 1 (poor) to 4 (excellent).

- | | | | | |
|-----------------------------------|---|---|---|---|
| 1. Overall quality of the article | 1 | 2 | 3 | 4 |
| 2. Relevance to pharmacy practice | 1 | 2 | 3 | 4 |
| 3. Value of the content | 1 | 2 | 3 | 4 |

Please answer if you agree or disagree

4. The program met the stated learning objectives:
☐ Agree ☐ Disagree

Impact of the Activity

5. The information presented (check all that applies):
- ☐ Reinforced my current practice/treatment habits
- ☐ Will improve my practice/patient outcomes
- ☐ Provided new ideas or information I expect to use
- ☐ Adds to my knowledge
6. Will the information presented cause you to make any changes in how you do your job? ☐ Yes ☐ No

7. How committed are you to making these changes?

(Not committed) 1 2 3 4 (Very committed)

8. Do you feel future activities on this subject matter are necessary and/or important? ☐ Yes ☐ No

Follow-Up

As part of our ongoing quality-improvement effort, we would like to be able to contact you in the event we conduct a follow-up survey to assess the impact of our educational interventions on professional practice. Are you willing to participate in such a survey? ☐ Yes ☐ No

This lesson is a knowledge-based CE activity and is targeted to pharmacists and pharmacy technicians. This program has been approved for 1 contact hour of continuing education credit (0.1 CEU). To receive continuing education credit, please provide the following information:

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continuing education for pharmacists

Volume XXXI, No. 11

FDA Safety Warnings and Prescribing Updates: Zolpidem, Valproate, Ketoconazole, and Acetaminophen

Mona T. Thompson, R.Ph., PharmD

Mona T. Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide a review of select U.S. Food and Drug Administration (FDA) safety warnings and associated prescribing updates that were issued over the past several months regarding zolpidem-containing products, valproate use in pregnancy, ketoconazole and acetaminophen.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate an understanding of the safety warnings and associated prescribing changes, if applicable, issued for each of the entities discussed;
2. identify the patient population at risk for adverse events in relation to the safety warnings for the entities discussed; and
3. list fundamental patient counseling points secondary to the safety warnings and associated prescribing changes, if applicable, for the entities discussed.

Zolpidem-Containing Medications

Zolpidem is a sedative-hypnotic medication used for the treatment of insomnia. In 2011, approximately nine million patients received zolpidem products from U.S. outpatient retail pharmacies, of which over half were dispensed

to females.

In January 2013, FDA notified the public that new data indicated that blood levels of zolpidem may be high enough the morning after use to impair activities that require alertness, including driving. While this specific warning focused on zolpidem-containing products such as Ambien, Ambien CR, Edluar, and Zolpimist, drowsiness the day after taking virtually any insomnia product is possible and warrants caution. FDA announced that they were requiring manufacturers to reduce the recommended dose of these agents in order to lower resulting blood levels the following morning. For over 20 years, FDA has received reports of possible driving impairment and motor vehicle accidents associated with zolpidem. However, in most cases it was difficult to determine if the driving impairment was related to zolpidem or a specific zolpidem drug level. The availability of this new data and driving simulation studies has led to the approval of new drug labels reflecting these dosing changes as of May 2013.

The recommended initial dose of immediate-release products Ambien and Edluar is now 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR) is 6.25 mg for women, and either 6.25 mg or 12.5 mg for men. These initial doses are expected to be effective in most patients. However, if they

are not, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release with the cautionary statement that the higher dose can increase the risk of next-day impairment of driving and other activities that require full alertness. Because labeling for Intermezzo already recommends a lower dose in women compared to men, FDA is not requiring additional changes. Table 1 lists a summary of these dosing changes.

Data submitted to FDA indicated that individuals with zolpidem blood levels greater than 50 ng/mL may be impaired enough to increase the risk of a motor vehicle accident. In pharmacokinetic trials utilizing zolpidem products at the 10 mg dose, 15 percent of women and 3 percent of men had zolpidem concentrations that exceeded 50 ng/mL eight hours after dosing. Of the total 250 women and 250 men tested, three women and one man had levels exceeding 90 ng/mL.

