**President’s Message**

**Multitasking and Public Safety**

by Joseph Tarallo, Jr., RPh

Community pharmacists routinely perform a number of business activities in a normal day along with prescription dispensing and counseling. Pharmacists have become very familiar with budgeting their time in order to fulfill immediate demands while servicing the needs of patients; always work in progress.

We are the link between the physician and the patient. We have a professional responsibility to the prescriber to accurately dispense and label the ordered medication, as well as, to the patient by providing proper instruction in order to improve their understanding and adherence to their therapy.

As you know, society faces a serious health dilemma concerning opioid abuse. This has lead to additional challenges, such as, to identify prescriber authenticity of the prescription, obtain patient identification, and review the prescribed dosage treatment. This review becomes complex when patients use more than one physician and/or more than one pharmacy. Perhaps this can be an opportunity to collaborate with the physician and provide patient counseling within a specific individual treatment plan.

As professionals in public service, pharmacists are encouraged to monitor any developing concerns which may lead to drug misuse by using the electronic Prescription Monitoring Program (PMP).

Likewise, drug and alcohol abuse and early recognition of these problems will take a total team approach towards any chance of successful prevention. Therefore, in the interest of public safety and greater perception of our profession, pharmacists need to step forward by becoming proactive on these important matters within the community.

Pharmacists can become advocates in their communities in another form of collaboration by attending periodic regional meetings for drug and alcohol abuse prevention. Please see the following link, New Jersey Prevention Network:

http://www.njpn.org/networks/regional-coalition/

If each of the regions throughout the state can have pharmacist participation, then we will make a significant difference regarding patient safety and further enhance the image of our profession.

Thank you.
From The Editors’ Desks...

Dear Colleagues,

Thank you for the feedback on the updated New Jersey Journal of Pharmacy! Your input will be valuable in our efforts to improve the journal and tailor it to serve our members. The Journal Committee has already reached out to numerous members who showed interest in getting involved. Although the survey portal has since closed, feel free to provide us with additional feedback anytime.

We would also like to thank all the authors and reviewers who contributed to our first peer-reviewed issue. We are confident the peer-review process will continue to improve the overall quality of the journal issues, and as a benefit to our reviewers we will acknowledge their contribution in the final issue of each calendar year. The current issue focuses on cardiovascular diseases, an important therapeutic area that no doubt deserves more attention than what could possibly be covered in one issue. The featured “Practice Spotlight” discusses pharmacist involvement in a nurse practitioner-run outpatient heart failure clinic at The Valley Hospital (Ridgewood, NJ). The success of this program not only supports the positive patient outcomes achieved in disease management programs involving pharmacists, but it also highlights a unique opportunity for pharmacists to get involved.

If you are interested in submitting an article for this issue, please contact us as soon as possible. In addition to featuring oncologic diseases and treatments, we are pleased to announce that the issue will include abstracts (with the exception of “encore presentations”) of posters presented at this year’s NJPhA Annual Meeting. This will allow pharmacists who could not attend the meeting the opportunity to review what was presented and provide presenters/authors with an important citable reference of their work. We also invite presenters/authors to take the next step and develop their presentation into a full-text manuscript for submission to the New Jersey Journal of Pharmacy.

Looking ahead to 2014 – and based on feedback provided during the survey – we will be featuring issues dedicated to general wellness/public health, neurology/psychiatry, infectious diseases, and endocrinology. Please stay tuned for details regarding submission deadlines!

Warm regards,

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Message from the CEO

In early October, the New Jersey Pharmacists Association’s 143rd Annual Convention convened in Atlantic City. The three-day schedule provided dedicated time for regional, academy and committee business meetings for all convention attendees. There were two APhA certificate programs (Medication Therapy Management and Diabetes) and more than a dozen accredited educational programs. Dr. Brian Isetts, a former CMS fellow, presented an important keynote address on health care reform and the pharmacists’ role during Saturday’s luncheon. Lots of social events and networking opportunities were woven into the program, with plenty of time to stroll along the Boardwalk to seek out one of many fine restaurants.

Our Journal co-editors combed through the results of the recent member survey that asked for an evaluation of the content in previous issues, and for suggestions for future topics. Please read the From the Editors’ Desks column by co-editors’ Maria Leibfried and Rutu Patel, outlining the peer-review process inaugurated in this issue, and the interesting articles that cover various aspects of cardiovascular diseases. I encourage each reader to ponder the topics proposed for upcoming issues and consider authoring an article. NJPhA sends call for article notices periodically, please look for the next one.

This issue has two theme related continuing education studies. NJPhA offers The Cardiovascular Effects of Stimulants in Children and Adults with Attention Deficit and Hyperactivity Disorder (ADHD): A Closer Look at the Controversy, free to current NJPhA members (CE credit fee for nonmembers), and the second offering entitled Phytosterols and Cardiovascular Health, that is provided through the Ohio Pharmacists Foundation. There is a nominal charge for this CE as described on the quiz sheet.

Incredibly, this issue surpasses the last. I commend the co-editors for another fine publication.

What extraordinary resources for pharmacists!
A Look at the NJPhA 143rd Annual Convention

Anne Crochunis, PharmD, receives the Upsher-Smith Laboratories - NASPA Excellence in Innovation Award

Moriah Weissman, PharmD, the Pharmacist Mutual Distinguished Young Pharmacist Award

Dr. Grace Earl was awarded the NJPHA Donald J. Wernik Academic Achievement Award

David DeFelice from Pharmacist Mutual awarded Moriah Weissman, PharmD, the Pharmacist Mutual Distinguished Young Pharmacist Award

The student team from Fairleigh Dickinson University who competed in the Pharmacy Student Competition-College Bowl.

Send us your convention photos for the next issue!
Improving Health Outcomes in Cardiovascular Disease through Pharmacist-based Collaborative Medication Therapy Management

by Theodore E. Ray, Pharm.D. Candidate and John L. Colaizzi, Ph.D., R.Ph.

