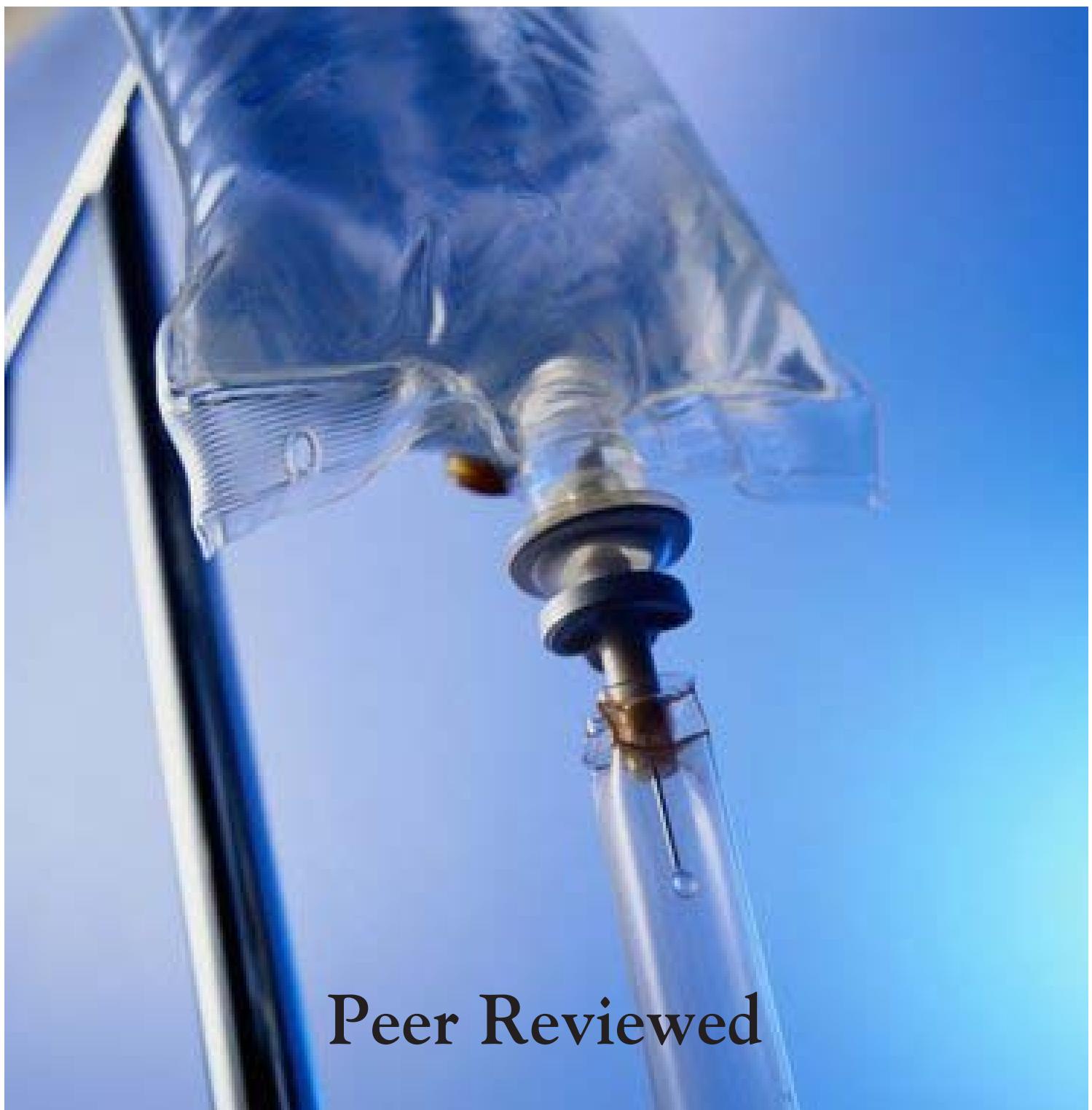


The New Jersey **JOURNAL of Pharmacy**

New Jersey Pharmacists Association

Fall/Winter 2013 • Volume LXXXVII • Number 4

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The New Jersey Journal of Pharmacy (ISSN0028-5773 USPS #380-360) is published seasonally by the NJ Pharmacists Association 760 Alexander Road, PO Box 1 Princeton, NJ 08543-0001 609-275-4246 Fax 609-275-4066 www.njpharmacist.org

Periodicals Postage Paid at Princeton, NJ and additional mailing offices. Subscriptions paid for through allocation of membership dues. US Subscription \$50 per year; Foreign Rate \$100 per year.

POSTMASTER: Send address changes to The New Jersey Journal of Pharmacy, 760 Alexander Rd., PO Box 1, Princeton, NJ 08543-0001. 609-275-4246. www.njpharma.org

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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

As you delve into the pages of our first NJPhA Journal issue for 2014, and you learn new and different information in the oncology realm, think about how far we have come in the understanding and treatment of cancer in all its various forms. Then, think about how far we have come as pharmacists - and how much further we have to go.

I use this forum to engage you, NJPhA Journal Reader, to discover what about NJPhA that speaks to you and get more involved in that way. For example, before we know it - in only a few short months - we will be seeking award nominations, a 2nd Vice President

candidate and a treasurer candidate for the next 2-year term. Start thinking now about who you would recommend. Maybe it's a colleague at work, maybe it's a colleague you have met at a Regional Meeting, maybe it's you.

With warmest wishes for a successful and healthy New Year,

Carrie Corboy, RPh, PharmD, CCP
2013-2014 President

From The Editors' Desks...

Dear Colleagues,

We introduce our second peer –reviewed issue of the NJ Journal of Pharmacy! This oncology issue highlights the role of the pharmacist in Safe Communities Coalition of Somerset and Hunterdon Counties in our Practice Spotlight. In addition to the theme of oncology, the issue brings to you highlights from the NJPhA Annual Convention that was held in Atlantic City, NJ, October 3 – 5, 2013. This year's convention was the debut of the Poster Sessions, whose titles are published here. The convention also offered educational programs, networking opportunities, student programming, and vendor support. Save the date for next year September 19-21, 2014!

We also thank our peer-reviewers, without whom the quality of the Journal would not be upheld. Please reach out to us if you wish to join this distinguished list and participate in the peer-review process.

The schedule for upcoming issues is as follows:

Public Health/Wellness
Neurology/Psychiatry
Infectious Diseases
Endocrinology

We welcome submissions! Please let us know if you have a topic idea. If you are interested in writing but are stumped for ideas, reach out to our team and we can brainstorm with you!

Warm regards,

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This issue of *The New Jersey Journal of Pharmacy* marks the second peer-reviewed issue! We are grateful to the experts that review the submissions, for their recommendations greatly contribute to the quality of the Journal.

The Journal wishes to acknowledge the following clinicians who have participated in peer review:

Vivek Bajnath, BS, MBA

Mei Chang, BA, PharmD

John L. Colaizzi, RPh, PhD

Carrie Corboy, PharmD, CCP

Asha Gupta, PharmD

Ruth Kim, PharmD

Melissa Kuhn, PharmD

Jeremy Lim, PharmD

Nicole Lovullo, PharmD

Christine Martinez, BS, PharmD

Madhavi Patel, PharmD

Moriah Weissman, PharmD, CCP

Message from the BOT Chairman

Membership and Support of NJPHA, Your State Pharmacy Organization

As we enter a new year, NJPHA encourages your support to help us confront the many challenges that may arise in the new health-care initiative, which will influence pharmacy and how we service patients.

Basically, you can make a difference.

Your membership proclaims your solidarity within our organization. Each member becomes a valuable component to further our cause. Pharmacists can help to establish unity and a strong voice to address immediate matters that influence our daily practices. Membership equals strength and demonstrates that we are working together. This enables us to be heard when we speak on important pharmacy issues.

Please join me and encourage your colleagues to support and promote our organization for the good of our profession of pharmacy in the State of New Jersey. Therefore, encouraging your colleagues to become members will enable us to grow and help to maintain a solid foundation that is needed to properly represent all of us in our profession. Thus, membership should be continuous from year to year and should not be taken for granted.

In addition, your membership will enable you to participate in live regional meetings held at various times throughout the year, in

order to obtain necessary CE credits for licensure, as well as, providing current professional information to support your practice. Another resource to access is the NJPHA website (www.njpharmacist.org) which also provides information on a variety of interesting topics, periodic messages, and important news announcements related to our profession.

Furthermore, if you would like to become more active within the profession, then I would like to extend to you an invitation to participate with one of several committees within NJPHA. Each committee meets periodically during the year; meetings often may be held by telephone conference call. Please contact, Elise Barry, CEO, NJPHA, for more information.

Positive changes are needed to allow us to provide the necessary services to support proper patient care and enhance our profession. When there are crucial issues that can affect pharmacy, these matters need to be defined and addressed promptly by providing accurate and immediate responses.

We need to continue together towards provider recognition. You can make a difference.

Joseph Tarallo, Jr., RPH
NJPJA, BOT Chairman

Letters To The Editors'...

Dear Editors and Colleagues,

Today more than ever before, pharmacists are increasingly being recognized as integral members of various health care teams. According to July 2013 U.S. News & World Report, Pharmacy is the third best profession in the United States. Across the continuum of healthcare delivery, pharmacists can be found applying patient centered care competencies and clinical expertise in community pharmacies, hospitals, accountable care organizations and within Pharmaceutical and Biotechnology companies. While traditional pharmacy practice employment remains challenging, when all health care arenas in need of enhanced skills and therapeutic expertise of pharmacists are taken into consideration, the range of employment opportunities for pharmacy graduates is endless.

Pharmacists have been extremely well respected as one of the most trusted professionals in opinion polls year after year, however as pharmacists roles continue to evolve so must their competencies in pharmacy practice settings never before con-

sidered. Such expanded roles require a very different set of clinical practice and leadership skills embracing enhanced critical thinking and communication aligning with technologies nonexistent a few years ago. Clinical accuracy is no longer enough for today's pharmacists realized by Pharmacy Students during Introductory and Advanced practice experiences.

Various automation technologies have now replaced previous dispensing and compounding functions creating a greater need for pharmacists' professionalism and interpersonal communication skills. Community Pharmacy environments have evolved to include welcoming freestanding prescription counters for Medication Therapy Management services and hospital pharmacists visibly reside on patient care hospital units for the provision of medication interventions. Ensuring development of enhanced pharmacy practice competencies in response to patient centered care practice changes is paramount in experiential education programs.

continued on page 6

Responsibilities of today's experiential site preceptors have also evolved and encompass much more than what was expected of them in the past. Their importance cannot be understated . Preceptors are considered adjunct faculty providing input in experiential syllabi development for student progression. They serve on Pharmacy School Advisory Boards and are trained as mentors in educating future pharmacists. Their feedback is solicited in student evaluations for experiential programmatic assessment. The fact that experiential education comprises approximately 30 percent of pharmacy education demonstrates the paramount importance of experiential preceptors for without their efforts experiential education could not be delivered.

One might challenge the components of experiential pharmacy education described above are not much different than those of the past. The difference lies in the inability of current technologically savvy students to recognize the importance of interpersonal emotional soft skills. Self-sufficient GenX'er students often lack soft skills which embrace taking responsibility instead of making excuses or shifting blame; taking feedback constructively and relinquishing the entitlement spotlight. Experiential programs must heighten an awareness of the equal importance of acquiring both "Clinical Skills" and "Soft Emotional Intelligence Skills" for successful pharmacy practice careers. Soft skills like clinical competencies must be acquired and assessed and therein lays the crucial added dimension within the scope of pharmacy experiential education that did not exist years ago. If all clinical competencies are equal, soft skills often undervalued, differentiate one's ability to excel as a leader and open most career opportunity doors. Soft skills align with the ASHP Statement on Professionalism, which includes leadership (a soft skill) as one of ten characteristics of a professional. The ASHP Statement on the Roles and Responsibilities of the Pharmacy Executive presents formal leadership as a professional obligation. Such skills enhance clinical proficiency; while synergistically fostering the delivery of effective patient centered care and inter-professional collaboration.

Many facets of pharmacy practice are now driven by automation in drug dispensing, IV Compounding and drug information however leadership can never be automated. Leadership is ever-present, doesn't need any down time, is accountable and devoid of an entitlement mentality all of which demonstrate the value and purpose of experiential education in cultivating future pharmacists' ability to lead. As pharmacy continues to be driven by advancements in technology, consideration must be given to what such technologies can and cannot do. POS Systems and Bar Code Scanning technologies have enabled pharmacy to truly become a "portable profession" enabling instant access of knowledge at pharmacists' fingertips. But technology

cannot provide a personal intervention positively impacting medication compliance; technology cannot advocate for the patient or implement a new program relative to safe and effective medication delivery. Technology cannot be programmed with empathy or cultural competencies to understand health decisions of various ethnicities.

As the practice of pharmacy continues to transition from drug dispensing to medication therapy management, it is the professional obligation of experiential education departments to facilitate and encourage development of both clinical and emotional competencies crucial for successful pharmacy practice. It is through experiential education programs that students are afforded opportunities to learn the delivery of patient centered care amidst a culture of entitlement. Experiential education allows pharmacy students to observe first hand the personal and confidential nature of being a professional, the trust patients place in pharmacists and the appropriate ethical and moral conduct becoming a pharmacist all of which cannot be realistically observed in the classroom yet equally crucial for success. Experiential education at its best tangibly demonstrates one's white coat does not make one a professional; that professionalism comes from within and is defined by one's attitudes and behavior; that one does not need a title to lead but leads by example thinking, communicating, advocating, leading and implementing programs and services that will serve to help all people lead healthy lives.