In trials involving zolpidem extended-release 12.5 mg, 33 percent of women and 25 percent of men had zolpidem blood concentrations exceeding 50 ng/mL, approximately eight hours after dosing. Eight hours following 6.25 mg extended-release doses of zolpidem, 15 percent of adult women and 5 percent of adult men had levels exceeding the proposed threshold. Ten percent of both elderly men and women were also found to have such levels, indicating that in-

Table 1
2013 Dosing recommendations for zolpidem*

Ambien, Edluar, Zolpimist	Women: 5 mg once daily, immediately before bedtime
	Men: 5 or 10 mg once daily, immediately before bedtime
Ambien CR	Women: 6.25 mg once daily, immediately before bedtime
	Men: 6.25 or 12.5 mg once daily, immediately before bedtime

*for non-elderly adults

creased age may slow the metabolism of zolpidem.

Hence, data supports that the risk for next-morning impairment is greatest in patients taking the extended-release forms of these drugs (i.e., Ambien CR and generics), in women, and the elderly. The pharmacokinetic trials conducted did not find a relationship between zolpidem blood levels and the body weight or ethnicity of the patient.

FDA notes that next-morning impairment is different than complex sleep-related behaviors. Next-morning impairment occurs in patients who are awake, while complex sleep-related behaviors occur when patients get out of bed and perform activities such as sleepwalk, drive a car, or prepare and eat food while they are not fully awake and without memory of the activity. In 2007, the zolpidem label's *Warnings and Precautions* section was updated to reflect the concern of complex sleep-related behaviors. The co-administration of central nervous system (CNS) depressants with zolpidem increases the risk of such behaviors.

An article published in 2011 in the *Journal of Clinical Sleep Medicine* by Poceta examined a series of clinical and legal cases following the ingestion of zolpidem. The author described cases of zolpidem-associated complex behaviors including daytime automatisms and sleep-related parasomnia,

and concluded that risk factors for these behaviors include concomitant ingestion of other sedating drugs, a higher dose of zolpidem, a history of parasomnia, ingestion at times other than bedtime or when sleep is unlikely, poor management of pill bottles, and living alone. Parasomnias are sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages or during arousal from sleep. Family history, sleep deprivation, fever, alcohol, and medications predispose people to parasomnia. FDA states that the new dosing recommendations are expected to decrease both complex sleep-related behaviors and next morning impairment.

The zolpidem drug label carries other noteworthy precautions. Since it is a CNS depressant, its effect can be additive when used concurrently with other CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants, and alcohol. Sleep disturbances can present with physical and/or psychiatric disorder(s). Therefore, symptomatic treatment of insomnia should be prescribed with caution and careful evaluation as well as re-evaluation. Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics such as zolpidem. These changes include decreased inhibition, bizarre behavior, agita-

tion, and depersonalization. Visual and auditory hallucinations have been reported.

Worsening depression and suicidal thoughts and actions have been reported in patients treated with sedative-hypnotics who are primarily depressed. Providers are cautioned to prescribe minimal tablets of zolpidem as intentional overdose is common in this group of patients.

The risk of respiratory depression when used at hypnotic doses should be considered in patients with respiratory impairment including those with sleep apnea and myasthenia gravis. Patients should be monitored for tolerance, abuse, and dependence of zolpidem. Reports of withdrawal signs and symptoms following rapid dose decrease or abrupt discontinuation have been reported.

In order to reduce the risk of next-morning impairment, patients should take the lowest dose that manages their symptoms. Zolpidem should not be taken if less than seven to eight hours of sleep is anticipated. Poceta suggests instructing the patient to not only "ingest immediately prior to going to bed," but to add that it should be taken "at your usual bedtime only."