Cardiovascular disease poses major healthcare risks for our nation. Conditions such as acute myocardial infarctions (heart attacks), congestive heart failure, strokes, and pulmonary embolisms are leading causes of hospital admissions, readmissions, and even death in America. Through properly implemented medication regimens, diet and regular exercise, adverse cardiovascular events are often preventable. Nevertheless, heart disease, vascular disease, and stroke remain major causes of mortality in America.1 Over 27 million institutionalized patients and over 59 million non-institutionalized Americans have been diagnosed with cardiovascular diseases.2 Hypertension accounts for over 50 percent of chronic disease diagnoses in American adults3 and causes approximately half of all cases of stroke and ischemic heart disease.4 Despite the impressive advancements in cardiovascular drug therapy over the past four decades, significant challenges remain in treating cardiovascular and related chronic diseases. For example, from 2007 to 2009, 46.6% of emergency hospitalizations among the elderly were due to adverse drug events (ADEs) caused by warfarin and antiplatelet drugs.5 Failure to properly monitor patients for ADEs and non-adherence to medication regimens are widely recognized as significant barriers to controlling risk factors for cardiovascular disease, as evidenced by increases in the number of hospitalizations resulting from cardiovascular diseases.

An Opportunity for Pharmacists

As Medicare, Medicaid, and private insurers seek to minimize healthcare costs and decrease hospital admissions, a question that must be answered is: “With whom does the responsibility for preventing these hospital admissions lie?” Some say the responsibility lies with the individual patient; however approximately 90 million Americans find it difficult to process health information, resulting in their inability to be their own advocates when seeking healthcare services.6-8 Many patients do not fully understand the purpose of their medications, and some cannot list all the medications they take. This is certainly true in patients suffering from cardiovascular diseases, who are often prescribed multiple chronic medications. On the other hand, in attempting to determine responsibility for preventing avoidable hospital admissions, some blame the physician for prescribing combinations of medications that put patients at risk for developing adverse reactions. However, many patients see multiple specialists who are unaware of all the medications patients are taking. Finding a primary care physician who could provide the necessary coordination of care has become increasingly difficult due to a growing shortage of primary care physicians.9-11 Furthermore, the additional millions of Americans expected to become insured under the Affordable Care Act will substantially increase the demand for primary care physicians. While deficiencies in health literacy prevent many patients from taking the appropriate steps to avoid hospital admissions, and the shortage of primary care physicians translates to a lack of professional oversight in regard to medication therapy, pharmacists are in the perfect position to provide collaborative medication therapy management (MTM) services that will improve therapeutic outcomes and reduce the risk of ADEs.

Pharmacists are the most widely accessible healthcare professionals, and virtually all patients in the U.S. have relatively easy access to a community pharmacist. A recent communication from the Pharmaceutical Care Management Association pointed out that America “has more pharmacies than it has McDonald’s, Burger Kings, Pizza Huts, Wendy’s, Taco Bells, Kentucky Fried Chickens, Domino’s Pizzas, and Dunkin’ Donuts combined.”12 Since the average Medicare Part D enrollee uses approximately 17 to 23 prescriptions per year, interaction with a pharmacist is frequent, positioning the pharmacist at the forefront of patient care.13 Pharmacists offering MTM services can work with patients to minimize risk factors for cardiovascular diseases, as well as diseases that can lead to or exacerbate cardiovascular diseases, such as diabetes. A majority of patients feel comfortable in seeking advice on medications and other health issues from pharmacists, who consistently rank among the most trusted professionals.14 Because of their positive pharmacist-patient relationships, their unrivaled accessibility among healthcare professionals, and their specialized knowledge of medications, pharmacists are ideally positioned to be the principal providers of MTM services, and they deserve to be fairly compensated for their services by third party insurance payers. The concepts behind pharmacist-provided MTM are not new; Brodie first introduced the concept and defined pharmaceutical care in 1973.15 Despite the healthcare industry’s recognition of the need for and the benefits of pharmacist-provided MTM, inclusion of these services has been hindered by a lack of adequate third party reimbursement. Expansion of MTM services for patients with cardiovascular diseases and cardiac risk factors would result in improved patient compliance, decreased hospital admissions and readmissions for cardiovascular events, and an overall decrease in healthcare expenditures. Furthermore, expanded implementation and evaluation of pharmacist-provided MTM for patients with cardiovascular
disease, could serve as a model for future reimbursement for MTM services focused on other disease states as well.

**Documentation of the Value of Pharmacist-provided MTM in Cardiovascular Diseases**

Medication therapy management consists of multiple functions provided by the pharmacist, in collaboration with the prescriber, to optimize medication outcomes and eliminate drug-related misadventures through review and analysis of medication therapy, development of personal medication records and medication-related action plans, intervention or referral, and documentation and follow-up. Numerous studies and programs have corroborated the value of pharmacists in the provision of direct patient care; pharmacists have significantly improved medication adherence and health outcomes, improved efficacy and safety of medication therapies, and reduced overall healthcare costs. In addition to medication therapy, pharmacists are also able to address important lifestyle changes such as diet, exercise, and smoking cessation. One such study, which analyzed the long-term clinical and economic outcomes of the Asheville Diabetes Care Program over a five-year period, determined that initial improvements in glycemic control and cholesterol levels provided by educational intervention were sustained through pharmacist-provided care services. At every follow-up, 57.7% to 81.8% of patients showed improved A1C levels compared to baseline. Not only were clinical improvements maintained, but third-party payers experienced a decline in direct medical costs over the five-year period. The Asheville Project for patients with hypertension or hyperlipidemia and with asthma demonstrated similar outcomes, both clinical and economic. The analysis of the outcomes of the Asheville Project for patients diagnosed with hypertension or dyslipidemia evidenced that statistically significant improvements in both systolic and diastolic blood pressure and in LDL and HDL cholesterol levels were associated with an overall reduction in the number of cardiovascular events each year. The risk of experiencing an adverse event was decreased by 53%, which further resulted in a 46.5% reduction in cardiovascular-related medication costs. Despite a three-fold increase in cardiovascular medication costs, overall healthcare expenditures decreased. In evaluating the impact of medication on healthcare utilization and cost, Sokol et al. recognized that high levels of adherence resulted in an economic benefit driven through a reduction in hospitalization rates.

Pharmacists have further demonstrated their ability to provide effective patient care services and have expanded their role in direct patient care through immunization programs implemented in community pharmacies. These programs have become widely accepted by patients and have been shown to improve overall influenza vaccination rates. The success of pharmacist-administered immunization confirms the willingness of patients to accept pharmacists as providers of direct patient care services. A 2005 American Pharmacists Association-commissioned report prepared by The Lewin Group (a healthcare consulting firm), indicated that, while MTM services led to cost savings and improved health outcomes, it was unlikely that these services would be provided if differences between the pharmacist’s roles as dispensers and MTM provider were not “recognized, encouraged, and ultimately rewarded financially.”