The fact that a pharmacist's accessibility and expertise has the ability to influence medication related health decisions of thousands of people cannot be disputed. As the delivery of healthcare continues to evolve so must experiential education programs in their alignment and provision of practice environments conducive for students to acquire competencies for pharmacy careers and roles that have yet to be created.

Pharmacy Preceptors and Practice Sites,
"Thank you for what you do!"

Tell me, I'll forget. Show me, I may remember. But involve me, and I'll understand. -Chinese Proverb

Regards,
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A Review of Olmesartan-Induced Sprue-Like Enteropathy

by Samad Tirmizi, Pharm.D. and Priti Patel, Pharm.D., BCPS

Olmesartan (Benicar) is an angiotensin II receptor blocker (ARB) approved in 2002 that is indicated for the treatment of hypertension. Recent correlation to severe sprue-like enteropathy has resulted in an FDA Drug Safety Communication and the manufacturer of olmesartan, Daiichi Sankyo adding new warning to its label.^[1] Patients experiencing the sprue-like enteropathy present with severe symptoms such as severe weight loss, dehydration, prerenal azotemia, hypotension, and chronic diarrhea over several months.^[2]

It is known that sprue-like enteropathy is a clinical manifestation similar in presentation to that of Celiac disease. Patients with this ailment most commonly present with chronic diarrhea and intestinal villous atrophy, a process by which the intestinal lining becomes flattened causing maldigestion and malabsorption of food.^{[3][4]} The actual mechanism behind the sprue-like enteropathy, however, is unknown. The reaction can take months to years to present, so it is believed to be cell-mediated rather than a simple type I hypersensitivity, which can occur minutes to hours after exposure to a stimulus. Pathological presentation also mimics celiac disease as findings were in the duodenum, unlike a tropical sprue, which is most commonly in the jejunum and ileum.

The link between olmesartan and sprue-like enteropathy was first considered via two consecutive case reports from the Mayo Clinic in Rochester, Minnesota. Both patients were shown to have negative celiac serology with similar symptoms including hypotension, weight loss, and lack of response to gluten exclusion. Symptoms of diarrhea were improved during hospitalization and after cessation of hypertensive medications due to hypotension; however, relapse occurred upon discharge and continuation of their home antihypertensive medications.^[5]

Based on these reports, a case series at the Mayo Clinic was conducted.^[5] Inclusion criteria were that patients had diarrhea for more than 4 weeks, were taking olmesartan, and did not have a definitive diagnosis of the cause of their enteropathy. One patient was excluded due to diagnosis of tropical sprue, and another excluded who improved clinically before discontinuing olmesartan. All included patients were unresponsive to antibiotics or a gluten-free diet. Patients also lacked the IgA antibodies, which are present during Celiac disease due to its immune-mediated damage of small bowel villi from gluten exposure. Additionally, 68% of the patients with olmesartan-induced enteropathy were shown to be positive for HLA-DQ2, which is above the normal prevalence expected to be about 25% in the general population.^[5] It is noteworthy that prevalence of HLA-DQ2 is the most common gene associated with Celiac disease.^[6]

Of the 22 patients included in the case series, 13 (59%) were women, median age was 69.5 years ranging from 47 to 81 years, and 21 Caucasian patients along with one Hispanic patient. Mean duration of treatment with olmesartan before onset of symptoms was 3.1 years in 14 of the patients, 5 were documented to have taken olmesartan for at minimum one year, and data on 3 patients were unavailable. In all patients, a re-challenge with olmesartan

was not conducted due to the life threatening risks involved. However, two patients from the case series reported that their symptoms worsened when restarting their olmesartan regimen.

Given that approximately 1.9 million patients received an olmesartan prescription in 2012, it is important for clinicians to note the correlation between olmesartan and sprue-like enteropathy.^[1] Although this adverse reaction seems to be very rare, its warning is important so that clinicians become aware of this drug-induced disease for which discontinuation of olmesartan resolves symptoms.

The drug-induced enteropathy experienced with olmesartan has also been seen in other drugs as well. Azathioprine, an immunosuppressant commonly used for autoimmune hepatitis, inflammatory bowel disease, and other treatment regimens, was shown to have a chronic diarrhea develop several weeks after azathioprine administration, and to resolve after discontinuation. A case report by Ziegler et al., reports that a young adult male developed small-bowel villous atrophy and severe diarrhea, associated with administration of azathioprine for approximately 1.5 years.^[7] In this patient, treatment with a gluten-free diet did not work, nor were anti-gliadin antibodies present. Discontinuation of the azathioprine led to normalized duodenal mucosa and resolved diarrhea. Since the mechanism behind the drug-induced severe diarrhea was unclear, the adverse reaction was believed to be a form of an acute hypersensitivity reaction.

The second drug associated with enteropathy is mycophenolate, an immunosuppressant used after renal transplant. Mycophenolate is documented to have incidence of diarrhea in 31% to 51% of patients.^[8] A case report by Kamar et al., depicts 4 different patients to whom mycophenolate was administered, and a chronic diarrhea associated with duodenal villous atrophy was profound.^[9] All patients had been administered mycophenolate, had severe chronic watery diarrhea, were *C difficile* negative, had substantial weight loss, and experienced electrolyte imbalances caused by the gastrointestinal disorder. Once again, discontinuation of the drug resolved the chronic diarrhea and severe malabsorption caused by the medication.

In summary, olmesartan was implicated in numerous cases of drug-induced chronic diarrhea associated with sprue-like enteropathy.^{[3][5][10][11]} Very similar presentations with patients of olmesartan-induced enteropathy seemed to match those with mycophenolate- and azathioprine-induced enteropathy. However, the mechanism behind each of these reports still seems to be unknown. Additionally, reports of these adverse drug reactions are rare when compared with the number of patients taking this medication. Nonetheless, it is important to note that the warning exists for clinicians who decide whether to prescribe the medication. Although more studies need to be reported, care should be taken when prescribing olmesartan to patients. Other antihypertensive medications have not been linked to these findings of olmesartan, so switching within the same class of medications or to other therapeutic classes does not appear to be an issue.

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This year's New Jersey Pharmacists Association Annual Convention marked the introduction of Poster Sessions. The posters offer a platform for members of the pharmacy community to highlight research or projects at their practice sites. First-time presentations, as well as encore presentations, were included. The Journal is proud to acknowledge the poster presentations:

Anastasia Rivkin, PharmD, BCPS, et. al.

Fairleigh Dickinson University

Title: Administration of High-Stakes Examinations in an Active-Learning Classroom.

Originally presented at American Association of Colleges of Pharmacy Annual Meeting,

July 13-17, 2013 in Chicago, IL.

Anastasia Rivkin, PharmD, BCPS, et. al.

Fairleigh Dickinson University

Title: Integration of iPads into a Pharmacy Classroom.

Originally presented at American Association of Colleges of Pharmacy Annual Meeting,

July 13-17, 2013 in Chicago, IL.

Maria Leibfried, BS, PharmD, BCNSP, CCP

St. John's University College of Pharmacy & Health Sciences

Title: Designing Pharmacy Mobile Applications: A Collaboration between Pharmacy and HIT Students.

Originally presented at American Association of Colleges of Pharmacy Annual Meeting,

July 13-17, 2013 in Chicago, IL.

Michael J. Avaltroni, PhD, et. al.

Fairleigh Dickinson University

Title: Advancing Pharmacy Education through a Series of Innovative Curricular and Co-Curricular Strategies.

Originally presented at American Association of Colleges of Pharmacy Annual Meeting,

July 13-17, 2013 in Chicago, IL.

Frank Breve, PharmD, MBA

Mid-Atlantic PharmaTech Consultants, LLC

Dean Gianarkis, MS, PharmD

Pfizer, Inc.

Title: Assessment of Residents with Pain in a Long-Term Care.

Originally presented at PAINWeek 2013, Sept. 4-7, 2013 in Las Vegas, NV.

A Case of Methylene Blue Overdose In The Treatment of Ifosfamide Toxicity

by Gregory J. Hughes, PharmD, BCPS, CGP

We report a case of a methylene blue dosing error and adverse event in the setting of the management of ifosfamide-induced encephalopathy. For the treatment of ifosfamide-induced encephalopathy, methylene blue can be given orally or intravenously and is typically dosed 50 mg three to four times a day. For patients who have experienced encephalopathy from ifosfamide in the past, methylene blue can be used prophylactically to prevent future episodes at similar doses.¹ Methylene blue is available as a 1% solution (10 milligrams per milliliter) for injection in one milliliter and ten milliliter vials and can be injected either directly or after dilution.

Methylene blue is an oxidizing agent used in the treatment of a variety of conditions. It is indicated for the treatment of drug-induced methemoglobinemia², a condition generally caused by the use of a number of different medications, including sulfonamides, phenazopyridine, metoclopramide, benzocaine, lidocaine, chloroquine, dapsone, nitrites, and nitrates.³ Methemoglobinemia is generally characterized by hypoxia as this abnormal hemoglobin is unable to carry oxygen as hemoglobin does. Patients with methemoglobinemia frequently suffer from hemolysis (especially those who also are deficient in glucose-6-phosphate dehydrogenase). The glucose-6-phosphate dehydrogenase enzyme generally assists in regenerating normal hemoglobin after exposure to oxidants and its deficiency leaves a person at risk of accumulating methemoglobin.³

Methylene blue has also been used off-label in the treatment of a number of oncologic conditions, shock, hypotension, parathyroid tumor localization, and ifosfamide-induced encephalopathy.¹

A patient being treated with high-dose ifosfamide was given repeated doses of methylene blue at a dose of 50 milliliters rather than 50 milligrams. Fifty milliliters is equivalent to 500 milligrams, which was ten times the intended dose. As a result, the patient's skin took on a distinct blue color. This error occurred due to a substitution in the computerized physician order entry system where the dose is generally requested in milligrams. For this medication however, the milliliter unit was selected, resulting in the ten-fold overdose. This entry was made by the prescriber, verified by the pharmacist, and administered repeatedly by the nurse. Of note, the order was changed from an intravenous push to an intravenous piggyback due to the large volume (50 milliliters) that needed to be administered. Preparation of each dose required the use of five vials of methylene blue (10 milliliters each) and the error was detected when the pharmacy ran out of methylene blue. The patient experienced no other adverse events, his mental status improved in the following days, and skin color returned to normal after approximately one week without intervention.

Ifosfamide is an alkylating agent with the Food and Drug Administration indication for germ cell testicular cancer and is frequently used off-label for a number of sarcomas.⁴ It is an

analog of cyclophosphamide and shares a number of toxicities including nausea, vomiting, hemorrhagic cystitis, and bone marrow suppression which can be severe enough to limit the dose that can be used. Additional toxicities of ifosfamide include neurotoxicity.⁴ This encephalopathy occurs in 10-40% of patients receiving high-dose ifosfamide and can range in severity from mild somnolence and agitation to severe somnolence, disorientation, and hallucinations.^{5,6} The most severe of cases can result in coma, seizures, or toxic psychosis.⁶

Development of encephalopathy following ifosfamide administration likely involves multiple metabolic steps though the exact pathophysiology is not completely understood. Ifosfamide first undergoes hepatic metabolism through cytochrome P450 3A4 and 2B6 to several active and inactive metabolites. These metabolites likely include several dechloroethylated products which can lead to an accumulation of chloroacetylaldehyde. Chloroacetylaldehyde is potentially the causative neurotoxin as it is structurally similar to chloral hydrate, a hypnotic, and acetaldehyde, a neurotoxic metabolite of ethanol.^{5,6}

Methylene blue has multiple proposed mechanisms for correcting methemoglobinemia and reducing ifosfamide-induced toxicity. As a potent oxidizing agent, it is first reduced to leukomethylene blue which reduces methemoglobin to hemoglobin. Methylene blue greatly enhances the ability of nicotinamide adenine dinucleotide phosphate to reduce methemoglobin to hemoglobin, making it the treatment of choice for methemoglobinemia.⁷ As for prevention of ifosfamide-induced encephalopathy, methylene blue may act as an alternative electron acceptor and by inhibiting monoamine oxidase, disrupting the formation of the toxic products mentioned above. It is not believed that methylene blue interferes with any part of the absorption, distribution, metabolism, or elimination of ifosfamide.⁶

Other adverse events of methylene blue include hypertension, dysuria, and paradoxical methemoglobinemia and hemolysis.¹ A Food and Drug Administration warning reported that patients given methylene blue who were also taking serotonergic psychiatric agents experienced symptoms consistent with serotonin syndrome. This is consistent with the proposed mechanism of action for methylene blue and its inhibition of monoamine oxidase, which is responsible for breaking down serotonin in the brain. Patients who are already taking serotonergic agents such as selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and some other psychiatric medications should have the benefits and risks of using methylene blue considered prior to administration.⁸ No dosage adjustment is recommended for renal or hepatic impairment.

Medication errors are a ubiquitous problem across healthcare settings. Selecting the incorrect unit or failing to acknowledge the unit

of measure is one of the caveats of moving to a computerized physician order entry process. In order to limit events like this from occurring in the future, it is important to acknowledge the shortcomings of technology, promote reporting of errors, and to work with the health information technology department to eliminate inconsistent or unnecessary options. Additionally, every member of the patient care team can have the opportunity to identify and prevent medication errors. As we see in the case above, the physician, pharmacist, and nurse could have all noticed this odd dosing regimen.

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Region News

REGION 5 NEWS

By Alan "Scoop" Aronovitz, RPh, C.C.P.

Paul and Amelia Batastini were present and assisted at the White Coat ceremony held in September at Temple University Pharmacy School. More than 150 students were in attendance. A reception was held immediately after. Caroline Vizzi, daughter of Lyn Vizzi and granddaughter of Amelia Batastini, will attend pharmacy school in September, 2014. Her grandmother and mother hope she chooses their Alma Mater, Temple.