Valproate Sodium Use in Pregnancy

FDA alerted health care professionals and women in May 2013 that recent studies provide evidence that the anti-seizure medications, valproate sodium and related products, can cause decreased IQ scores in children whose mothers took them while pregnant. Stronger warnings about use during pregnancy will be added to the drug labels and valproate's pregnancy category will be changed from "D" to "X" when prescribed for migraines. However, valproate products will remain in pregnancy category "D" for treating epilepsy and manic episodes associated with bipolar disorders. Pregnancy risk category D indicates that adequate well-controlled or observational studies in pregnant women have

demonstrated a risk to the fetus. Yet, the benefits of therapy may outweigh the potential risk such as cases where the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective. Pregnancy category X means that adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of category X agents is contraindicated in women who are or who may become pregnant.

Health care professionals are advised to prescribe these products in pregnant women with epilepsy or bipolar disorders when other medications are not effective or otherwise unacceptable. In addition, for women of childbearing age who are not pregnant, valproate products should be resorted to only when the medication is considered essential and prescribed along with effective birth control.

Meador *et al.* reported a prospective, observational study that involved children of women who were taking one of four antiepileptic drugs as monotherapy: lamotrigine, carbamazepine, phenytoin, or valproate products. The study compared results of IQ tests of six-year-olds who had been exposed to one of these antiepileptic drugs *in utero*. Children exposed to valproate products during pregnancy had statistically significant lower IQ scores, when compared to all other monotherapies that were studied. The mean IQ for the valproate was 97 compared to 105, 108, and 108 for carbamazepine, lamotrigine, and phenytoin respectively. Additionally, the mean IQs were higher in groups whose mothers reported periconceptional folate use. However, the authors warn that these findings should be interpreted with caution as the effect of periconceptional folate use was not a primary outcome of the study and the information for this outcome was collected retrospectively. It is important to note that the women studied were exposed to antiepilep-

tic drugs throughout their pregnancies, and it is unknown if the timing of exposure during pregnancy may affect the severity of cognitive effects in children.

Valproate products include: valproate sodium (e.g., Depacon), divalproex sodium (e.g., Depakote, Depakote CP, Depakote ER), valproic acid (e.g., Depakene and Stavzor). While the exact mechanism of action is unknown, their antiepileptic action may be attributed to increased gamma-aminobutyric acid (GABA) levels in the brain. Divalproex sodium is approved for use in simple and complex absence seizures, complex partial epileptic seizure, manic bipolar I disorder, and prophylaxis of migraines. Off label, these agents may also be prescribed for alcohol withdrawal syndrome, maintenance of bipolar I and II disorder, chronic headache disorder, post-traumatic headache, and bipolar type schizoaffective disorder.

The label of valproate products carries a black box warning for the risk of hepatotoxicity which usually occurs within the first six months of treatment. Liver function tests are recommended at the start of therapy and at frequent intervals, particularly during the first six months. Children younger than two years of age and patients with hereditary mitochondrial disease are at a higher risk of developing fatal hepatotoxicity. Use may be contraindicated in these populations.

In addition to impaired cognitive development during prenatal exposure, valproate products may produce major congenital malformations such as neural tube defects (i.e., spina bifida). Life-threatening pancreatitis has also been reported in adults and children taking these agents.

Affected patients should be advised that taking valproate during pregnancy can decrease the child's IQ score and a higher risk for birth defects exists. These women should speak with their health care professional immediately, but should not stop valproate treatment suddenly as this can cause serious and life-

threatening medical problems to both the mother and baby. Health care providers should counsel patients on the importance of effective birth control, if they are not pregnant but of child bearing age. Folic acid supplementation before conception and during early pregnancy has been shown to reduce the chance of neural tube defects in babies and should be routinely recommended.

Additionally, health care providers can share information with their patients about the North American Antiepileptic Drug Pregnancy Registry. The registry was established in 1997 for pregnant women in the United States and Canada at Massachusetts General Hospital in Boston, Massachusetts. The major objective of the registry is to obtain and publish information on the frequency of major malformations (such as heart defects, spina bifida, and cleft lip), with the highest priority placed on new information related to the use of newer antiepileptic drugs (AEDs) marketed in the past ten years. Prior to the creation of this registry, data regarding the safety of antiepileptic drugs was conducted by manufacturers and there was no systematic method to determine whether or not specific anticonvulsants were associated with increases in malformations. As of April 2012, 8,500 women had enrolled in the registry.