**Medicare Part D and Reimbursement for Pharmacist-provided MTM**

Public Law 108-173, Medicare Prescription Drug, Improvement, and Modernization Act of 2003 provided clear governmental recognition and acknowledgment of the pharmacist’s role in providing MTM services. The 2003 Act has opened the door for pharmacist reimbursement for patient care services by amending Title XVIII of the Social Security Act and mandating establishment of MTM that “may be furnished by a pharmacist” for Medicare Part D patients in order to ensure that their covered Part D prescription medications are appropriately used so as “to optimize therapeutic outcomes,” and “to reduce the risk of adverse events, including adverse drug interactions.” The legislation targets patients who are diagnosed with multiple chronic diseases, and specifically mentions cardiovascular diseases such as hypertension, hyperlipidemia, and congestive heart failure. In addition to acknowledging the need for MTM and recognizing the pharmacist as a provider, the legislation also recognized the importance of taking “into account, in establishing fees for pharmacists and others providing services under such plan, the resources used, and time required to implement the medication therapy management program.” Since the implementation of Medicare Part D programs in 2006, various studies have confirmed that MTM is effective both clinically and economically. The studies also point out that the combined cost of providing MTM services and the increased cost of prescription medications, were more than offset by the estimated savings resulting from avoidance of emergency room visits, hospital admissions, and nursing home admissions.

**MTM Improves Adherence, Reduces Overall Health Spending for Cardiac Patients**

Results of a recently published investigation demonstrated that pharmacist case management achieved better control of blood pressure compared to “usual care” over a 12 month period, and that the improvement in blood pressure control persisted during six months of follow-up. This study noted that the most potent methods to improve blood pressure control involve empowerment of non-physician practitioners to adjust antihypertensive therapy, and that pharmacists and nurses are effective in team-based care for hypertensive patients. The potential of considerable cost savings resulting from pharmacist-provided MTM is particularly significant when evaluating the need for expanded implementation of
MTM services for cardiac patients. Multiple studies have concluded that pharmacist-provided MTM results in a marked improvement in medication adherence for patients diagnosed with high-risk conditions for cardiovascular disease, and that increased medication adherence, in turn, decreases the risk of hospitalization.\textsuperscript{20,28} One such study which examined the effect of a pharmaceutical care program on medical adherence, blood pressure, and low-density lipoprotein cholesterol, utilized strategies to improve medication compliance that led to a sustained increase in adherence from 61% to 96%, and meaningful reductions in blood pressure and LDL cholesterol levels.\textsuperscript{30} Another study on the impact of medication adherence on hospitalization risk and healthcare costs for patients diagnosed with hypertension, dyslipidemia, congestive heart failure, and diabetes provided similar results; 80% to 100% medication adherence resulted in significantly lower risk of hospitalization.\textsuperscript{20} These findings are especially noteworthy in advocating for third-party reimbursement for pharmacist-provided MTM, considering that in patients diagnosed with heart failure with reduced ejection fraction, medication non-adherence is associated with a considerably higher risk of mortality or cardiovascular hospitalization.\textsuperscript{29} Furthermore, serious complications and ADEs are associated with many cardiac therapies. For example, patients prescribed certain anticoagulants are at significantly increased risk for suffering hemorrhages and thromboembolisms.\textsuperscript{30} In 2009, total aggregate costs for hospital stays in the U.S. due to cardiac diseases and stroke amounted to $54.7 billion,\textsuperscript{31} and between 2006 and 2009, the national average 30-day admission rates for patients with heart attack and heart failure discharged to non-acute care settings was 19.97% and 24.73%, respectively.\textsuperscript{32} In a 2011 policy statement, the American Heart Association projected that direct medical costs attributed to cardiovascular disease will exceed $470 billion by 2020, assuming no change in policy, and taking into account an aging population.\textsuperscript{33} In researching drug-related morbidity, Hepler and Segal concluded that the prevalence of preventable drug-related hospital admissions is comparable to the prevalence of admissions for diseases such as cancer, heart attacks, diabetes, and asthma; and therefore, “preventable hospital admissions, transfers to intensive care, and deaths represent needless human suffering and unnecessary expenditures.”\textsuperscript{34} It has been shown that suboptimal drug therapy frequently results in visits to physicians’ offices, visits to hospital emergency rooms, and hospital admissions, many of which are preventable. Yet many third-party payers, in their efforts to decrease hospital readmission rates, have failed to recognize the considerable impact pharmacist-provided MTM can have in reducing overall costs. The incorporation of pharmacists as part of the integrative care teams of healthcare providers in Accountable Care Organizations (ACOs) that are rapidly being developed as part of the Affordable Care Act legislation, will provide further evidence of the value of pharmacists in improving adherence to drug therapy regimens and improving outcomes.\textsuperscript{35}

The Case for Expanded MTM Coverage in Medicare Part D

The legislation passed in 2003 provided only for reimbursement for MTM services for patients who exceed a certain annual cost for Medicare Part D drugs. However, even if a patient’s total annual drug costs do not exceed the threshold, improperly managed medications and ADEs will adversely affect the patient’s health, and may lead to hospitalization and a considerable increase in overall healthcare expenditures. It is estimated that only 14% of Medicare beneficiaries exceed the threshold spending amount required to qualify for reimbursement for MTM services.\textsuperscript{36} In a 2011 policy insight brief prepared by the Center for Strategic Planning, Policy and Data Analysis Group at the Centers for Medicare and Medicaid Services, it was reported that 2011 Medicare costs for preventable hospital admissions were expected to exceed $7 billion, with congestive heart failure being the leading condition responsible for these preventable admissions.\textsuperscript{37} When taking into consideration the fact that many preventable hospital admissions are the outcome of non-adherence resulting from improper dosing, polypharmacy and complex drug regimens, it becomes apparent that reimbursement for MTM should be expanded to include cases where MTM would address the problem of potentially preventable future healthcare costs.