We wish Ron Sorr a speedy recovery after his recent surgery. Ron, owner of Trenton Avenue Pharmacy in Atlantic City, has served as our CE Chairman and we look forward to his continued attendance at our meetings.

NJPhA Region 5 has donated a medicine cart to the Atlantic County Office of Emergency Preparedness (OEP) for use in securely storing medication at the County's Medical Needs Shelter. The Region 5 Board of Directors approved the expenditure after they were made aware of the lack of secure storage for medication. The members of the New Jersey Pharmacists Association's Academy of Disaster Management Pharmacist (ADMP) have been instrumental in developing the formulary of drugs that are now available for use in the County's Medical Needs Shelter. While no drugs were on hand during Hurricane Irene, the development of a formulary lead to the successful availability of medications to treat shelter patients during Hurricane Sandy. Region 5 President Steven Chang of Parkway Pharmacy observed that the mission of the New Jersey Pharmacists Association (NJPhA) is to advance the profession of pharmacy and pharmacists as health care providers while providing optimal care to the patients they serve. "Once we saw there was a need for a med cart we gave the project our approval



August 22, 2013 - Jack Schiffler and Don Weger from the Atlantic County Office of Emergency Preparedness are presented with the NJPhA Region 5 Med Cart

in support the Region 5 ADMP and the community we serve in Atlantic County." Region 5 Treasurer Mark Taylor of Jersey Shore Pharmacy oversaw the dispersal of the funds, while Region 5 Second Vice President and Secretary Alan S. Aronovitz of ShopRite Pharmacy delivered the cart and set it up for the OEP.

NJPhA Region 5 is currently seeking members interested in serving on our Regional Board of Directors (RBOD), these include Secretary, County Directors - one representative from each county, and our Committee Chairpersons. Our Committees include continuing education, finance, awards and scholarships, membership, public health and relations, permanent organization, Students, sunshine, and Technicians. If you are interested in serving please send an e-mail to ASAXPCS@aol.com.

Practice Spotlight:

Safe Communities Coalition of Somerset/Hunterdon Counties

by Leonard F. Weinfeld, R.Ph., M.S.

The Safe Communities Coalition of Somerset and Hunterdon Counties is a coalition of several substance abuse treatment and counseling agencies. The Coalition has over 60 members, the majority of whom are healthcare professionals and enforcement officers. The mission is to reduce drug abuse, the use of marijuana, tobacco, and underage drinking through widespread community collaboration and community education. I am a practicing pharmacist for over 40 years and am the only pharmacist member of the Coalition. I serve on a workgroup for reducing prescription drug abuse.

The group has two major endeavors. The first is to reduce the availability of expired and unwanted prescription drugs, and the second is to increase the utilization of the state Prescription Monitoring Program (PMP) by pharmacists and physicians.

The Coalition held a student poster contest that included the message that prescribed drugs can be abused and lead to the use of dangerous street drugs, and that unwanted drugs can be safely discarded in drop-off boxes. I have placed the winning posters in several pharmacies. In addition, the Coalition supports drug drop-off events during which residents can discard unwanted drugs at drug drop-off events. The Coalition has also worked to obtain three additional drop-off boxes, making it easier to drop off drugs.

In order to increase the effectiveness of the PMP, meetings with James Mielo, RPh, Administrator of the PMP, and Coalition members including myself have been held to discuss how the PMP database

can be improved to increase the detection of doctor shopping and excessive/duplicate filling of controlled drug prescriptions. Also, the Coalition is supporting PMP efforts to increase physician awareness of the PMP and to register physicians for access to the database. A presentation and PMP registration is being scheduled at Hunterdon Medical Center. I have attended the meetings of the local chapters of NJPhA and NJSHP and informed the attendees of the mission of the Safe Communities Coalition. Furthermore, I discussed using the PMP database to identify patients potentially abusing CDS drugs.

In conclusion, pharmacists can support the Coalition by their continued diligence in dispensing CDS drugs and by identifying patients abusing those drugs. Also, pharmacists can inform patients of the availability of drop off boxes to safely discard medications. Posters can be obtained from the Coalition and placed in pharmacies.

More information about the Safe Communities Coalition and their activities is available on the website - www.safecoalition.org.

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Academy News

Academy of Disaster Management Pharmacists News (ADMP)

By Ace Reporter Alan "Scoop" Aronovitz, R.Ph., C.C.P.

Harold Bobrow, ADMP Vice-President, will be traveling to the Center for Domestic Preparedness (CDP) in Anniston, AL in February. The CDP develops and delivers advanced training for emergency response providers, emergency managers and other government officials from state, local and tribal governments. The Center offers more than 50 training courses focusing on incident management, mass casualty response, and emergency response to a catastrophic natural disaster or terrorist act. Harold has been accepted in the Pandemic Planning and Preparedness program, a three-day course that provides planning and management level responders, the tools necessary to assemble an effective pandemic response.

The course culminates in a practical exercise that casts students in various government roles where they must participate in planning and responding to a pandemic. Pandemics have the potential to kill millions worldwide. The 1918 pandemic, an antigenic shift of the flu from Europe, caused 149,540 cases in NJ alone with 4,398 New Jersey residents dying in just one month. In an age where one can easily travel and are come in contact with people from the far reaches of the globe and terrorists plot increasingly sophisticated attacks the need for this type of training is invaluable. We wish Harold success and look forward to the knowledge he brings back to NJ from the CDP.

The membership of NJPhA Region 5 recently donated a medicine

cart to the Atlantic County Office of Emergency Preparedness for use in their Medical Needs Shelter. (See the full story under Region News.) The ADMP encourages each Region to work with their Counties' Offices of Emergency Preparedness and Medical Reserve Corps. If you have any questions about doing so, please feel free to contact ADMP Secretary Alan S. Aronovitz at ASAXPCS@aol.com.

On October 29th Lt. Governor Kim Guadagno was joined by Atlantic County and Cape May County elected officials in a ceremony at the Anthony "Tony" Canale Training Center in Atlantic County. The gathering was staged on the one year anniversary of Superstorm Sandy to thank the Office of Emergency Preparedness professionals, volunteers, and first responders from the area. In attendance was ADMP Secretary Alan S. Aronovitz, who was one of many health professionals who volunteered during Sandy.

The ADMP continues to recruit new members (request a membership brochure by sending an e-mail to ASAXPCS@aol.com) and encourages our members to join the Medical Reserve Corps (MRC) in their county. You can apply online at <http://www.njmrc.nj.gov/hcpr/>.

Finally, as the Regions continue to develop their Regional Board of Directors (RBOD), the ADMP recommends that an ADMP member from each county within the Region be appointed to report to the RBOD to provide input and expertise on disaster management issues.

Pharmacy Continuing Education Activity: Prescription Drug Abuse

by Michele Pisano, PharmD, CGP

OBJECTIVES:

Upon completion of this activity, participants should be able to:

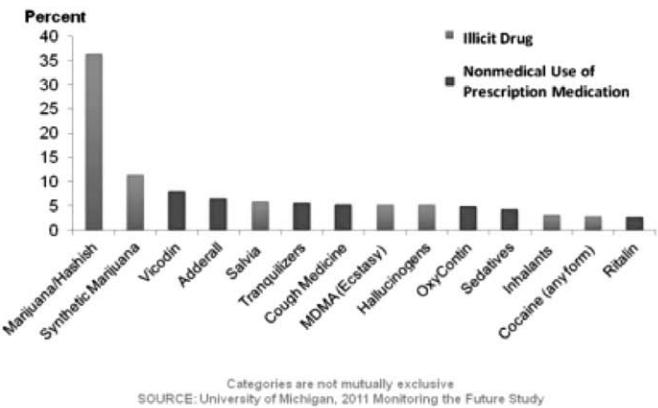
1. Describe the demographics of prescription drug abuse
2. Describe methods of drug diversion
3. Recognize patient characteristics that may suggest drug diversion
4. Describe the role of the pharmacist in prescription drug abuse
5. Explain prescription drug monitoring programs and I-STOP

Patient Case

A 23-year-old male, Tim died on his bedroom floor from a prescription drug overdose. Tim's addiction began when he was 19 and suffered from severe headaches; he went to see his physician who started him on a course of oxycodone, which led to an addiction and eventually use of street drugs; taking over his life.¹

"Prescription drug abuse is the *intentional* use of medication without a prescription in a way other than prescribed for the experience or feeling that it causes."² Prescription drug abuse is rapidly becoming one of the most serious public health concerns of this country. In 2010, 2.7% of the US population (~7 million people) used psychotherapeutic drugs for nonmedical purposes. The medications most commonly abused psychotherapeutic drugs are pain relievers, tranquilizers, stimulants, and sedatives.² In 2010, 2 million people reported using prescription painkillers nonmedically for the first time in the previous year, according to a National Survey on Drug Use and Health.³ Nearly 1 in 12 high school seniors reported nonmedical use of Vicodin; 1 in 20 reported abuse of OxyContin.² Three recent studies surveyed young people who injected heroin and nearly half of them reported abusing prescription opioids before starting to use heroin.⁴

After Cannabis, Nonmedical use of Prescription and Over-the-Counter Medications Account for Most of the Commonly Abused Drugs in 12th Graders (in the past year)



NIH, National Institute on Drug Abuse. Topics in Brief: Prescription Drug Abuse
<http://www.drugabuse.gov/publications/topics-in-brief/prescription-drug-abuse>²

Drug overdose death rates in the United States have more than tripled since 1990 and have never been higher. In 2008, more than 36,000 people died from drug overdoses, prescription drugs caused most of these deaths. 100 people die from drug overdoses every day in the United States.³ In 2010, more than 200,000 visits to the emergency room (ER) were due to opioid misuse or abuse.⁵ The CDC reported that there were 20,044 prescription drug overdose deaths, of that 14,800 were from opioid pain relievers, in 2008.⁶ "In 2009, 1.2 million emergency department (ED) visits (an increase of 98.4% since 2004) were related to misuse or abuse of pharmaceuticals, compared with 1.0 million ED visits related to use of illicit drugs such as heroin and cocaine. Prominent among these prescription drug-related deaths and ED visits are opioid pain relievers (OPR), also known as narcotic or opioid analgesics, a class of drugs that includes oxycodone, methadone, and hydrocodone, among others. OPR now account for more overdose deaths than heroin and cocaine combined."⁶ According to the Centers for Disease Control and Prevention (CDC), the numbers of deaths from prescription painkiller drug overdose increased five fold among women from 1999 to 2010. In 2010, over 6,600 women, or 18 women every day, died from a prescription painkiller overdose.⁵

Drug Diversion

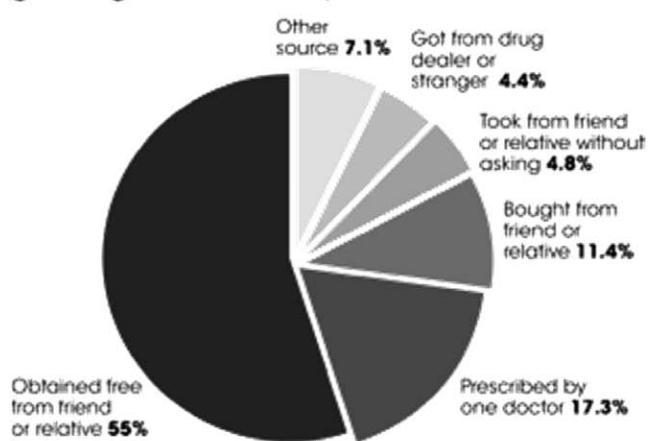
Drug diversion is the use of prescription medications for illegitimate recreational purposes. The Drug Enforcement Administration (DEA) has estimated that prescription drug diversion is a \$25 billion-a-year industry and can occur at any point in the drug delivery process.⁷ Diversion can occur in many ways, for example, robberies and thefts from manufacturers, distributors, or pharmacies, residential burglaries, and medicine cabinet thefts from family members or cleaning and repair personnel. Other methods of drug diversion are illegal sale of prescriptions by physicians, and theft, forgery, or alteration of prescriptions by health care workers or patients.

A Staten Island mother visited eight doctors who wrote nine prescriptions for oxycodone, which she filled at seven pharmacies. This occurred over a month's time and netted 1798 pills with a possible street value of tens of thousands of dollars.⁸

Doctor Shopping

Doctor shopping is when individuals visit numerous physicians to obtain multiple prescriptions. States have either general doctor shopping laws, specific doctor shopping laws or both. Almost all states have a general fraud statute that prohibits obtaining drugs from fraud, deceit, misrepresentation, or concealment of material fact. Specific doctor shopping laws prohibit patients from withholding from health care practitioners that they have received prescriptions for any controlled substance from another practitioner, even if in similar therapeutic class. New York has both general and specific doctor shopping laws and New Jersey has only general doctor shopping laws.⁹

People who abuse prescription painkillers get drugs from a variety of sources⁷



Centers for Disease Control and Prevention. Policy Impact: Prescription Painkiller Overdoses. <http://www.cdc.gov/homeandrecreationsafety/rxbrief/>⁷

The Role of the Pharmacist

Pharmacists are the most accessible health care professionals and play a vital role in helping to combat prescription drug abuse. According to the DEA, there is a corresponding responsibility for the pharmacist who fills the prescription. The pharmacist that knowingly fills the fraudulent prescription is subject to the same penalties as the physician issuing it. A pharmacist is required to exercise sound judgment when making a determination about the legitimacy of a controlled substance prescription. The pharmacist who deliberately ignores a questionable prescription when there is reason to believe it was not issued for a legitimate medical purpose may be prosecuted along with the issuing physician, for knowingly and intentionally distributing controlled substances, a felony offense.¹⁰

The DEA puts forth criteria that may help indicate whether or not a prescription written is for a legitimate medical purpose. They are as follows:

- The prescriber writes significantly more prescriptions (or in larger quantities) compared to other practitioners in the area.
- The patient returns to the pharmacy more frequently than expected. For example, a prescription, which should have lasted a month, is trying to be refilled earlier.
- The prescriber writes prescriptions for antagonistic drugs “uppers and downers” at the same time, ie amphetamines and benzodiazepines.
- Patient appears presenting multiple prescriptions for the same medication written out for different people or a number of people appear simultaneously, or within a short time, all bearing similar prescriptions from the same physician.¹¹

A pharmacist can also help identify patients that may be suffering from addiction. The Omnibus Budget Reconciliation Act (OBRA) states that all patients have a right to a consultation with a pharmacist. During the consultation, pharmacists can help patients understand instructions for how to take controlled substances correctly. They can also screen patients whenever substance abuse is suspected and either refer them to their physician or a treatment program. A screening tool that can be used by both physicians and pharmacists to assess whether patients are suffering from addiction is the CAGE Questionnaire for Prescription Drug Abuse.¹²

It consists of the following 4 questions.