The registry's most recent newsletter, published in 2012, announced new findings on the comparative safety of 11 AEDs used during pregnancy. The newsletter summarizing these findings, as well as additional information for providers and patients, can be found on their website at www.aed-pregnancyregistry.org. The registry staff emphasizes a need for the largest possible sample size as they study the safety of AEDs in order to report accurate findings. Women must register themselves and can do so by calling 1.888.233.2334.

Ketoconazole

Ketoconazole (Nizoral and others)

Table 2
Selected Drugs with Plasma Concentrations Altered by Nizoral®*

Systemic exposure to these drugs is increased significantly by ketoconazole:	Alprazolam, midazolam, triazolam Cisapride Dofetilide Eplerenone Ergot alkaloids	HMG-CoA reductase inhibitors (lovastatin, simvastatin) Nisoldipine Pimozide Quinidine
Concomitant use is contraindicated .		
Systemic exposure to these drugs is increased by ketoconazole:	Alfentanil, fentanyl, sufentanil Amlodipine, felodipine, nicardipine, nifedipine Bosentan Buspirone Busulfan Carbamazepine Cilostazol Cyclosporine Digoxin Docetaxel, paclitaxel Oral anticoagulants	Indinavir, saquinavir Methylprednisolone Rifabutin Sildenafil Sirolimus (<i>not recommended</i>) Tacrolimus Telithromycin Tolterodine Trimetrexate Verapamil Vinca alkaloids
Careful monitoring, with possible adjustment in dosing, is recommended.		
<i>*This list is not all-inclusive. From Nizoral package insert.</i>		

Table 3
Selected Drugs that may Alter Plasma Concentrations of Nizoral®*

Systemic exposure to ketoconazole is significantly reduced by these drugs and concomitant use is not recommended.	Carbamazepine Gastric acid suppressants (antacids, antimuscarinics, histamine H ₂ blockers, proton pump inhibitors, sucralfate)	Nevirapine Phenytoin Rifampin, rifabutin, isoniazid
Systemic exposure to ketoconazole is increased significantly by this drug: Dose reduction of ketoconazole should be considered.	Ritonavir	
<i>*This list is not all-inclusive. From Nizoral package insert.</i>		

is an imidazole antifungal agent that has been prescribed for the treatment of many superficial and systemic fungal infections. During 2012 alone, approximately 600,000 prescriptions for the tablet formulation were dispensed. While it has been associated with drug-induced liver injury for several years, FDA is now requiring the drug label to be updated and requesting that ketoconazole's use be limited. The announcement came from FDA on July 26, 2013 and includes several changes following a negative risk versus benefit assessment that was conducted by the European Medicines Agency (EMA). EMA made a public announcement recommend-

ing that marketing authorization of oral ketoconazole be suspended throughout the European Union. Similar action was taken in France, also because of high liver injury associated with ketoconazole use. The foreign agencies state that while hepatitis is a known side effect of other antifungal medicines, both incidence and severity of liver injury with oral ketoconazole were higher than with other antifungals, and it does not appear to be possible to identify measures to reduce the risk. Topical formulations of ketoconazole such as creams, ointments, and shampoo can continue to be used as the amount of drug absorbed throughout the body is

low.

Liver damage with ketoconazole is documented for patients receiving high doses for short periods of time or low doses for long periods of time, and may occur in those without obvious risk factors for liver disease. Hepatotoxicity associated with the agent is sometimes reversible upon discontinuation. However, damage leading to liver transplantation or death has occurred. Therefore, oral use is contraindicated in patients with acute or chronic liver disease. The new label recommends that liver function be assessed prior to treatment and monitored routinely (i.e., weekly), as well as at the first signs

or symptoms of possible hepatotoxicity. Signs and symptoms of hepatotoxicity include anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, or dark urine. Health care professionals should advise patients to avoid alcohol and other potentially hepatotoxic drugs while receiving ketoconazole tablets.