A recently published study indicated that poor medication adherence was associated with additional medical and hospital visits resulting in otherwise avoidable costs to Medicare Parts A and B ranging from $49 to $840 per patient per month.\textsuperscript{38} The study authors recommended that attention be given to Medicare Part D beneficiaries now excluded from MTM services, especially if they display suboptimal medication adherence patterns. In a study of physician-patient communications relating to ADEs, Weingart et al. interviewed patients, examined patient medical records, and surveyed physicians, and found that patients oftentimes do not comprehend the significance of symptoms associated with adverse drug reactions and, therefore, fail to report them to their physicians.\textsuperscript{39} Providing MTM at the time of a medication change would allow a patient to become acclimated to the new therapeutic regimen, thereby enabling the patient to recognize the symptoms of a possible adverse drug reaction and to seek the attention of a healthcare professional if needed. Expanded implementation of MTM services for at-risk Medicare Part D patients would result in improved health outcomes, decreased ADEs, reductions in hospitalizations, and significant savings in overall health-care expenditures.\textsuperscript{38} Likewise, private third-party insurers should seek to establish similar criteria to ensure that patients with chronic diseases who are at risk for ADEs receive the needed services, and thereby reduce associated medical costs.

In attempting to reduce Medicare yearly expenditures, the 111\textsuperscript{th} Congress, seemingly recognizing the benefits of MTM,
included additional Medicare Part D MTM mandates when passing the Patient Protection and Affordable Care Act in 2010. The most noteworthy changes are as follows: (1) targeted beneficiary will be offered annual comprehensive medical review, (2) if needed, follow-up interventions during the annual review, and (3) prescription drug plan sponsors will “assess, at least on a quarterly basis, the medication use of individuals who are at risk, but not enrolled in the MTM program, including individuals who have experienced a transition of care.” These changes are of particular importance in light of numerous studies demonstrating a significantly increased risk of ADEs during patient transitions from one care setting to another. Coleman et al. found that the transition from hospital to home was a particularly vulnerable time for elderly patients, wherein unintentional noncompliance was a major contributing factor for medication discrepancies. The study also determined that frequent medication adjustments, formulary-driven medication substitutions involving multiple medications, and complex discharge instructions created confusion for the patients whose receptivity was already impaired by pain, anxiety and sleep deprivation. Transitions of care are vulnerable times during which patients are likely to experience medication-related problems. MTM services provided by readily accessible community pharmacists can be very helpful in reducing drug therapy problems during transitions from inpatient to outpatient care settings.

State-based Programs Confirm the Value of Pharmacist-provided MTM
Medicare Part D legislation demonstrates that the federal government recognizes the benefits of MTM and the need to compensate pharmacists for their services. Additionally, some state governments, including Iowa and Minnesota, have successfully pioneered the development of sustainable MTM programs. The Iowa Medicaid Pharmaceutical Care Management Program, developed in 2000 and evaluated in 2003, reimburses pharmacists and physicians at the same rate for MTM services, using set fees for initial assessments, problem visits and preventive follow-ups. In 2005, Minnesota passed legislation authorizing pharmacist-provided MTM for recipients of Medical Assistance or “Minnesota Care,” to be paid for by the Department of Human Services. An analysis of the Minnesota experience revealed that patients receiving face-to-face MTM from pharmacists experienced improved clinical outcomes and lower total healthcare expenditures. Reduction in total annual health expenditures exceeded the cost of providing MTM services by more than 12 to 1. The Minnesota experience showed that economic outcomes support the inclusion of MTM services in health plan designs.

Pharmacist-specific Billing Codes for MTM Services
Once the Health Insurance Portability and Accountability Act (HIPAA) mandated that electronic data interchange standards be followed when electronically billing for healthcare services, and federal and state legislation provided a clear description of services included in MTM, pharmacist-specific CPT (current procedural terminology) codes that allow pharmacists to bill for MTM services were developed. These codes were approved with temporary status in 2005 and later became permanent in 2007. These pharmacist-specific CPT codes are not to be used to bill for reimbursement for product-specific information at the time of dispensing, or for any other routine dispensing-related activities. These federally recognized codes provide pharmacists with a system for submitting electronic claims for reimbursement for clinical services. Traditionally, CPT codes (which are developed by the American Medical Association) have been designated for physicians and dentists. The establishment of pharmacist-specific CPT codes offers a significant opportunity for reimbursement for pharmacist-provided MTM. It should be noted that the Minnesota program utilized the established CPT codes, and also associates these codes with factors such as time spent with the patient, the number of medical conditions being treated, the number of patient medications, and the number of medication problems identified, thereby taking into account the complexity of services provided, and identifies which of the three pharmacist-specific CPT codes should be used for billing for MTM services. Revisions and updating of the Pharmacy Practice Acts in the individual states have also provided a legal and regulatory basis for pharmacist-provided MTM services, usually on a collaborative basis with prescribers. Smith et al. found that as of 2010, at least 46 states had passed legislation allowing for pharmacy collaborative practice. They noted, however, that the lack of standardization in these state regulations regarding “practice settings, education and training requirements for pharmacists, and clinician or organizational approval processes,” has hindered the growth of pharmacist-provided patient care services.

Summary and Conclusion
In spite of these obstacles, federal and state programs are gradually expanding MTM services in an effort to control overall healthcare spending, and it is expected that the demonstrated successes of these programs will eventually influence private sector insurers who are also seeking ways to contain costs. The magnitude of drug-related morbidity and mortality associated with cardiovascular diseases illustrates the urgency for expansion of pharmacist-provided MTM. Community pharmacists are an underutilized resource for the expansion of MTM services. The successful integration of pharmacists into ambulatory care clinics associated with Accountable Care Organizations is another potentially valuable resource for providing MTM. The time has come for the government and private insurers to tap into the valuable resource provided by pharmacists as a means of controlling the costs associated with cardiovascular diseases, many of which are best treated and prevented with modern pharmacotherapy.
References


Sports medicine is a specialty branch of medicine dedicated to the prevention and treatment of injuries or illnesses resulting from athletic activities.\(^1\) It is a very popular field of medicine, as there is much demand by athletes for medical care. Sports teams have physicians and athletic trainers devoted to treating their athletes, and they have been the main contributors to this field of medicine. Additionally, in recent years, many people are increasing their levels of physical activity as exercise has become widely recognized as an essential factor in the maintenance of health. People in general are exercising more, which increases the demand for sports and exercise medicine. The growth in sports medicine is beginning to have an influence on pharmacy as well. More compounding pharmacies are specializing in the formulation of medications that are used specifically to treat athletes and their injuries.\(^2\)\(^-\)\(^5\)

There are many different classes of medications that are used specifically to treat athletes. The indications for these medications range from simple muscle soreness to less obvious conditions commonly affecting athletes such as hemorrhoids. Regardless of the injury or condition, each formulation is specific for use in athletes, because it offers some sort of advantage over the usual type of treatment. Some medications that are important in sports medicine are also used in treating non-athletes, but what makes them athlete-specific is the way they can be compounded by pharmacists to uniquely cater to the individual athlete.