Two “yes” responses indicate that the patient should be investigated further.

1. Have you ever felt the need to Cut down on your use of prescription drugs?
2. Have you ever felt Annoyed by remarks your friends or loved ones made about your use of prescription drugs?
3. Have you ever felt Guilty or remorseful about your use of prescription drugs?
4. Have you Ever used prescription drugs as a way to “get going” or to “calm down?”

http://www.prescriptiondrugmisuse.org/index.php?page=pharmacistsand_physicians¹²

Pharmacists that service patients in neighboring states must be familiar with the laws in other states as patients may travel to out-of-state pharmacies to circumvent legal barriers.

Prescription Drug Monitoring Programs

In an effort to try to combat prescription drug diversion and abuse, state and federal legislation has developed prescription drug monitoring programs (PMPs). PMPs are electronic databases that collect designated data on controlled substances dispensed in the state. Pharmacists are required to submit the data usually twice per month. As of October 16, 2011, 37 states have operational PMPs, including New York and New Jersey.¹³ In 2011, the Prescription Drug Abuse Prevention Plan, put forth by the White House Office of National Drug Control Policy (ONDCP), recommends better monitoring of drug diversion and “doctor shopping” through PMPs used by health care providers that can share data across states.¹⁴

I-STOP

On August 27, 2012, New York State signed into law the *Internet System for Tracking Over-Prescribing* (I-STOP) bill. This law establishes an on-line, “real time” controlled substance reporting system that requires practitioners to review a patient’s controlled substance prescription history on the system prior to prescribing. Pharmacists can review the system to confirm that the prescription is legitimate prior to dispensing; however, it is not mandated by law. I-STOP requires the Department of Health to establish and maintain an on-line, real time, controlled substance (CDS) reporting system. Controlled substance dispensing data from pharmacies will be uploaded to the system in “real time”. Under the previous law, pharmacies had to report medications dispensed on the 15th of the month following the month in which the prescription was dispensed.¹⁵

The goal of I-STOP is to reduce prescription drug abuse by providing a barrier to “doctor shopping”.¹⁵ Doctors will be able to see in “real time” the names of other doctors prescribing CDS for that patient, and which controlled substances were prescribed.

The pharmacist must go to <https://apps.health.ny.gov/pub/top.html> to set up an account in order to access patient information through I-STOP. Currently, only pharmacists with a license to practice in New York can set up an account.

Electronic Prescribing

I-STOP mandates the electronic submissions of all prescriptions by March 27, 2015. It requires that the prescription drug registry be compatible with the electronic transmission of prescriptions for controlled substances. This will help to eliminate diversion that results from alteration, forgery or theft of a prescription. The law also requires that by March 30, 2013 all official NYS prescription forms be modified to include a section where the prescriber may indicate whether the patient is limited English proficient and a line to specify the preferred language. However, if this area completed by the prescriber the prescription can still be filled.¹⁶

Updating the Controlled Substance Schedules in New York

Beginning February 23, 2013, hydrocodone will be treated as a Schedule II controlled substance in New York regardless of formulation and tramadol will be added to the list of Schedule IV controlled substances in New York.^{16,17}

Improving Education and Awareness

I-STOP is developing recommendations on continuing education for practitioners and pharmacists about the potential for abuse of controlled substances and the proper balance between pain management and abuse prevention.¹⁷

Safe Disposal

I-STOP requires the Department of Health (DOH) to institute a program for the safe disposal of unused controlled substances. DOH will work with local police departments to establish secure disposal sites.¹⁷ Currently, the recommended way to dispose of controlled substances by the FDA is either through drug take-back events in the community or follow any specific disposal instructions on the drug label. Drug take-back events are done in the community, usually at local hospitals, where patients can drop off their medications to DEA agents and pharmacists that collect the medications to dispose of them after the event. Pharmacists are also there to counsel on proper drug disposal and answer any medication related questions. If neither of these are available, patients should take the medication out of their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter, then put them in a sealable bag, empty can, or other container to prevent the medication from leaking or breaking out of a garbage bag.¹⁸

Clinical Implications

It is evident that prescription drug abuse is a growing problem and drug-abused morbidity and mortality continues to rise. Pharmacists and physicians should make every effort to limit drug diversion, however, prescribers should not be reluctant to prescribe opioid drugs to patients with a legitimate need.

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The author has no financial or other relevant relationships to disclose.



Continuing Education Quiz:

The New Jersey Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is approved for a maximum of 1 hour (0.1 CEU) of pharmacy continuing education credit. A Statement of Credits will be issued within 30 days subject to documented attendance and completion of evaluation materials. Expiration Date: 1/10/2017
UAN: 0136-0000-13-059-H04-P Prescription Drug Abuse

Questions

- 1) The class of prescription drugs most commonly abused is:
 - A) Antidepressants
 - B) Benzodiazepines
 - C) Anabolic Steroids
 - D) Opiates

- 2) Overdose from prescription drugs:
 - A) Has more than doubled since 1990
 - B) Has been on the rise but still behind cocaine and heroin overdoses
 - C) Has been declining due to increased awareness
 - D) Has increased five fold among women from 1999 to 2010

- 3) If a pharmacist believes that a prescription for a controlled substance was written for a nonmedical purpose he/she:
 - A) Must fill prescription
 - B) Should fill prescription only after verifying with office that was written by the physician
 - C) Should fill prescription only after speaking with physician directly and verifying that he/she wrote prescription
 - D) Should refuse to fill prescription even after verifying

CE Assessment Answers

Passing Score is 70% or above

Please circle your answers (one answer per question)

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

Program Evaluation – Must be completed for credit

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

- 4) According to the DEA criteria, which of the following would not be a reason to suspect a prescription is fraudulent:
 - A) A patient presents with prescriptions for both Adderall® and Xanax® from the same prescriber
 - B) The directions differ from the patients previous prescription for the same medication
 - C) A patient presents you with multiple prescriptions for the same medication for different people
 - D) A patient is trying to pick up their prescription for Percocet 10 days early
- 5) All of the following are true regarding I-STOP except:
 - A) It is the New York State prescription drug monitoring program that establishes an online, “real time” reporting system
 - B) Will mandate that all prescriptions be submitted electronically by March 2015
 - C) Requires that all pharmacies submit a record of controlled substances by the 15th of each month
 - D) Hydrocodone will now be treated as a schedule II controlled substance and Tramadol a Schedule IV in New York
 - E) All of the above are true

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:

Circle correct test answers and return to:

NEW JERSEY PHARMACIST ASSOCIATION
Attention: Journal C.E. Department, 760 Alexander Rd.,
PO Box 1, Princeton, NJ 08543-0001

Enclosed is my check for: NJPhA Member (**FREE**)

\$15.00 Non-member

Statements of Credit will be uploaded to www.mycpemonitor.net

Name _____

Address _____

City _____ State _____ Zip _____

Email _____

Phone Number _____ License No. _____

E-PID# _____ Birth mm/dd _____

continuing education for pharmacists

Volume XXXI, No. 6

Anemia: Disease Basics, Treatment and Appropriate Use of ESAs

Mona T. Thompson, R.Ph., PharmD

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

Goal. The goal of this lesson is to provide a basic background on anemia to include pathophysiology, epidemiology, and associated laboratory studies in the diagnosis of anemia; common types of anemia and their causes; and treatment options in adults.

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

1. demonstrate an understanding of the epidemiology, pathophysiology, and associated laboratory studies in the diagnosis of anemia;
2. recognize the general characteristics and causes for select types of anemia;
3. identify the general adult treatment options for anemia types, as well as key prescribing and counseling points for the entities discussed; and
4. demonstrate an understanding of the current recommendations for the use of erythropoietin stimulating agents (ESAs).

Background

Anemia is one of the most common hematologic problems in both adults and children. In a prevalence study conducted using data from 1993 to 2005, the World Health Organization (WHO) reported that globally, anemia affected 1.62 billion people, correlating to almost 25 percent of the population. Therefore, it is

considered a public health concern that affects both developed and developing countries. Estimates in the Americas and Europe were lower than in other regions such as Africa and Eastern Mediterranean.

Anemia is the result of one or more of the three independent mechanisms that occur secondary to various deficiencies and disorders: (1) decreased red blood cell (RBC) production, (2) increased RBC destruction, and (3) blood loss. Decreased RBC production is the result of nutrient deficiencies such as iron, vitamin B12, and folate; bone marrow suppression (drugs, chemotherapy, radiation); bone marrow disorders (aplastic anemia, myelodysplasia, tumor infiltration); low levels of erythropoietin (EPO); chronic kidney disease; and other chronic diseases. Iron deficiency is the cause in approximately 30 to 50 percent of anemia cases. Hemolytic anemias are caused by RBC destruction. Examples include sickle cell disease and thalassemias. In some cases, the cause of anemia is unexplained.

The WHO defines anemia as a hemoglobin (Hb) level less than 13 grams per dL in men, and less than 12 grams per dL in women. Other authors have proposed different ranges and lower limits of normal that vary based on age, sex, and race. Patients living at high altitude and athletes may also have different normal values.

Anemia occurs at all stages of life but most often in pregnant women and preschool-aged children, which are populations that

have an increased demand for iron. In the United States, the prevalence of iron-deficiency anemia among children declined during the 1970s in association with increased iron intake during infancy. It is estimated that 4 percent of women in the United States between the ages of 20 to 49 years have iron deficiency anemia. According to the WHO definition, more than 10 percent of persons older than 65 years are anemic. The prevalence increases with age, and one study found that it approaches 50 percent in chronically ill patients living in nursing homes.

Table 1 lists the normal red blood cell parameters in adults. Several studies have demonstrated that anemia is an independent risk factor for increased morbidity and mortality, and decreases quality of life in older persons living independently. Functional deterioration increases with decreased hemoglobin concentration in an inverse and linear fashion.

Red Blood Cells Life Cycle and Function of Erythropoietin

RBCs, also known as erythrocytes, are produced through the process of erythropoiesis which occurs in the bone marrow. While the process is dependent on various factors, erythropoietin (EPO) plays an integral role. EPO is an endocrine hormone produced in the kidney by cells that sense inadequate tissue oxygenation. Once hypoxia is sensed, EPO is produced and travels to the bone marrow where

Table 1
Normal Red Blood Cell Parameters for Adults

Red Cell Parameter	Men	Women
Hemoglobin, g/dL	15.7 +/- 1.7	13.8 +/- 1.5
Hematocrit, percent	46 +/- 4.0	40.0 +/- 4.0
RBC count, million/ μ L	5.2 +/- 0.7	4.6 +/- 0.5
Reticulocytes, percent	1.6 +/- 0.5	1.4 +/- 0.5
Mean corpuscular volume, fL	88.0 +/- 8.0	88.0 +/- 8.0

it augments and differentiates two erythroid progenitors – burst forming units-erythroid (BFU-E) and colony forming units-erythroid (CFU-E) – into normoblasts. Once the normoblast loses its nucleus, it is termed a reticulocyte or immature red blood cell. The reticulocyte spends about three days in the bone marrow, and an additional day in peripheral blood before it is fully matured. The mature RBC circulates in the body, delivering oxygen linked to hemoglobin from the lungs to tissue capillaries. After 110 to 120 days, the RBC is removed from circulation by macrophages sensing that the cell is aged. Under steady state conditions, the rate of RBC production equals the rate of RBC loss, and the reticulocyte count represents about 1 percent (normal for adults is 0.5 to 2 percent) of the total circulating RBC. The normal RBC count is five million μ L ($5 \times 10^{12}/\text{L}$). Therefore, the bone marrow must produce approximately 50,000 reticulocytes/ μ L of whole blood each day in order to maintain stable RBC mass. Persistent reduced rates of production lead to anemia. The rate of red blood cell production greatly increases under the influence of high levels of EPO. In fact, normal bone marrow can increase erythropoiesis in response to EPO approximately fivefold in adults.