In addition to warning of severe liver injury with ketoconazole, the drug safety communication identified that the antifungal is associated with adrenal insufficiency. Adrenal insufficiency is a decreased ability of the adrenal glands to produce corticosteroids. Health care professionals are advised to monitor adrenal function in patients taking ketoconazole tablets who have existing adrenal insufficiency or in patients experiencing extended periods of stress (i.e., following major surgery or increased stays in intensive care settings).

Lastly, the warning brings attention to the many drug interactions that are possible with ketoconazole which can lead to serious and potentially life-threatening outcomes. FDA is calling for all health care professionals to assess all other concurrent medications that the patient is taking in order to minimize this risk. The current drug label includes a black box warning indicating that ketoconazole is contraindicated with dofetilide, quinidine, pimozide, and cisapride. These combinations can cause elevated plasma concentrations of these drugs which may result in further QT prolongation and possibly life-threatening ventricular dysrhythmias such as torsades de pointes. Co-administration of ketoconazole tablets with oral midazolam, oral triazolam, or alprazolam is also contraindicated as it has resulted in elevated plasma concentrations of these drugs and may potentiate or prolong the sedative and hypnotic effects especially with repeated dosing. Other contraindicated agents include the CYP3A4 metabolized HMG-CoA reductase inhibitors simvastatin and lovastatin, as well as nisoldipine, eplerenone, and ergot alkaloids.

Careful monitoring and dosing adjustments may be required with several other commonly prescribed medications. Tables 2 and 3 include more drug interactions as detailed in the Nizoral package insert.

Under the new label, ketoconazole should not be used as a first-line agent for any fungal infection and should only be used for the treatment of certain fungal infections such as endemic mycoses when alternative antifungal therapies are not available. Indications for which the risk of ketoconazole therapy outweighs the benefit have been removed from the label. Therefore, the use of ketoconazole in *Candida* and dermatophyte infections is no longer indicated and this oral antifungal is no longer appropriate for fungal infections of the skin or nails. This labeling change will alter prescribing as reports from office-based physicians indicated that the most common diagnosis associated with use in recent years have included superficial skin and nail fungal infections. Ultimately, oral ketoconazole can now only be prescribed for the following infections: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis in patients who have failed other therapies or who are intolerant to them. A patient *Medication Guide* is now required by law each time a prescription is dispensed, and is summarized in Table 4.

Acetaminophen

A new safety warning with acetaminophen has been issued. On August 1, 2013, FDA published a statement to warn the public about rare but serious skin reactions that have been reported secondary to acetaminophen use. The skin reactions include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), and they can be fatal.

Stevens-Johnson Syndrome is described as severe, widespread vesiculobullous disease of the skin with involvement of two or more

Table 4 Summary of Nizoral® Medication Guide

- Nizoral (ketoconazole) tablets can cause serious side effects, including: *Liver Problems*. A healthcare provider should be contacted right away if any of the following symptoms are experienced: loss of appetite or weight loss, nausea or vomiting, tired feeling, stomach pain or tenderness, dark urine or light-colored stools, yellowing of the skin or the whites of the eyes, fever or rash. *QT Prolongation* can occur when taken with certain medications such as dofetilide, quinidine, pimozide, and cisapride. Patients should tell a health care provider right away if the following symptoms are experienced: feeling faint, lightheaded, dizzy, or irregular or fast heart beat.
- Nizoral is prescribed to treat serious fungal infections including: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis.
- Nizoral is not used to treat fungal nail infections.
- Nizoral has not been approved for the treatment of advanced prostate cancer or Cushing's syndrome. The safety and efficacy have not been established.
- Nizoral tablets should only be used in children if prescribed by a health care provider who has determined that the benefits outweigh the risks.
- Nizoral tablets should not be taken if a patient has liver problems or is taking any medications that are contraindicated with it.
- Before taking Nizoral tablets, patients should tell their health care provider if they (1) have had an abnormal heart rhythm or if a family member has had congenital long QT syndrome; (2) have adrenal insufficiency; (3) are pregnant or plan to become pregnant; (4) are breastfeeding or plan to breastfeed.
- Patients should avoid drinking alcohol while taking Nizoral tablets.