**Anti-hyperhidrosis Medications**

A class of medications that is widely used in sports medicine is antiperspirants, also called anti-sudorific agents, which are used to treat excessive sweating, a medical condition known as hyperhidrosis. This condition might sound trivial, but it can be very burdensome for athletes. In many sports, a firm grip is essential, and sweaty hands can have a negative impact on performance. Excessive sweating can also play a negative role in sports when it leads to dehydration and muscle cramps.\(^6\)

There are several pharmaceuticals that can be explored to prevent sweating, such as oral anticholinergics\(^2\). Examples of anticholinergic agents include propantheline, glycopyrrolate, oxybutynin, and benztropine.\(^7\) These medications offer a systemic approach to prevent the neurotransmitter acetylcholine from stimulating the glands that cause sweat production. Unfortunately, oral anticholinergics have negative side effects which include mydriasis, constipation, blurry vision, dry mouth and eyes, and difficulty urinating. Another systemic alternative is the use of beta-blockers, which can prevent sweating related to anxiety by slowing down the sympathetic nervous system. Beta-blockers are FDA-approved for patients with hypertension and several other cardiovascular indications, but their “off label” use in hyperhidrosis is relatively rare.\(^8\)

More realistic options for athletes with hyperhidrosis are topical medications. The commercially available prescription product Drysol\(^\text{®}\) (Person & Covey) consists of 20% aluminum chloride hexahydrate in an anhydrous alcohol base. It is applied to the skin at bedtime, then washed off in the morning to minimize irritation.\(^9\) The area of application on the skin can also be neutralized with sodium bicarbonate or by application of 1% hydrocortisone cream to reduce skin irritation. Another option for compounding pharmacists is to prepare 20% aluminum chloride in a gel base containing 4% salicylic acid. This approach causes less irritation to the skin, but is not available commercially; therefore, it is a valuable product for compounding pharmacists to offer.\(^2\) These topical applications involving aluminum chloride work by occluding the sweat ducts. This is how antiperspirant deodorants work as well, but these preparations used in sports medicine are much stronger.

**Hemorrhoid Preparations**

Another indication commonly encountered in sports medicine and pharmacy is hemorrhoids. Hemorrhoids are swollen veins in the rectum or anus that are especially painful when moving in a crouched or squatted position. Hemorrhoids are very common in baseball catchers, coaches, and any athlete where frequent crouching or squatting are involved.\(^10\),\(^11\) The main treatment options for hemorrhoids in athletes, and patients in general, are anti-inflammatory agents, which reduce the swelling of the veins in the rectum, thus reducing pain.\(^12\) The specific treatment for athletes involves a specialized suppository dosage form referred to as “rectal rockets,” which are suppositories that remain in place after insertion into the rectum or anus, even after rigorous activity.\(^3\) These specialized suppositories even include a slit to accommodate flatulence without losing the suppository. A common “rectal rocket” can be compounded with the topical anesthetic lidocaine and the anti-inflammatory corticosteroid hydrocortisone.\(^13\)

**Specialized Drug Administration Techniques**

There are highly specialized techniques sometimes used...
to administer certain medications that are prepared by pharmacists for use in athletes such as, iontophoresis and phonophoresis. Iontophoresis is a procedure that facilitates the delivery of medications into the tissue beneath the skin by electronic transport of ionized drug in solution. Many different drugs can be compounded and delivered in this way for a variety of indications. Acetic acid iontophoresis is used to treat heel pain, and dexamethasone iontophoresis for plantar fasciitis and hyperhidrosis. Another common medication administered through iontophoresis is clotrimazole in a dimethylsulfoxide (DMSO) solution. Clotrimazole is an antifungal drug, and when delivered in this way in a DMSO solution, it becomes a highly effective method of treatment for certain, more severe cases of athlete’s foot. Phonophoresis combines both topical drug delivery with ultrasound to deliver the medication to muscles and tissues beneath the skin. In this technique, the gels for ultrasound drug delivery are compounded to contain the medication for treatment. Many transdermal gels are compounded for this type of administration, most of which are used to treat pain and inflammation.

Topical Pain Relief
Perhaps the most common and athletically specific class of medications used in sports medicine is non-steroidal anti-inflammatory drug (NSAID) therapy. Muscle and joint pain and inflammation are two of the largest problems encountered by athletes. An easy way to treat these indications is with NSAIDs. They are non-selective COX inhibitors, which inhibit both COX-1 and COX-2 enzymes. When these medications are taken orally, adverse effects may occur, particularly with high doses or long term therapy. Inhibition of COX-2 is desirable because it prevents the production of prostaglandins, thereby reducing inflammation and pain. Inhibiting COX-1 is problematic, however, because COX-1 results in the production of mucus for the lining and protection of the stomach from the effects of gastric acid. Inhibiting COX-1 can damage the stomach lining, resulting in stomach ulcers, also known as peptic ulcers. In sports medicine, topical NSAIDs, which avoid the risk of inhibiting COX-1, can be compounded by the pharmacist. Commonly compounded topical NSAIDs are ibuprofen and ketoprofen. These are often formulated with other types of medications, such as corticosteroids, and can be formulated into gels by compounding pharmacists for either traditional topical use or using phonophoresis.

In sports medicine, getting the body ready to perform optimally before a game is essential. There are several topical medications that can be applied to muscles and joints to prepare athletes for strenuous activity. Combinations of emu oil and other anti-inflammatory agents are examples of ingredients that can be compounded into topical preparations by pharmacists. Emu oil is composed of fatty acids which are absorbed into the skin where they reduce pain and inflammation. The composition of fatty acids making up emu oil is quite similar to the composition of fatty acids in human sebum, which explains why emu oil is absorbed well into human skin. Other topical “pregame rubs” consist of active ingredients that include camphor, menthol, and methyl salicylate, the active ingredients in the commonly used OTC product Bengay®. These active ingredients can relieve pain and soothe sore muscles by a counterirritant effect. Camphor can be used for minor aches and pains and is FDA approved for this indication. It can be compounded in concentrations ranging from 3% to 11%, depending on the condition of the athlete. Topically applied camphor works by stimulating nerve endings, thus relieving the symptoms of pain. Menthol and methyl salicylate are used in combination with each other to achieve the “icy/hot” sensation that relieves minor muscle and joint pain. Like camphor, menthol and methyl salicylate can be compounded at different strengths depending on the prescriber’s judgment. Common side effects of these agents include burning, redness, and itching at the site of application, but these are relatively minor in most instances.