Signs and Symptoms of Anemia

The signs and symptoms of anemia are dependent on the degree of anemia, the rate at which it evolved, and the oxygen demands of the patient. Fatigue, pallor, shortness

of breath, dizziness, coldness in hands and feet, and chest pain are common, yet nonspecific, symptoms that are often experienced. These symptoms occur due to the lack of oxygen delivery to tissue and/or acute, marked bleeding causing hypovolemia. Clinicians are encouraged to complete a thorough and systematic approach so as not to overlook underlying causes. Angular cheilitis (cracking at the edges of the lips) and koilonychias (spooning of the nails) may accompany iron deficiency anemia. Neurological manifestations can accompany or predate anemia associated with vitamin B12 deficiency. The patient's past medical history can be helpful, as can a review of pharmacologic agents since certain medications, especially chemotherapy, may be associated with bone marrow suppression. In addition, some medications such as NSAIDs and anticoagulants can increase the risk of bleeding resulting in anemia secondary to blood loss.

Laboratory Studies for Diagnosing Anemia

This section will briefly review the laboratory studies that a clinician may utilize to not only confirm a diagnosis of anemia, but classify the type and determine the treatment approach. Upon confirmation of anemia (Hb <13g/dL in men; <12g/dL in women according to WHO), a complete blood count is generally obtained. The mean corpuscular volume (MCV) or red blood cell size is used to distinguish microcytic (MCV <80fL), normocytic (MCV 80 to 100fL), and macrocytic (>100fL) anemias.

The most commonly seen

microcytic anemias are iron deficiency, thalassemia, and anemia of chronic inflammation. Macrocytic anemias are often due to alcoholism, liver disease, folic acid and vitamin B12 deficiency. Ferritin serum levels, which measure iron storage in the body (but not the iron contained in heme or hemoglobin), may also be obtained with vitamin B12 and folate levels.

Peripheral blood smears entail examining a single layer of blood microscopically, in order to study the content of the cell. A reticulocyte count is a blood test that measures how fast red blood cells are made by the bone marrow and released into the blood. Reticulocyte counts usually rise secondary to blood loss or in cases of hemolytic anemia. Additionally, a low total white blood cell (WBC) count in a patient with anemia would lead to consideration of bone marrow suppression, whereas a high total WBC may correlate with infection, inflammation, or a hematologic malignancy.

Treatment of Select Anemias

The remainder of this lesson will review iron deficiency anemia (IDA), anemia of chronic disease (ACD), and anemia associated with chronic kidney disease (CKD) as these types of anemia are often encountered in the community setting. Various oral and intravenous iron agents as well as erythropoietin stimulating agents (ESAs) are prescribed for their treatment.

Iron Deficiency Anemia

Iron deficiency is the most common nutritional deficiency worldwide. Iron metabolism is controlled by absorption rather than excretion, and iron is only lost through blood loss or in RBCs as they slough. Men and non-menstruating women lose approximately 1mg of iron each day, while menstruating women lose 0.6 to 2.5 percent more. Pregnancy requires about 700mg of iron; a complete blood donation of 500mL contains 250mg of iron. Iron absorption occurs mostly in

Table 2
Causes and Examples of Iron Deficiency in Adults

Increased iron loss
Acute hemorrhage
Chronic or occult hemorrhage
Menstruation
Inflammation
Cancer
Vascular malformation
Hemolysis
Blood donation
Decreased iron in diet
Vegetarian diet
Malnutrition
Dementia
Psychiatric illness
Decreased iron absorption
Antacid therapy or high gastric pH
Celiac disease
Inflammatory bowel disease
Partial gastrectomy
Increased iron requirements
Pregnancy
Lactation

the jejunum, the middle section of the small intestine, and is only about 5 to 10 percent of the dietary intake. The absorption is also somewhat regulated by the body as it decreases in states of overload and increases in states of depletion.

There are two forms of dietary iron: heme iron, which is found in meat; and non-heme iron, which is found in plant and dairy foods. The bioavailability and absorption of non-heme iron requires acid digestion. It is enhanced by ascorbic acid and meat, while it is inhibited by calcium, fiber, tea, coffee, and wine. A large amount of iron is recycled daily for heme synthesis; therefore, only 1 to 2mg of (absorbed) iron is required to replace the iron losses. It is important to note that iron stores become depleted before iron deficiency anemia occurs. Table 2 lists common causes of iron deficiency in adults.

The U.S. Preventive Services Task Force recommends routine screening for iron deficiency in pregnant women. The task force found insufficient evidence to recommend for or against screening in other asymptomatic persons. The

Dietary Reference Intake (DRI) for iron is 8mg per day for healthy, non-menstruating adults, 18mg per day for menstruating women, and 16mg per day for vegetarians (due to the difference in absorption of non-heme iron).

IDA is usually a microcytic anemia. The most accurate initial diagnostic test for IDA is a serum ferritin measurement less than 40mcg/L. When iron deficiency is diagnosed and the underlying cause addressed, restoration of iron supply is necessary. While transfusion can be considered for patients experiencing fatigue, dyspnea on exertion, or for cardiac patients with Hb less than 10g/dL, oral iron therapy is the first line of therapy.

Anemia of Chronic Disease

Anemia of chronic disease (ACD) is an anemia of underproduction of red blood cells. The cause of ACD is multi-factorial and includes a mildly decreased life span of erythrocytes, deregulated iron absorption and transport, inhibition of hematopoiesis, and relative deficiency of erythropoietin. In simplified terms, researchers suggest that the underlying inflammatory medical condition causes the release of cytokines such as interleukins (IL-1 and IL-6), and tumor necrosis factor leading to a cascade of events that alters the RBC life cycle and hematopoiesis process as stated above. Interestingly, it has been observed that the treatment of patients with rheumatoid arthritis using an anti-TNF-alpha antibody led to a reduction in IL-6 levels and an improvement in anemia. In addition to IL-6, hepcidin, a protein generated in the liver, interferes with RBC production by decreasing iron availability for incorporation into erythroblasts. Increased hepcidin levels have been documented in patients with ACD, multiple myeloma, inflammatory bowel disease, and Hodgkin lymphoma. Precipitating illnesses to ACD include active infection, inflammatory condition, alcoholic liver disease, congestive heart failure, thrombosis, chronic pulmonary

disease, diabetes, trauma, etc.

ACD is generally mild, normocytic and normochromic (concentration of Hb in RBC is normal). However, it can become microcytic and hypochromic in long-standing cases, and can be severe. Laboratory findings usually reveal a low reticulocyte count (<25,000/ μ L) reflecting reduced RBC production. The differential diagnosis for ACD among other anemias can be challenging, and is most likely when the following are present: low serum iron, normal to low serum transferrin (glycoprotein that binds to iron and controls the level of free iron), normal to increased ferritin, and elevated erythrocyte sedimentation rate and/or C-reactive protein. The last two findings indicate systemic inflammation. Recognizing iron deficiency along with ACD may require additional testing, but is suggested by the finding of low serum ferritin levels.

Optimal treatment of ACD involves correction of the underlying disease process, if one can be clearly documented. Managing chronic diseases will minimize inflammation and lessen bone marrow suppression. Most patients with mild anemia will have no symptoms; therefore, treatment should be limited to those with severe, symptomatic anemia (Hb <10g/dL). Treatment options for these patients include blood transfusions and ESAs. Transfusions provide immediate relief of symptoms, yet are associated with the following risks: volume overload, iron overload, infections, and acute reactions. ESAs may be used for the treatment of ACD in limited situations, but their use remains controversial.

Anemia in Chronic Kidney Disease

Chronic kidney disease (CKD) affects approximately 26 million adults in the U.S. and is associated with significant morbidity and mortality. Among the medical problems facing this population is anemia with incidence increasing with declining glomerular filtra-

tion. One study suggested that the anemia incidence is less than 10 percent in CKD stage 1 and 2; 20-40 percent in CKD stage 3; 50-60 percent in CKD stage 4; and more than 70 percent in CKD stage 5. Among other factors, the most well-known cause is inadequate EPO production.

The problem can also be compounded by iron deficiency. The mechanism for how EPO production is hindered is not fully understood; however, as renal failure progresses, the contribution of EPO deficiency to anemia increases. Additionally, as previously discussed, acute and chronic inflammation impact CKD patients with anemia by the involvement of cytokines and hepcidin. RBCs have a decreased life span, and uremic toxins are thought to contribute to apoptosis (programmed cell death) in the development of RBCs. Studies have demonstrated an improvement in Hb levels and decreased ESA use with increased adequacy of dialysis (which removes the toxins). It has been hypothesized that one of the molecules in uremia is involved in bone marrow suppression.

The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative's (KDOQI) clinical practice guidelines and clinical practice recommendations advocate annual screening for anemia in all patients with CKD. Most of the anemic patients with CKD will have erythropoietin deficiency which is a diagnosis of exclusion. Many of these patients will also have coexisting iron deficiency. Iron deficiency is almost always present in hemodialysis patients due to bleeding when needles are removed from vascular access, blood infiltration of the vascular access, vascular access procedures, frequent blood testing, and clotting or general blood loss in the extracorporeal circuit. Iron deficiency in patients not yet on hemodialysis is likely due to dietary protein restriction or decreased appetite for red meat. According to the NKF/KDOQI guidelines, ESA therapy should be initiated when the patient's Hb

Table 3
Common Oral Iron Salt Preparations

Preparation	Dose	Elemental Iron Content
Ferrous sulfate tab	325mg	65mg
Ferrous gluconate tab	300mg	36mg
Ferrous fumarate tab	100mg	33mg
Ferrous sulfate elixir	220mg/5mL	44mg

drops below 10g/dL with target Hb level for treatment being 11 to 12g/dL. Treatment levels should not exceed a Hb of 13g/dL. If not already present, iron deficiency often develops with ESA therapy due to the depletion of existing iron stores when stimulating new RBCs.

Iron is usually administered orally in patients on peritoneal dialysis, but not in patients on hemodialysis. Hemodialysis patients, and those unable to respond to oral supplements, will require intravenous iron therapy. Despite adequate dosing of ESAs and iron therapy, patients may still require blood transfusions depending on symptoms.

Iron Treatment

The three most common salts found in oral iron preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate. Oral iron is available as non-enteric coated tablets, enteric coated tablets, prolonged release formulations, or elixirs. Table 3 lists the elemental iron content of common iron salt tablet preparations.

Non-enteric coated iron tablets are the most commonly used agents because of their low cost and effectiveness. Delayed-release and enteric coated preparations are often promoted because they have better gastrointestinal tolerance. However, they are not recommended for initial therapy as they contain less iron and are released further down in the intestinal tract leading to decreased absorption.

Many factors alter the absorption of iron. Iron is best absorbed in a mildly acidic medium. Hence, the co-administration of ascorbic acid 250mg improves the degree of

absorption and is recommended. Phytates (bran, cereal), tannates (tea), and phosphate-containing carbonated beverages bind to iron. Therefore, iron salts should not be given with these foods or beverages. Other factors that limit absorption include medications that raise the gastric pH such as antacids, proton pump inhibitors, and histamine blockers. Certain antibiotics (quinolones and tetracyclines) also bind to iron. Ideally, iron should be taken two hours before or four hours after the ingestion of antacids, quinolones and tetracyclines. Multivitamins should never be used as the sole supplement for IDA, since calcium, phosphate, and magnesium found in the tablet can alter absorption.

The recommended oral daily dose for the treatment of IDA in adults ranges from 150 to 200mg of elemental iron. A common starting regimen is ferrous sulfate tablets 325mg, three times a day. This yields an oral dose of 195mg of elemental iron each day. Using the assumption that 10 percent of the iron is absorbed, hemoglobin may correct in four weeks in patients with moderate, uncomplicated anemia. The duration of therapy varies as some experts recommend continuing iron therapy for six months after hemoglobin is restored so that iron stores are replenished. Others stop therapy upon Hb restoration, and assess for repeated anemia alerting the patient and physician to determine the cause of iron deficiency. Patients predicted to have ongoing iron deficits may require individualized maintenance dosing.

Dose dependent gastrointestinal symptoms, such as abdominal discomfort, nausea, vomiting, diar-

rhea, and constipation, are common and occur in up to 20 percent of patients. Changing the iron salt and formulation are commonly tried; however, these involve dose reductions leading to extended treatment duration. Ferrous sulfate elixir is an option for patients with persistent gastric intolerance. It allows the dose to be titrated up or down until it is tolerated by the patient. While absorption will be affected, taking iron salts with food may alleviate symptoms. Laxatives, stool softeners, and adequate intake of liquids may also reduce constipation.

Indications for intravenous iron include chronic uncorrectable bleeding, intestinal malabsorption, and intolerance to oral iron. As previously discussed, intravenous iron is commonly used in hemodialysis patients. It is important to state that the hematologic response to parenteral iron treatment is not faster than that of oral therapy.

Hypersensitivity reactions have been reported with all of the intravenous iron products. Patients should be closely monitored during administration and for at least 30 minutes following administration of the iron preparation. Deaths have been reported following anaphylactic-type reactions; therefore, these agents should only be used where resuscitation equipment and personnel are available.

At the time of writing this lesson, there were four intravenous preparations available in the U.S. which are described briefly. Refer to product labeling for full prescribing information.

Iron dextran complex contains 50mg of elemental iron per mL and can be given IM or IV. It is indicated for IDA in patients in whom oral iron is not feasible or ineffective. INFeD® and Dexferrum® are two brands of iron dextran, but differ in that they are low and high molecular weight preparations, respectively. Anaphylactic reactions occur in about 1 percent of patients with either the low or high molecular weight products, and are thought to be caused by the free

iron present in the preparation. High molecular weight products are associated with a considerably higher incidence of adverse events than the low molecular weight product. Local reactions include pain, muscle atrophy, and phlebitis. Systemic reactions include fever, urticaria, and a flare in arthritis in patients with rheumatoid arthritis.