mucosal surfaces such as eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa. SJS results in mucosal erosions and epidermal detachment affecting less than 10 percent of the body surface area. TEN is the most extreme form of the disease with

epidermal detachment affecting more than 30 percent of the body surface area. The cutaneous eruption is usually preceded by nonspecific symptoms of fever and fatigue occurring one to 14 days before the skin lesion. Cough may be present and fever may be high during the active stages of the disease.

AGEP is a rare, acute skin eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema. In about 90 percent of cases, it is caused by drugs but there have been isolated reports linked to viral, bacterial, or parasitic infections. The eruption develops within hours or days after drug exposure and resolves spontaneously in one to two weeks after drug discontinuation.

While it is rare for these reactions to occur, the data collected by FDA does indicate that an association has been found. The review of medical literature conducted by FDA found three cases of confirmed serious skin reaction with acetaminophen following a positive rechallenge, as well as 26 other cases where acetaminophen was the only drug used prior to the reaction or hypersensitivity was demonstrated by skin testing or other means. The majority of these patients were hospitalized with no deaths reported in the literature, and the cases resolved upon discontinuation of the drug. Furthermore, a search of the FDA Adverse Event Reporting System (FAERS) from 1969 to 2012 identified 91 cases of SJS/TEN and 16 cases of AGEP which resulted in 67 hospitalizations and 12 deaths. The cases were ranked as either possible or probable in conjunction with acetaminophen use. FDA reviewed five SJS/TEN case-control studies and one of AGEP indicating that risks of SJS/TEN may be increased with the use of acetaminophen and were generally independent of the effects of other drugs. FDA noted that all but two of these case control studies failed to address the possible presence of protopathic bias. Protopathic

bias occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected. In this instance, protopathic bias refers to a false increase in the risk of SJS/TENS attributed to acetaminophen when used to treat fever because fever is also an early symptom of SJS/TEN. In one of the studies that did control for protopathic bias, acetaminophen was still associated with SJS/TEN.

FDA states that it is difficult to determine how frequently serious skin reactions occur with acetaminophen due to the widespread use, difference in usage among individuals, and the fact that the medication has been available for so long. FDA is requiring that a warning be added to the labels of acetaminophen-containing prescription drugs and requesting the same from manufacturers of OTC acetaminophen drug products.

While health care professionals should be aware of this risk, they should recall that it is rare and consider other drugs that carry the same warnings in their label. Drugs that are most commonly associated with SJS include anticonvulsants such as phenytoin, phenobarbital, carbamazepine, lamotrigine, and valproic acid; sulfonamides; penicillins; nonsteroidal anti-inflammatory drugs (NSAIDs); allopurinol; and tetracyclines. Drugs that are rarely associated with SJS include: leflunomide, venlafaxine, furosemide, nevirapine, and following vaccination from smallpox and chickenpox. SJS has also occurred rarely following certain fungal and protozoal infections and in children with Epstein-Barr virus and enterovirus infections. Overall incidence of SJS is 0.1 to 0.7 cases per 100,000 per year. It occurs mainly in children and young adults, affecting males two times more than females.

AGEP is most often caused by antibiotics such as aminopenicillins and macrolides, calcium channel blockers, and antimalarials. Among many other drugs, aspirin

and NSAIDs such as celecoxib, etodolac, and ibuprofen have been linked. The estimated incidence is one to five cases per million per year. While it can occur at any age, AGEP most often affects adults with a slight female predominance.