Topical anesthetics are another class of medications commonly employed in sports medicine. These medications are used in situations where muscle and joint pain exist, but can also be helpful when pain is experienced due to laceration type injuries. What distinguishes the local anesthetics from the topical NSAIDs is the mechanism by which they act. NSAIDs act by reducing inflammation, thus leading to the reduction of pain, whereas local anesthetics block nerve conduction. This distinction between the local anesthetics and the NSAIDs is also relevant in situations where muscle and joint pain are not the result of inflammation, because in such cases local anesthetics are more effective. Lidocaine, adrenaline, and tetracaine (“LAT”) gel is a commonly used topical anesthetic in sports medicine. The adrenaline (epinephrine) causes vasoconstriction which stops bleeding secondary to injury, and prolongs the local anesthetic effect by limiting percutaneous absorption of the local anesthetics into the systemic circulation. The side effects of topically applied local anesthetics are fairly minor. Irritation such as burning, itching and redness to the site of application can occur. More problematic situations can occur when plasma concentrations of local anesthetics become too high, causing adverse cardiovascular or central nervous system effects. But systemic side effects are unlikely unless there is serious skin damage over the applied site, facilitating greater systemic absorption of the anesthetic.

The Demand for Compounding Pharmacy
The demand for pharmacy compounding in sports medicine is growing as the benefits are being increasingly recognized.
The availability of personalized treatment is extremely valuable, especially for athletes where injuries are so common and are so unique to each individual athlete and each specific sports activity. Compounding pharmacies are beginning to proactively reach out to local, collegiate and professional sports organizations, and are creating partnerships with these organizations to enhance medication therapy. One specific example is The Compounding Pharmacy of North Carolina, an independent pharmacy that has created a partnership with the NFL’s Carolina Panthers, the NBA’s Charlotte Bobcats, and several college athletic programs in North Carolina. This North Carolina compounding pharmacy takes pride in its ability to take into account not only the athlete’s injury when formulating the medication, but also the athlete’s lifestyle and environmental factors in order to individualize the therapy.5

The branch of medicine designated to sports and athletes is a large and growing field. It consists of many different subcategories such as physical therapy, athletic training, and even strength and conditioning. But pharmacy has also made its way into sports medicine and is playing a larger role. The compounding pharmacist has become a valuable part of the sports medicine team and will play an increasingly important role in the future.

References
Apixaban: A New Oral Anticoagulant

by Jonathan Sin, PharmD Candidate 2014
Maria Leibfried, BS, PharmD, BCNSP, CCP

Atrial fibrillation (AF), the most common form of arrhythmia, carries a stroke risk of up to 20% annually. Since over 3 million people in the United States have AF, with an incidence of almost 9% in those older than 80 years, and because stroke remains the fourth leading cause of death in the US, attention is put on anticoagulation for prophylaxis. An oral anticoagulant, apixaban (Eliquis®, Bristol-Myers Squibb), was approved by the Food and Drug Administration (FDA) in December 2012.

Apixaban, a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular AF, is available as 2.5 and 5 mg oral tablets. Usual dosage is 5 mg twice daily.

Warnings

Apixaban has a black box warning: discontinuation of the drug increases the risk of thrombotic events. Apixaban should not be used in patients with prosthetic heart valves. Pharmacists should dispense the Medication Guide and counsel appropriately on signs of bleeding.

Pharmacology

In the coagulation cascade, factor Xa cleaves prothrombin to generate thrombin. Thrombin converts soluble fibrinogen to insoluble fibrin, which forms stable clots. Apixaban selectively inhibits factor Xa. Like other factor Xa inhibitors, apixaban does not require the mediator antithrombin III for activity. This may be important in patients with antithrombin III deficiency or heparin resistance. Apixaban has an added benefit of indirect inhibition of platelet aggregation.

Pharmacokinetics

Bioavailability of apixaban is approximately 50%, regardless of food. Apixaban is metabolized by cytochrome P450 (CYP450)-3A4 and is a substrate of P-glycoprotein. When co-administered with drugs that are both strong CYP450-3A4 and P-glycoprotein inhibitors (e.g., ketoconazole, clarithromycin, ritonavir), the apixaban dose should be reduced to 2.5 mg twice daily. Concomitant use of apixaban with strong dual CYP450-3A4 and P-glycoprotein inducers (e.g., rifampin, St. John’s wort) is not recommended. Dosage adjustments are summarized in Table 1. No dosage adjustments are needed in mild hepatic impairment. There are no recommendations for patients with moderate hepatic impairment, as that population was not studied.

Clinical Trials

In the randomized, double-blind study, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), 5,599 patients who were unsuitable for vitamin K antagonist therapy (if they used warfarin and could not maintain therapeutic international normalized ratios [INRs], INRs could not be obtained as requested, they had low risk of stroke [CHADS2 scores of 1], or they simply did not want to take warfarin) were randomized to receive apixaban 5 mg or 2.5 mg twice daily depending on necessary dosage adjustments, or aspirin 81 or 324 mg daily. The primary efficacy outcome was incidence of stroke or systemic embolism; the primary safety outcome was major bleeding requiring hospitalization. The mean duration of follow-up was 1.1 years.

AVERROES showed apixaban’s superiority over aspirin in reducing stroke or systemic embolism without significantly increasing risk of major bleeding. Fewer patients in the apixaban group (1.6% per year) experienced a stroke or systemic embolism when compared to the aspirin group (3.7% per year). This difference was statistically significant (P<0.001). There was no statistically significant difference in the number of major bleeding events requiring hospitalization: 1.4% per year with apixaban and 1.2% per year with aspirin. AVERROES was terminated early because after the first interim efficacy analysis, apixaban was shown to be superior to aspirin for the primary efficacy outcome.