Patients receiving iron dextran for the first time must receive a 0.5mL test dose given by slow IV push over five minutes. The remainder of the dose, which is calculated and individualized for the patient based on Hb, may be administered following a one-hour observation period. Fatal reactions have occurred, even in patients who tolerated the test dose. It may be administered by IV bolus at a rate of $\leq 50\text{mg}/\text{minute}$ or diluted in 250 to 1000mL of normal saline over one to six hours. Subsequent doses do not require a test dose. While it may be given IM, IV is the preferred route. IM administration has not been shown to be safer or less toxic, and may be associated with bruising due to repeated injections and variable absorption. Iron dextran complex use has decreased since the introduction of other intravenous iron preparations associated with fewer adverse events.

Ferric gluconate complex (Ferrlecit®) is approved for the treatment of iron deficiency anemia in patients with CKD who are undergoing hemodialysis and receiving ESAs. Off-label use includes cancer-/chemotherapy-associated anemia. It is dosed as 125mg undiluted by slow IV push at a rate of 12.5mg/min or diluted in 100mL of normal saline and infused over 30 to 60 minutes. The dose may be repeated up to a cumulative dose of 1000mg. A 2mL test dose was previously recommended, but is not in current manufacturer labeling. Doses greater than 125mg are associated with increased adverse events. Data indicates that, in comparison to iron dextran, Ferrlecit use results in 3.3 versus 8.7 aller-

gic events per one million doses per year.

Iron sucrose (Venofer®) is approved for IV use only and appears to be safe even in patients with a prior history of sensitivity to iron dextran. It is indicated for the treatment of iron-deficiency anemia in CKD, including non-dialysis dependent patients (with or without ESAs) and dialysis-dependent patients receiving ESA therapy. It may be used off-label for cancer- or chemotherapy-associated anemia. Dosing varies by indication, but is generally either 100mg or 200mg per infusion with a cumulative dose of 1000mg. It may be given slow IV push over two to five minutes, or diluted in normal saline for a slower infusion. Adverse reactions include hypotension (up to 39 percent in hemodialysis patients), peripheral edema, headache, diarrhea, nausea, vomiting, and muscle cramps (29 percent in hemodialysis patients). Life-threatening reactions, including anaphylaxis, may occur in fewer than 1 percent of patients. Product labeling does not indicate the need for a test dose in product-naïve patients, but a test dose is strongly recommended in patients who are sensitive to iron dextran or have other drug allergies.

Ferumoxytol (Feraheme®) is approved for the treatment of IDA in adult patients with chronic kidney disease. It is administered as a 510mg intravenous dose at a rate of 30mg/second as a single dose, followed by a second 510mg dose three to eight days later. A test dose is not required, however, patients should be monitored during and for 30 minutes, or until clinically stable, following administration. Anaphylactic-type reactions presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in post-marketing experience. Feraheme may interfere with MRI imaging for up to three months after the last dose.

Table 4
Guidelines for Use of ESAs in Patients with Anemia

Indications approved by FDA

EpoGen/Procrit

Treatment of anemia

- due to Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
- secondary to Zidovudine use in HIV-infected patients.
- due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Aranesp

Treatment of anemia due to

- Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis.
- the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

ESA to another.

The use of these agents has reduced the need for RBC transfusions, but their use is not without risk. All three product labels carry similar black box warnings regarding greater risk for death, serious adverse cardiovascular reactions, and stroke when the ESA is administered to target a Hb level greater than 11g/dL. Possible causes include complete and/or too rapid correction of anemia that can increase blood pressure and the risk of thrombosis, by accentuating vasoconstriction and increasing platelet adhesiveness and blood viscosity. All of the agents are contraindicated in uncontrolled hypertension. Additional warnings and prescribing restrictions are included for ESAs that are approved for use in patients in treating anemia due to myelosuppressive chemotherapy. Clinicians are reminded to use the lowest ESA dose sufficient to reduce the need for RBC transfusions. In terms of efficacy, epoetin alfa and darbepoetin are widely considered equal when dosed accordingly. ESA doses should be individualized based on causes of anemia and symptoms.

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 0129-0000-13-006-H01-P

Release date: 6-15-13

Expiration date: 6-15-16

CE Hours: 1.5 (0.15 CEU)

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Erythropoietin Stimulating Agents

ESAs are used to prevent the need for RBC transfusions. They have not been shown to improve quality of life, fatigue or patient well-being. ESAs stimulate erythropoiesis through the same process as endogenous EPO. Increases in Hb levels are generally seen two to six weeks after administration. During treatment with ESAs, iron repletion must be maintained to ensure effectiveness.

Currently there are three ESAs available in the U.S. Epoetin alfa, the first ESA available, was marketed as EpoGen® and Procrit® in 1989. Darbepoetin alfa (Aranesp®) was introduced in 2001. Most recently, peginesatide (Omontys®), a synthetic peptide analog of EPO, was approved in 2012, and voluntarily recalled in February 2013. Table 4 summarizes the FDA-approved indications for these products. Refer to product information for approved indications, dosing, monitoring, subsequent dosing adjustments, and information regarding converting patients from one

Summary

Iron deficiency anemia, anemia of chronic disease, and anemia due to chronic kidney disease are among the most common types of anemia. Anemia can have a profound effect on quality of life with symptoms including fatigue, dizziness, shortness of breath, and decreased sense of well being. Complications of anemia include reduced cognitive function and mental acuity, impaired quality of life, and the need for blood transfusions. Untreated anemias can lead to cardiovascular disease with left ventricular hypertrophy and congestive heart failure, or worsen existing heart disease. Anemia may also be responsible for declining renal function in some groups. Oral and parenteral iron supplements, as well as ESAs, are available treatment options. Iron must be administered with ESA therapy to avoid depletion.

continuing education quiz

Anemia: Disease Basics, Treatment and Appropriate Use of ESAs

- An example of hemolytic anemia caused by red blood cell destruction is:
 - iron deficiency.
 - folate deficiency.
 - chronic kidney disease.
 - sickle cell disease.
 - Anemia occurs most often in all of the following EXCEPT:
 - pregnant women.
 - preschool aged children.
 - newborns.
 - Erythropoiesis occurs in the bone marrow.
 - True
 - False
 - All of the following symptoms are common in anemia EXCEPT:
 - fatigue.
 - palor.
 - headache.
 - shortness of breath.
 - Macrocytic anemias are often due to all of the following EXCEPT:
 - alcoholism.
 - thalassemia.
 - liver disease.
 - vitamin B12 deficiency.
 - Iron absorption occurs mostly in the:
 - cecum.
 - duodenum.
 - ileum.
 - jejunum.
 - Iron deficiency anemia is usually a:
 - microcytic anemia.
 - macrocytic anemia.
 - normocytic anemia

Completely fill in the lettered box corresponding to your answer.

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

I am enclosing \$5 for this month's quiz made payable to: Ohio Pharmacists Association.

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8. Recognizing iron deficiency along with ACD is suggested by the finding of low:

 - sedimentation rate.
 - serum iron levels.
 - serum ferritin levels.

9. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends screening for anemia in all patients with CKD:

 - only at diagnosis.
 - biannually.
 - annually.
 - every five years.

10. The oral iron salt containing the highest amount of elemental iron is:

 - ferrous sulfate.
 - ferrous gluconate.
 - ferrous fumarate.

11. Iron is best absorbed in a mildly:

 - basic medium.
 - acidic medium.

12. The preferred route of administration for iron dextran complex is:

 - intravenous.
 - intramuscular.

13. Which of the following requires a test dose prior to administration?

 - Ferumoxytol
 - Iron sucrose
 - Iron dextran complex
 - Ferric gluconate complex

14. All ESA products carry a black box warning regarding greater risk of all of the following EXCEPT:

 - stroke.
 - death.
 - serious cardiovascular reactions.
 - serious hypersensitivity reactions.

15. All erythropoietin stimulating agents are contraindicated in:

 - HIV infection.
 - rheumatoid arthritis.
 - uncontrolled hypertension.

To receive CE credit, your quiz must be received no later than June 15, 2016. A passing grade of 80% must be attained. All quizzes received after July 1, 2012 will be uploaded to the CPE Monitor and a statement of credit will not be mailed. Send inquiries to opa@ohiopharmacists.org.

june 2013

continuing education for pharmacists

Volume XXXI, No. 10

Melanoma-Targeted Therapy: Focus on Mekinist and Tafinlar

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on melanoma and its treatment with targeted therapy, with focus on two new drugs, dabrafenib (Tafinlar®) and trametinib (Mekinist™).

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

1. recognize signs, symptoms, and key features of melanoma, including information on its prevalence;
2. recognize important therapeutic uses for the new drugs and projected benefits over other approved medications for melanoma;
3. select the indication(s), pharmacologic action(s), clinical application(s), and the mode and other considerations for administration of the drugs;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions reported for each agent; and
5. choose important patient information to convey to patients and/or their caregivers.

Introduction

Melanoma is a highly aggressive cancer and remains a major health problem worldwide. An estimated 76,690 adults, 45,060 men and 31,630 women, in the United States will be diagnosed

with melanoma in 2013. Of these, 9,480 deaths (6,280 men and 3,200 women) will be attributed to this cancer. Worldwide, 48,000 melanoma-related deaths occur each year.

Although melanoma tumors account for less than 5 percent of all skin cancers, it is the most pathologic skin cancer, and is responsible for the majority of skin cancer deaths. It is the fifth most common cancer among men, and the seventh most common cancer in women. Twice as many women than men are diagnosed with melanoma before age 40; after 40, predominance shifts to men. By age 80 and older, the mortality rate in men is three times higher than in women. Melanoma mortality rates are 23 times higher in Caucasians than African-Americans. The Annual Report to the Nation on the Status of Cancer, 1975 to 2009, shows that overall cancer death rates continued to decline in the United States among persons of both genders, among all major racial and ethnic groups, and for all of the most common cancer sites including lung, colon and rectum, female breast, and prostate. The report also shows that death rates continued to increase during the latest time period (2000 through 2009) for melanoma (among men only), and for cancers of the liver, pancreas, and uterus. The increase in melanoma over the past 30 years is approximately 4 percent annually.

Melanoma

The onset of melanoma occurs

when melanocytes, the skin's pigment-producing cells, begin to grow uncontrollably. Skin is comprised of two layers: an outer layer, epidermis, and deeper layer, the dermis. Melanocytes are found in the deeper areas of the epidermis. The cancer can invade deep into the dermis to invade lymph and blood vessels, and metastasize to other sites of the body. At the time of diagnosis, the initial treatment is determined by the thickness of the tumor, and more often, by whether the disease has metastasized to regional or distant lymph nodes or to other areas of the body.

Four major types of melanoma can be categorized as follows.

• **Superficial spreading melanoma** is usually flat and irregular in shape and color, with different shades of black and brown. It is the most common melanoma in Caucasians and the most common type overall.

• **Nodular melanoma** usually starts as a raised area appearing dark blackish-blue or bluish-red. Some are devoid of any color.

• **Lentigo maligna melanoma** is most common in sun-damaged skin on the face, neck, and arms. The areas are usually large and flat, and tan with areas of brown. This melanoma is common in the elderly.

• **Acral lentiginous melanoma** usually occurs on the palms, soles, or under the nails. This is the least common melanoma, occurring most often in African-Americans.

Melanoma most often appears on the skin of the trunk (back and

Table 1
New drugs for melanoma

Generic (Proprietary) Name	Distributor	Indication	Dose*	Dosage Form	Most Common Adverse Reactions	Med Guide [†]
Dabrafenib (Tafinlar)	GlaxoSmithKline	Unresectable or metastatic melanoma with BRAF ^{V600E} mutation	150 mg orally twice daily	50, 75 mg capsules	hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, palmar-plantar erythrodysesthesia syndrome	Yes
Trametinib (Mekinist)	GlaxoSmithKline	Unresectable or metastatic melanoma with BRAF ^{V600E} or BRAF ^{V600K} mutation	2 mg orally once daily	0.5, 1, 2 mg tablets	rash, diarrhea, lymphedema	No

*Recommended dose for most patients

†Status at the time of publication

chest) in men and legs in women, but can occur anywhere on the body. Rarely, it appears in the mouth, or in the iris or retina of the eye. Other sites of involvement include the head and neck, skin under the fingernails, soles of the feet or palms of the hands, vagina, esophagus, anus, urinary tract, and small intestine. It may develop from a pre-existing mole. The median age at diagnosis is the early 50s, but melanoma occurs with greater frequency than many other cancer types in young adults as well.

Risk Factors. Some factors that favor melanoma development include:

- fair skin, blue or green eyes, or red or blond hair;
- sunny climates or high altitudes,
- a history of one or more severe sunburns during childhood;
- use of tanning devices;
- close relatives with a history of melanoma;
- certain types of moles (atypical or dysplastic) or multiple birthmarks;
- weakened immune system due to disease or medication.

Symptoms. These may include a mole, sore, lump, or growth on the skin, which can be a sign of melanoma or other skin cancer. A sore or growth that bleeds or

changes color may also be a sign of skin cancer. The “ABCDE rule” may help people remember possible symptoms of melanoma.

Asymmetry: The shape of half of the abnormal area differs from the other half.

Borders: The edges of the growth appear ragged, notched, blurred, or in some manner, irregular.

Color: Color changes from one area to another are apparent, with shades of tan, brown, or black, and sometimes white, gray, red, or blue. A medley of colors may appear within a lesion.

Diameter: The spot is usually larger than 6 mm in diameter – about the size of a pencil eraser; however, the lesion may be smaller (<5 mm) when first discovered.

Evolution: The cancer keeps changing appearance, including size, shape, or color. When it develops in a pre-existing mole, the texture of the mole may change to become hard or lumpy.