AGEP symptoms include reddening of the skin, rash, blisters, and detachment of the upper surface of the skin. During the acute phase, fever and leukocytosis can occur. Those who experience symptoms are advised to stop taking the drug and seek medical attention right away. It is important for patients to understand that these reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Individuals who have experienced a serious skin reaction with acetaminophen should not take the medication again.

Summary

The safety information and prescribing updates discussed in this lesson provide a detailed review of FDA drug safety communications recently issued for zolpidem-containing products, valproate use in pregnancy, ketoconazole, and acetaminophen. The updated product leaflets should be consulted for full prescribing information.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

Program 0129-0000-13-011-H05-P

Release date: 11-15-13

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CE Hours: 1.5 (0.15 CEU)

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continuing education quiz

FDA Safety Warnings and Prescribing Updates: Zolpidem, Valproate, Ketoconazole, and Acetaminophen

- The recommended initial dose of extended-release zolpidem for women is now:
 - 5 mg.
 - 6.25 mg.
 - 10 mg.
 - 12.5 mg.
- Data suggests that the risk for next-morning impairment is greatest in patients taking which of the following formulations of zolpidem?
 - Immediate-release
 - Oral spray
 - Sublingual
 - Extended-release
- Zolpidem's effects can be additive with all of the following drugs EXCEPT:
 - alcohol.
 - benzodiazepines.
 - tricyclic antidepressants.
 - ketoconazole.
- Zolpidem should not be taken if fewer than how many hours of sleep are anticipated?
 - 5 to 6 hours
 - 7 to 8 hours
- The pregnancy category for valproate products prescribed for migraines is now:
 - Category X.
 - Category D.
 - Category C.
 - Category B.
- It has been confirmed that the timing of exposure to valproate during pregnancy affects the severity of cognitive effects in children.
 - True
 - False
- The label of valproate products carries a black box warning for the risk of:
 - renal toxicity.
 - respiratory depression.
 - hepatotoxicity.
 - adrenal insufficiency.

.....
Completely fill in the lettered box corresponding to your answer.

- | | | |
|--------------------|---------------------|---------------------|
| 1. [a] [b] [c] [d] | 6. [a] [b] | 11. [a] [b] [c] [d] |
| 2. [a] [b] [c] [d] | 7. [a] [b] [c] [d] | 12. [a] [b] |
| 3. [a] [b] [c] [d] | 8. [a] [b] [c] [d] | 13. [a] [b] [c] [d] |
| 4. [a] [b] | 9. [a] [b] [c] | 14. [a] [b] [c] [d] |
| 5. [a] [b] [c] [d] | 10. [a] [b] [c] [d] | 15. [a] [b] |

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- Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
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If no, list any unmet _____
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☐ yes ☐ no
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- The major objective of the North American Antiepileptic Drug Pregnancy Registry is to publish information on the frequency of:
 - major malformations in babies.
 - colonic obstruction.
 - fistulas and perianal disease.
 - small bowel obstruction.
- Liver damage with ketoconazole is documented in patients receiving all of the following EXCEPT:
 - low doses for short periods of time.
 - low doses for long periods of time.
 - high doses for short periods of time.
- In addition to severe liver injury, ketoconazole is associated with:
 - renal toxicity.
 - respiratory depression.
 - pancreatitis.
 - adrenal insufficiency.
- All of the following medications are contraindicated with ketoconazole EXCEPT:
 - alprazolam.
 - dofetilide.
 - carbamazepine.
 - simvastatin.
- Ketoconazole is appropriate therapy for fungal infections of the skin or nails.
 - True
 - False
- Patients taking ketoconazole should be advised to avoid:
 - alcohol.
 - acetaminophen.
 - caffeine.
 - NSAIDs.
- Rare but serious skin reactions associated with acetaminophen use include all of the following EXCEPT:
 - AGEP.
 - SJS.
 - TEN.
 - LDE.
- The estimated incidence of acute generalized exanthematous pustulosis is:
 - 0.1 to 0.7 cases per 100,000 per year.
 - 1 to 5 cases per million per year.

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