In the randomized, double-blind trial, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), 18,201 AF patients with at least one additional risk factor for stroke randomly received apixaban 5 mg or 2.5 mg twice daily based on dosage

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient Criteria</th>
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<tbody>
<tr>
<td>Decrease: 2.5 mg twice daily</td>
<td>Use of strong dual CYP450-3A4 and P-glycoprotein inhibitors</td>
</tr>
<tr>
<td>Use not recommended</td>
<td>Use of strong dual CYP450-3A4 and P-glycoprotein inducers</td>
</tr>
<tr>
<td></td>
<td>Severe hepatic impairment</td>
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</table>

Table 1. Apixaban dosage adjustments

Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), 5,599 patients who were unsuitable for vitamin K antagonist therapy (if they used warfarin and could not maintain therapeutic international normalized ratios [INRs], INRs could not be obtained as requested, they had low risk of stroke [CHADS2 scores of 1], or they simply did not want to take warfarin) were randomized to receive apixaban 5 mg or 2.5 mg twice daily depending on necessary dosage adjustments, or aspirin 81 or 324 mg daily. The primary efficacy outcome was incidence of stroke or systemic embolism; the primary safety outcome was major bleeding requiring hospitalization. The mean duration of follow-up was 1.1 years.

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adjustments, or INR-adjusted warfarin. Primary efficacy and safety outcomes were the same as AVERROES, with an additional secondary efficacy outcome: death from any cause. Patients were followed for an average of 1.8 years.9

ARISTOTLE showed, with statistical and clinical significance, that apixaban was superior to warfarin at preventing stroke or systemic embolism, caused less incidences of major bleeding, and resulted in lower mortality rates. Fewer patients in the apixaban group (1.27% per year) suffered a stroke or systemic embolism when compared to the warfarin group (1.6% per year). Fewer patients in the apixaban group (2.13% per year) reported major bleeding when compared with the warfarin group (3.09% per year). Death from any cause was 3.52% per year in the apixaban group and 3.94% per year in the warfarin group.9

Place in Therapy
Apixaban is safe, efficacious, and does not necessitate INR-monitoring. Apixaban also does not require the dietary restrictions associated with warfarin. However, there is more data on long-term efficacy and safety of warfarin, which remains the mainstay of treatment.1

Two other oral anticoagulants approved recently are dabigatran (direct thrombin inhibitor) and rivaroxaban (factor Xa inhibitor).10,11,12,13 Guidance on switching to and from warfarin is available in their respective package inserts. Currently, no published studies are available that directly compare these drugs to one another. In regards to anticoagulant reversal, there are no antidotes that have been evaluated in clinical trials for these drugs.5,12,13

Current guidelines from the American College of Chest Physicians mention apixaban, not for AF, but for venous thromboembolism (VTE) prophylaxis in patients undergoing total knee or hip arthroplasty. If these patients refuse low-molecular-weight-heparin injections or intermittent pneumatic compression devices, then apixaban, dabigatran, or rivaroxaban are recommended.14

In Europe, apixaban is approved by the European Medicines Agency for VTE prophylaxis in adults following knee or hip-replacement operations,15 although it’s not approved by the US FDA for that indication.

References

Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>US FDA-approved indication(s)</th>
<th>Usual Dosage</th>
<th>Dosage Adjustments</th>
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<tr>
<td>Dabigatran (Pradaxa®)13</td>
<td>Prevention of stroke and systemic embolism in non-valvular AF</td>
<td>150 mg twice daily</td>
<td>CrCl 15-30 mL/min: 75 mg twice daily; no recommendations for CrCl &lt; 15 mL/min or dialysis patients</td>
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<tr>
<td>Rivaroxaban (Xarelto®)12</td>
<td>Prevention of stroke and systemic embolism in non-valvular AF</td>
<td>20 mg once daily with dinner</td>
<td>CrCl 15-50 mL/min: 15 mg daily with dinner</td>
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<tr>
<td></td>
<td>Prevention of VTE after knee or hip replacement</td>
<td>10 mg once daily with dinner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment of DVT/PE and prevention of recurrence</td>
<td>15 mg twice daily with dinner x 21 days, then 20 mg once daily with dinner</td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis®)9</td>
<td>Prevention of stroke and systemic embolism in non-valvular AF</td>
<td>5 mg twice daily</td>
<td>Table 1</td>
</tr>
</tbody>
</table>

Table 2. Three new oral anticoagulants5,12,13

CrCl: Creatinine clearance; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism
Heart failure is a debilitating, chronic disease affecting approximately 6.5 million people across the United States. Patients are often on an average of 14 medications which leads to confusion, non-compliance and increased adverse effects. Thirty percent of heart failure patients are readmitted or die from complications within 90 days of discharge, with 25% of these patients readmitted within 30 days. The Center for Medicare and Medicaid Services (CMS) has implemented strict policies regarding hospital reimbursement and payment reductions for these readmissions. Hospitals across the United States are investigating new and innovative strategies to better optimize patient care, maximize use of beneficial therapeutic agents, and ensure patient knowledge of their disease state and adherence to their regimen. Recently published studies have shown effectiveness of aggressive management of this patient population. Collaboration between pharmacists and other members of the healthcare team help improve outcomes. Medication counseling and reconciliation aid to clarify questions patients may have about their complicated regimens and studies have shown that pharmacist involvement in care of heart failure patients significantly reduces all-cause hospitalizations and hospitalizations due to decompensation.

Pharmacists at The Valley Hospital have been working in the nurse-practitioner run outpatient heart failure clinic since August 2012. The clinic sees patients twice a week where nurse practitioners assess their volume status and make adjustments to their medications as needed. Through medication therapy management, pharmacists are able to perform medication reconciliation and educate patients about their medication regimen as well as answer any questions they may have. Patients are encouraged to bring in all their medications during their preliminary visit so that pharmacists may assess the medication regimen and determine if there are any potential drug interactions as well as make dose adjustment recommendations. In addition, pharmacists have been working with nurses to perform follow-up phone calls for recently discharged patients admitted for heart failure exacerbation. Pharmacists have been able to speak to patients at home and make sure they understand their medication regimen and importance of taking doses as directed by their physician. The heart failure clinic has been successful and pharmacists at the Valley Hospital have been excited for the opportunity to help make a positive impact in the lives of these patients.

For more information, please contact Carlo Lupano, RPh, MBA, Pharmacy Manager at The Valley Hospital-Luckow Pavilion, or visit www.valleyhealth.com/pharmacy.