Prognosis. Most patients with early-detected melanoma can be cured after surgery, with a five-year survival rate of 91 percent. Overall survival depends upon numerous influences including thickness of the primary tumor, whether or not lymph nodes are involved, or if melanoma cells have

metastasized to distant sites. For melanoma remaining localized to the site where it originated, the five-year survival rate is 98 percent. The five-year survival rates for melanoma that has spread only to nearby lymph nodes or to distant sites in the body, are 82 percent and 15 percent, respectively. Melanoma survival statistics must always be interpreted with caution, though. The data are based on information obtained from thousands of melanoma patients in the United States each year. The actual risk for a particular individual may differ greatly because survival statistics are measured in five-year intervals, and the data may not represent recent pharmacotherapeutic advances in treatment of the particular cancer. Targeted therapy for melanoma introduced during the past couple years may greatly modify survival statistics.

Treatment

Patients with thin cutaneous melanoma usually have a good prognosis following surgical resection, but prognosis remains poor for those who present with, or develop, metastatic malignant melanoma (stage IV disease). Overall survival for melanomas averages less than 12 months.

Treatment recommendations

for melanoma have remained nearly unchanged for the past 40 years. The mainstay of treatment for advanced melanoma has focused on the use of the chemotherapeutic drug dacarbazine (DTIC-Dome), approved for this indication in 1976, which leads to a median survival of eight to 10 months. Poly-chemotherapy containing cisplatin (Platinol) and dacarbazine, or combination of carboplatin (Paraplatin) and paclitaxel (Taxol), may benefit 20 to 40 percent of patients. The impact on disease-free or overall survival with chemotherapy has never been shown in randomized trials. However, these therapies do have substantial persisting toxic effects. Biochemotherapy, a combination of interleukin-2 (aldesleukin, Proleukin) and/or interferon-alpha (Intron A), along with therapeutic agents such as dacarbazine, cisplatin and vinblastine (Velban), has demonstrated a high response rate although this has not translated into improved survival. Such combinations are associated with increased toxicity.

Targeted Therapy

Several key pathways and genes involved in melanoma have been recently identified, and form the basis for intensive research into the pathology of the cancer. These advances have allowed clinicians to begin to classify melanoma into specific molecular subtypes based upon the tumor's genetic characteristics. As a result, the treatment plan may be tailored or personalized to the patient. This approach, referred to as *targeted therapy*, is designed to target specific genes or pathways that contribute to melanoma cell growth. A major research focus is, therefore, directed to continued development of new therapies that target specific molecular pathways and genes that are abnormal or activated in melanoma.

Ongoing research has shown that approximately 50 percent of patients with melanoma have a mutated *BRAF* gene. A *BRAF* (or B-RAF) gene makes a pro-

tein kinase called *BRAF*, which is involved in sending signals in cells and in cell growth. This gene may be mutated in many types of cancer, including melanoma, which signals a change in the *BRAF* protein. In turn, this can increase the growth and spread of cancerous cells. This discovery was a major advancement in the treatment of melanoma. Targeted therapies can slow the growth of melanoma cells by inhibiting the mutated gene. The first *BRAF* inhibitor, sorafenib (Nexavar), had limited efficacy in melanoma, and the benefit appeared to be unrelated to the mutation status of the tumor, raising doubts in the early days about the relevance of *BRAF* mutation in melanoma. That doubt was to be short-lived, however.

A major breakthrough in targeted therapy for melanoma was FDA's approval of vemurafenib (Zelboraf) in August 2011. Vemurafenib is an orally-administered *BRAF* inhibitor specifically indicated for patients with melanoma whose tumors have the V600E mutation in their *BRAF* gene, referred to as *BRAF^{V600E}*. The second most common *BRAF* mutation, V600K, along with V600E, account for 95 percent of *BRAF* mutations found in patients with melanomas. Since so many patients with melanoma have this type of mutation, a mutation that does not occur in normal cells, drug action directed toward the defective gene would be a logical means to achieve control.

In an early clinical trial with metastatic melanoma patients whose tumors were positive for the mutated *BRAF^{V600E}* gene, vemurafenib shrunk the tumors in the majority of those patients and extended their survival. Based on those findings, vemurafenib was approved for standard use in patients with locally advanced Stage III melanoma that cannot be excised by surgery, or for patients with Stage IV melanoma, provided their melanoma has the mutated *BRAF^{V600E}* gene. The results of that early clinical trial stimulated further research into other compounds

shown to possess anti-*BRAF^{V600E}* activity. These drugs are emerging as standard of care in patients with metastatic melanoma carrying the noted oncogenic mutation.

The New Drugs

In late-May, 2013, FDA approved two additional drugs, Tafinlar and Mekinist (Table 1), for patients with advanced (metastatic) or unresectable (cannot be removed by surgery) melanoma. Both drugs were approved for use with provision that the mutated gene is present, identified with the THxID™ *BRAF* kit, a companion diagnostic that confirms if a patient's melanoma cells contain the defective V600E or V600K mutation. Information on the FDA-approved test for detection of *BRAF* mutations in melanoma may be accessed at www.fda.gov/CompanionDiagnos-tics.

UV Influence. The anatomic site of primary melanoma is associated with distinct features in the melanoma genome that relate to the amount of ultraviolet (UV) radiation exposure at the anatomic location. For example, melanomas arising on mucosal surfaces of the upper respiratory tract or anogenital regions that are not exposed directly to UV radiation are associated with low rates of *BRAF* mutations, pegged at 3 to 14 percent. In contrast, melanomas on the trunk that are associated with intermittent UV radiation exposure have the opposite pattern of mutation, with approximately 70 percent having the mutated *BRAF* gene. Melanomas arising in anatomic locations on the head and neck that are exposed to chronic UV light exposure also show the high rate of *BRAF^{V600E}* mutations. Therefore, the histologic classification of melanomas according to site of origin – cutaneous nonacral, cutaneous acral, and mucosal melanomas – predicts the frequency of mutations that are benefitted by the new targeted therapies. What remains less clear is whether this benefit is secondary to inherent biologic differences in melanocytes

at these sites, or to the direct effect of the UV carcinogen on specific alterations in the commonly mutated *BRAF* genes.

Dabrafenib (Tafinlar)

Indication and Use. Tafinlar (TAFF-in-lar) is a potent kinase inhibitor of mutated *BRAF*, indicated for treatment of patients with unresectable or metastatic melanoma with *BRAF^{V600E}* mutation as detected by an FDA-approved test. It is not indicated for treatment of patients with wild-type *BRAF* melanoma. *Wild-type* is the term used for the typical form of a gene as it was first observed in nature or in the wild. It means that the gene is *normal*, without detectable mutation. Dabrafenib has a response rate and progression-free survival rate similar to that of vemurafenib, but shows a moderately improved toxicity profile. Dabrafenib has good activity in patients with brain metastases, which are common in advanced melanoma, and associated with a poor prognosis and greatly impaired quality of life.

Dabrafenib was studied in 250 patients (60 percent male) with a *BRAF^{V600E}* gene mutation-positive metastatic or unresectable melanoma. Patients were randomly assigned to receive dabrafenib or the chemotherapeutic drug, dacarbazine. Those who received dabrafenib experienced a delay in tumor growth that was 2.4 months later than those receiving dacarbazine.

Mechanism of Action.

Dabrafenib is an inhibitor of some mutated forms of *BRAF* kinases. As stated earlier, some mutations in the *BRAF* gene, including those that result in *BRAF^{V600E}* mutation, can result in constitutively activated *BRAF* kinases that may stimulate tumor cell growth.

Safety. The most common adverse reactions (≥ 20 percent) noted in clinical trials included thickening of the skin (hyperkeratosis), headache, fever, joint pain, noncancerous skin tumors, alopecia, and palmar-plantar erythrodysesthesia syndrome (persistent tingling in

the palms and soles that may progress to severe pain and discomfort).

The most serious adverse effects reported in patients receiving dabrafenib included an increased risk of skin cancer (cutaneous squamous cell carcinoma), fevers that may be complicated by hypotension, severe rigors (shaking chills), dehydration, kidney failure, and hyperglycemia requiring changes in diabetes medication or the need to start medication to control diabetes.

Warnings, Precautions and Contraindications.

The following warnings and precautions are listed:

- *New primary cutaneous malignancies including squamous cell carcinoma, keratoacanthoma, and melanoma:* perform dermatologic evaluations prior to initiation of therapy, every two months while on therapy, and for up to six months following discontinuation of Tafinlar. In one trial, the incidence of new primary malignant melanomas was 2 percent for patients treated with dabrafenib, with no new cases following treatment with chemotherapy.

- *Tumor promotion in BRAF wild-type melanoma:* increased cell proliferation can occur with *BRAF* inhibitors. This is a paradoxical activation of kinase signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF^{V600E}* mutation status prior to initiation of Tafinlar.

- *Serious febrile drug reactions:* these are defined as serious cases of fever, or fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of another identifiable cause. Withhold Tafinlar for fever $\geq 101.3^{\circ}\text{F}$, or if complicated fever occurs.

- *Hyperglycemia:* monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia.

- *Uveitis and iritis:* monitor patients routinely for visual symptoms.

- *Glucose-6-phosphate dehydrogenase (G6PD) deficiency:* Tafinlar contains a sulfonamide moiety, which confers a potential risk for hemolytic anemia in patients with G6PD deficiency. Closely monitor for hemolytic anemia.

- *Embryofetal toxicity:* can cause fetal harm. Advise females of childbearing age that Tafinlar may render hormonal contraceptives less effective, and an alternative method of contraception should be used during treatment, and for four weeks after.

There are no **contraindications** listed.

Drug Interactions.

Potential drug interactions include:

- Concurrent administration of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) of CYP3A4 or CYP2C8 is not recommended.

- Concurrent administration of strong inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's Wort) of CYP3A4 or CYP2C8 is not recommended.

- Drugs that increase gastric pH (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of dabrafenib, and reduce its bioavailability, thus decreasing dabrafenib concentrations.

- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 (e.g., warfarin, dexamethasone, or hormonal contraceptives) may result in loss of efficacy of these agents.

Administration and Dosing.

Before initiating therapy, the presence of *BRAF^{V600E}* mutation in tumor specimens must be confirmed. The recommended dose is 150 mg orally twice daily, until disease progression or unacceptable toxicity occurs. Doses should be taken approximately 12 hours apart, at least one hour before or two hours after a meal. A missed dose can be taken up to six hours prior to the next dose. Tafinlar capsules should not be opened or crushed, and should be stored at 25°C (77°F),

Table 2
Patient counseling information for Tafinlar

Inform patients:

- to read the *Medication Guide* before starting Tafinlar, and to reread it each time the prescription is filled;
- that this medication increases the risk of developing new skin malignancies. Advise them to contact their doctor right away if any new lesions or changes in existing lesions on their skin;
- Tafinlar causes fever, including serious febrile drug reactions. Instruct patients to contact their doctor if they experience a fever while taking this drug;
- Tafinlar can impair glucose control in diabetic patients resulting in the need to increase intensive hypoglycemic treatment. Advise patients to contact their doctor to report symptoms of severe hyperglycemia;
- Tafinlar may cause a certain type of anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Advise patients with known G6PD deficiency to contact their doctor to report signs or symptoms of anemia or hemolysis;
- women of child bearing age that the use of Tafinlar during pregnancy has not been studied in humans. Tafinlar should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. Patients should report pregnancies to their doctor as soon as possible;
- that nursing mothers should talk to their doctor about the best way to feed the infant, weighing the risks and benefits of the drug to the mother;
- that female patients should use highly effective non-hormonal contraception during treatment and for four weeks after treatment;
- males are at increased risk for infertility due to drug-induced impaired spermatogenesis;
- to take the drug exactly as their doctor and pharmacist recommend, at least one hour before or two hours after a meal.

with excursions permitted to 15° to 30°C (59° to 86°F).

Tafinlar capsules contain 50 mg or 75 mg dabrafenib.

Patient Counseling Information. An FDA-approved Medi-

cation Guide must be dispensed with each prescription and refill for Tafinlar and patients should be urged to read it carefully. Specific points for counseling are summarized in Table 2.

Trametinib (Mekinist)

Indication and Usage. Mekinist (MEK-in-ist) is a kinase inhibitor indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Mekinist is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.

Mekinist was studied in 322 patients with metastatic or unresectable melanoma with the V600E or V600K gene mutation. Patients were randomly assigned to receive either Mekinist or chemotherapy. Those who received Mekinist had a delay in tumor growth that was 3.3 months later than those on chemotherapy. Patients who previously used Tafinlar or other inhibitors of BRAF did not appear to benefit from Mekinist, and were ineligible for the trial.

Mechanism of Action. Trametinib is a potent, but reversible, inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1), and MEK2 activation and of MEK1 and MEK2 kinase activity. Thus, its mechanism of action differs from that of dabrafenib. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF^{V600E} mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits BRAF^{V600} mutation-positive melanoma cell growth *in vitro* and *in vivo*.

Safety. The most common adverse reactions (≥ 20 percent) for trametinib shown in clinical trials include rash, diarrhea, and lymphedema. Serious adverse reactions included cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial

lung disease, and serious skin toxicity that resembled severe acne.

The most serious adverse reactions included heart failure, lung inflammation, skin infections, and loss of vision.

Warnings, Precautions and Contraindications. The following warnings and precautions are listed:

- *Cardiomyopathy defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction (LVEF):* re-assess LVEF after one month of treatment, and evaluate approximately every two to three months thereafter.

- *Retinal pigment epithelial detachment (RPED), often bilateral and multifocal, occurring in the macular region of the retina:* perform ophthalmologic evaluation for any visual disturbances. Withhold Mekinist if RPED is diagnosed, and discontinue if no improvement is noted after three weeks.

- *Retinal vein occlusion (RVO) that may lead to macular edema, decreased visual function, neovascularization, and glaucoma:* discontinue drug and provide immediate treatment.

- *Interstitial lung disease (ILD):* withhold drug for new, progressive, or unexplained pulmonary symptoms or findings, such as cough, dyspnea, hypoxia, or infiltrate. Permanently discontinue drug for treatment-related ILD or pneumonitis.

- *Serious skin toxicity including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema:* monitor for skin toxicities and for secondary infection. Discontinue for intolerable Grade 2; or Grade 3 or 4 rash not improving within three weeks despite interruption of Mekinist therapy.

- *Embryofetal toxicity: can cause fetal harm:* advise females of childbearing age of the risk to the fetus, and to use highly effective contraception during treatment with Mekinist and for four months after treatment.

Table 3
Patient counseling information for Mekinist

Inform patients:

- that this medication can cause heart problems, and to immediately report any signs or symptoms of heart failure to their doctor;
- that this medicine causes severe visual disturbances that can lead to blindness. Tell patients to contact their doctor if they experience any changes in their vision;
- that Mekinist can cause lung disease. Advise patients to contact their doctor as soon as possible if they experience shortness of breath;
- that Mekinist often causes skin toxicities including severe rash. Advise them to contact their doctor for progressive or intolerable rash;
- that Mekinist can raise blood pressure. Advise them to monitor their blood pressure and contact their doctor if they develop symptoms of hypertension;
- that the drug causes diarrhea that can be severe. Inform patients of the need to contact their doctor if severe diarrhea occurs during treatment;
- to take the tablets at least one hour before or two hours after a meal;
- women of child bearing age that the use of Mekinist during pregnancy has not been studied in humans. The drug should be used during pregnancy only after weighing potential benefit/risks. Patients should report pregnancies to their doctor as soon as possible;
- that nursing infants may experience serious adverse reactions if the mother is taking Mekinist. Discontinue nursing while taking the drug;
- that female patients should use highly effective contraception during treatment and for four months after treatment;
- to take the drug exactly as their doctor and pharmacist recommend.

There are no **contraindications** listed.

Drug Interactions. No formal clinical trials have been conducted to evaluate human cytochrome P450 enzyme-mediated drug interactions.

Administration and Dosing. The recommended dose is 2 mg orally once daily until disease pro-

gression or unacceptable toxicity. Patients should take the medication at least one hour before or two hours after a meal, and should not take a missed dose within 12 hours of the next dose. Tablets should be stored at 2° to 8°C (36° to 46°F); protected from freezing, moisture, and light; and dispensed in their original bottles. The desiccant should not be removed and the tablets should not be placed in pill boxes or envelopes.

Mekinist tablets contain 0.5 mg, 1 mg, or 2 mg of trametinib.

Patient Counseling Information. Specific points for counseling are summarized in Table 3.

Drug Combinations

One study suggests that the combination of two targeted drugs, dabrafenib and trametinib, may delay progression of advanced melanoma longer than dabrafenib alone. This defends the notion that a combination of targeted drugs for melanoma is more effective and less toxic than a single targeted drug.

As noted previously, dabrafenib and trametinib target different components of a cell signaling pathway that has been altered in melanoma by the *BRAF^{V600E}* mutation. Single drugs that block *BRAF* activity shrink melanoma, but the tumors inevitably develop resistance that nullifies further drug action. Researchers hoped that adding a second drug with a different target would slow development of resistance along with disease progression.

Initially, researchers enrolled 85 patients in a randomized phase II trial to determine the combination's safety and the doses to be employed. The researchers then randomly assigned 162 patients to one of three treatment groups: dabrafenib alone, dabrafenib plus a low dose of trametinib, or dabrafenib plus a higher dose of trametinib. Patients whose cancer progressed with dabrafenib alone were permitted to add the higher dose of trametinib to their treatment regimen.

The patients who received the

higher dose of trametinib along with dabrafenib had a median progression-free survival of 9.4 months, compared with 5.8 months for those receiving dabrafenib alone. After one year of follow-up, 41 percent of the group receiving the higher-dose of trametinib plus dabrafenib showed no disease progression, compared with 9 percent of those who received dabrafenib alone.

Overall, 79 percent of patients in the higher-dose combination group were alive after one year. The researchers commented that they had never previously encountered a 12-month survival of that extent in metastatic melanoma. Moreover, cutaneous toxicities seen with the individual drugs were significantly reduced when the drugs were combined.

Adverse effects differed between the treatment groups, and patients in all arms of the trial frequently required temporary or permanent dose reductions. More patients receiving dabrafenib alone (19 percent) developed a secondary squamous-cell skin cancer than patients receiving the higher-dose combination (7 percent), although this difference was not statistically significant. Most patients in the higher-dose combination group (71 percent) experienced fever, compared with a minority of those receiving dabrafenib alone (26 percent).

Good Advice Concerning Melanoma

The American Cancer Society recommends professional skin examinations every year for persons over 40 years of age, and every three years for individuals ages 20 to 40 years. Other actions to reduce the incidence of melanoma are shown in Table 4.

An excellent, easy-to-read article entitled *Melanoma* can be recommended to patients to aid their understanding of the cancer. It includes extensive information on prevention, staging, and treatment, and is available at www.cancer.net/print/19251. The article will also

Table 4 **Skin cancer prevention advice**

- Examine the skin once a month. Call your doctor if you notice any changes.
- Reduce exposure to sunlight. UV radiation is most intense between 10 a.m. and 4 p.m. Protect the skin by wearing wide-brimmed hats, closely-knit long-sleeved shirts, and long skirts or pants.
- Apply a high-quality sunscreen with sun protection factor (SPF) ratings of at least 15, even when going outdoors for only a short time.
- Apply a large amount of sunscreen on all exposed areas, including ears, nose, and feet.
- Look for sunscreens that block both UVA and UVB radiation.
- Use a waterproof formula.
- Apply sunscreen at least 30 minutes before going outside and reapply it frequently, especially after swimming.
- Use sunscreen in winter and on cloudy days.
- Wear sunglasses to protect the skin around the eyes.
- Avoid surfaces that reflect light, such as water, sand, concrete, and white-painted areas.
- Be aware that the dangers are greater closer to the start of summer.
- Be aware that skin burns faster at higher altitudes.
- Avoid sunlamps, tanning beds, and tanning salons.
- Children should be protected from the sun because severe sunburns in childhood may greatly increase the risk of melanoma in later life.
- Have any new or unusual lesions or a progressive change in a lesion's appearance (size, shape, or color, etc.) evaluated promptly by a physician.

aid pharmacists in their review of the cancer and understanding of melanoma.

Overview and Summary

Melanoma is a highly aggressive malignant tumor with the potential to metastasize from a relatively small primary tumor. Prevention and early detection of primary melanomas are vital to the treatment of this cancer. These two new drugs provide targeted therapies that cre-

ate new and exciting pathways for treating melanomas.



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 0129-0000-13-010-H01-P

Release date: 10-15-13

Expiration date: 10-15-16

CE Hours: 1.5 (0.15 CEU)

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continuing education quiz

Melanoma-Targeted Therapy: Focus on Mekinist and Tafinlar

- All of the following are true about melanoma EXCEPT:
 - mortality rates are higher in Caucasians than African-Americans.
 - by age 80, the mortality rate is three times higher in men than in women.
 - it is the most common skin cancer.
 - acral lentiginous melanoma is the least common type.
 - The median age at diagnosis of melanoma is:
 - early 40s.
 - late 40s.
 - early 50s.
 - late 50s.
 - Before the advent of targeted therapy for melanoma, the mainstay of treatment was:
 - dacarbazine.
 - paclitaxel.
 - interleukin-2.
 - interferon-alpha.
 - The second most common *BRAF* mutation is:
 - V600B.
 - V600K.
 - V600E.
 - V600M.
 - A major breakthrough in targeted therapy for melanoma was:
 - Intron A.
 - Platinol.
 - Proleukin.
 - Zelboraf.
 - A potential drug-drug interaction is reported with Tafinlar and all of the following EXCEPT:
 - strong CYP inhibitors.
 - strong CYP inducers.
 - proton pump inhibitors.
 - highly protein-bound drugs.
 - Tafinlar doses should be withheld with fever of:
 - 99.5°F.
 - 100.2°F.
 - 100.9°F.
 - 101.3°F.

Completely fill in the lettered box corresponding to your answer.

- | | | |
|--------------------|---------------------|---------------------|
| 1. [a] [b] [c] [d] | 6. [a] [b] [c] [d] | 11. [a] [b] [c] [d] |
| 2. [a] [b] [c] [d] | 7. [a] [b] [c] [d] | 12. [a] [b] [c] [d] |
| 3. [a] [b] [c] [d] | 8. [a] [b] [c] [d] | 13. [a] [b] [c] [d] |
| 4. [a] [b] [c] [d] | 9. [a] [b] [c] [d] | 14. [a] [b] [c] [d] |
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8. All of the following are true about dabrafenib EXCEPT:

 - good activity in patients with brain metastases.
 - same mechanism of action as trametinib.
 - a common adverse reaction is hyperkeratosis.
 - no contraindications are noted.

9. If a dose of Tafinlar is missed, it may be taken up to how many hours prior to the next scheduled dose?

 - One
 - Two
 - Four
 - Six

10. One of the most serious adverse reactions reported with Mekinist is:

 - hyperglycemia.
 - kidney failure.
 - lung inflammation.
 - severe rigors.

11. Which of the following drugs is/are not approved for treatment of patients who have received prior *BRAF*-inhibitor therapy?

 - Dabrafenib
 - Trametinib
 - Both dabrafenib and trametinib
 - Neither dabrafenib nor trametinib

12. Which of the following drugs is/are approved for use only if the mutated *BRAF* gene is present?

 - Mekinist
 - Tafinlar
 - Both Mekinist and Tafinlar
 - Neither Mekinist nor Tafinlar

13. Which of the following drugs place males at increased risk for infertility due to impaired spermatogenesis?

 - Mekinist
 - Tafinlar
 - Both Mekinist and Tafinlar
 - Neither Mekinist nor Tafinlar

14. Patients should be counseled that which of the following drugs may cause severe visual disturbance that can lead to blindness?

 - Mekinist
 - Tafinlar
 - Both Mekinist and Tafinlar
 - Neither Mekinist nor Tafinlar

15. To help prevent skin cancer, all of the following are true EXCEPT:

 - use sunscreen with an SPF rating of at least 50.
 - apply sunscreen at least 30 minutes before going outside.
 - sun toxicity potential is greater closer to early summer.
 - severe sunburn in childhood increases the risk of melanoma in later life.

To receive CE credit, your quiz must be received no later than October 15, 2016. A passing grade of 80% must be attained. CE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CE statements of credit will not be mailed, but can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.

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Statement of Ownership, Management, and Circulation POSTAL SERVICE® (All Periodicals Publications Except Requester Publications)			
1. Publication Title New Jersey Journal of Pharmacy	2. Publication Number 0 0 2 8 - 5 7 7 3	3. Filing Date Oct. 16, 2013	14. Issue Date for Circulation Data Below Fall/Winter 2013
4. Issue Frequency quarterly	5. Number of Issues Published Annually	6. Annual Subscription Price \$50 US subscription \$100 International	15. Extent and Nature of Circulation Members & Paid Subscriptions
7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4) 760 Alexander Road, Princeton, NJ 08543-0001		Contact Person E. Barry	Average No. Copies Each Issue During Preceding 12 Months
		Telephone (Include area code) 609-275-4246	No. Copies of Single Issue Published Nearest to Filing Date
8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer) same as above			
9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank) Publisher (Name and complete mailing address) Elise M. Barry NJPhA, 760 Alexander Road, Princeton, NJ 08543			
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Managing Editor (Name and complete mailing address) N/A			
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12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one) The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: <input checked="" type="checkbox"/> Has Not Changed During Preceding 12 Months <input type="checkbox"/> Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)			
13. Publication Title The New Jersey Journal of Pharmacy			
14. Issue Date for Circulation Data Below Fall/Winter 2013			
15. Extent and Nature of Circulation Members & Paid Subscriptions			
a. Total Number of Copies (Net press run) 1000 1000			
b. Paid Circulation (By Mail and Outside the Mail) (1) Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies) 732 732 (2) Mailed In-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies) 36 36 (3) Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS® (4) Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®) 			
c. Total Paid Distribution (Sum of 15b (1), (2), (3), and (4)) 768 768			
d. Free or Nominal Rate Distribution (By Mail and Outside the Mail) (1) Free or Nominal Rate Outside-County Copies included on PS Form 3541 (2) Free or Nominal Rate In-County Copies Included on PS Form 3541 (3) Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail) (4) Free or Nominal Rate Distribution Outside the Mail (Carriers or other means) 227 227			
e. Total Free or Nominal Rate Distribution (Sum of 15d (1), (2), (3) and (4)) 227 227			
f. Total Distribution (Sum of 15c and 15e) 995 995			
g. Copies not Distributed (See Instructions to Publishers #4 (page #3)) 5 5			
h. Total (Sum of 15f and g) 1000 1000			
i. Percent Paid (15c divided by 15f times 100) 77.19 77.19			
16. <input type="checkbox"/> Total circulation includes electronic copies. Report circulation on PS Form 3526-X worksheet			
17. Publication of Statement of Ownership <input checked="" type="checkbox"/> If the publication is a general publication, publication of this statement is required. Will be printed in the Fall/Winter 2013 issue of this publication. <input type="checkbox"/> Publication not required.			
18. Signature and Title of Editor, Publisher, Business Manager, or Owner The signature of Elise M. Barry is handwritten in cursive ink.			
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