Practice Spotlight:

Outpatient Heart Failure Clinic at The Valley Hospital, Paramus, NJ

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For more information, please contact Carlo Lupano, RPh, MBA, Pharmacy Manager at The Valley Hospital-Luckow Pavilion, or visit www.valleyhealth.com/pharmacy.

Avoid diminishing the value of your pharmacy.
Don’t leave money on the table when you transition the ownership of your business.

CONSIDER THESE IMPORTANT ISSUES...

1. Confidentiality is CRITICAL to maintaining business value. The more people who know about a sale (employees, suppliers, customers), the less value it will ultimately have. Limit your conversations to trusted advisors, associates and family members.

2. Connect to the largest group of QUALIFIED BUYERS to create the highest price, by leveraging the highest level of interest in your business. Limiting your buyer pool (e.g. ONLY your wholesaler’s customers), limits your ability to sell and sale price.

3. DO NOT engage in conversations, information sharing or negotiations with ANY buyer without professional representation, particularly if contemplating a sale to a chain. Thirteen years of experience selling pharmacies has shown us time after time that direct engagement rarely—if ever—gets the independent owner the best price or the best deal.
A 14-year-old male collapsed in school and died 10 days later, after receiving treatment in the hospital. The only contributing medical history was that he had been taking Adderall XR® (amphetamine, dextroamphetamine mixed salts; extended release capsules) for three years. Could this be just a mere coincidence? This article aims to provide pharmacists with a closer look into the controversy surrounding serious cardiovascular effects associated with prescription stimulant medications used to treat attention-deficit and hyperactivity disorder (ADHD) in children and adults.

I. Background and Epidemiology

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V) guidelines approved in May 2013, ADHD is a neurobehavioral disorder characterized by various symptoms of inattention, hyperactivity, and impulsivity, which present before age 12 and can continue into adulthood. This disorder is commonly diagnosed in children, in boys more than girls. However, there has been a rise in diagnosis of ADHD in adults, because there is evidence that symptoms can persist from childhood into adulthood.

The classic ADHD symptoms of inattention, hyperactivity, and impulsivity occur because of a lack of catecholamine activity in the brain. Prescription schedule II (C-II) central nervous system (CNS) stimulants are considered first-line pharmacotherapy for treatment of ADHD, with or without behavioral therapy. By inhibiting norepinephrine and dopamine reuptake and increasing their release into extracellular space, stimulants raise neurotransmitter levels in the body and “stimulate” the patient, but they also increase the risk of cardiovascular adverse effects with their sympathomimetic activity. A systematic review concluded that stimulants have shown to increase blood pressure and heart rate, induce vasospasm, cause vasculitis (by promoting the circulation of proinflammatory molecules), and they prolong the cardiac QT interval, thereby increasing the risk of Torsades de pointes. In adults and children, ADHD medications have been shown to raise blood pressure (<5 mmHg) and heart rate (<7 bpm); however further data is needed to evaluate long-term effects. Although stimulant medications are generally well-tolerated, they have a black box warning for psychiatric effects such as the potential for suicidal ideation, abuse and dependence, and they have warnings for potential serious cardiovascular effects such as acute myocardial infarction (MI), sudden death, stroke.

II. Regulatory and Medical Guidance on Stimulant Prescribing and Use

In light of the cardiovascular concerns of ADHD medications, the Food and Drug Administration (FDA), American Heart Association (AHA), and the American Academy of Pediatrics (AAP) developed and revised guidance over the years for drug manufacturers and healthcare professionals (Table 1).

In April 2013, the results of a national ambulatory audit were published, which assessed if the FDA’s public health advisories issued between 2005 and 2007 had an impact on the prescribing habits of office-based physicians. The market share of Adderall® (which included Adderall XR®), all stimulants (Adderall and non-Adderall stimulants), atomoxetine, and substitutes (clonidine, guanfacine, bupropion), prescribed at each office visit is depicted in Figure 1. For example, in 2004 there were 9,495,000 physician office visits, in which prescriptions for Adderall® and atomoxetine, a non-stimulant medication used to treat ADHD, comprised 36% and 19% of the market share, respectively. After the FDA issued a few advisories, by 2008, prescription market share for the two medications decreased to 24% and 8%, respectively. The study investigators concluded that despite the declines in stimulant...
The Progression of Regulatory and Medical Guidance on the Cardiovascular Effects of Stimulants

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulatory and Medical Guidance</th>
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| 2005 | • FDA issued PHA acknowledging case reports of sudden death associated with amphetamine and dextroamphetamine- and methylphenidate-containing products  
  • FDA advised that patients with underlying heart defects should “ordinarily not be treated” with such stimulant products |
| 2006 | • After the FDA’s Pediatric Advisory Committee voted against issuing a black box warning, a class-specific warning was issued for prescription ADHD medications regarding potential increased risk for CV adverse events |
| 2007 | • FDA directed manufacturers to provide patient medication guide to warn about CV and psychiatric effects |
| 2008 | • AAP & AHA released consensus statement suggesting to perform ECG prior to initiating stimulant therapy, but not mandatory  
  • Treatment should not be withheld on the basis of not having ECG done |
| 2011 | • FDA did not change recommendations for treating ADHD  
  • FDA recommended that patients should continue ADHD treatment as prescribed and should be monitored periodically for changes in heart rate or blood pressure  
  • FDA advised that stimulant products and atomoxetine should “generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic” |

*ADHD medications involved in FDA’s safety review:  
Stimulants – methylphenidate (Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin-LA, Ritalin-SR); dexamfetamine HCl (Focalin, Focalin XR); dextroamphetamine sulfate (Dexedrine, Dexedrine Sponsors, Dextroamphetamine ER, Dextrostat); lisdexamfetamine dimesylate (Vyvanse); amphetamine, mixed salts (Adderall, Adderall XR), methamphetamine (Desoxyn); Non-stimulants – pemoline (Cylert—no longer marketed); atomoxetine (Strattera).  
Abbreviations: AAP=American Academy of Pediatrics; ADHD=Attention-deficit and hyperactivity disorder; AHA=American Heart Association; CV=Cardiovascular; ECG=electrocardiogram; FDA=Food and Drug Administration; PHA=public health advisory. 

use over the study period, the FDA advisories did not have a statistically significant effect on ADHD medication prescribing.11 It will be interesting to see how this market-share trend is affected by the new DSM-V guidelines and the FDA-approved medical device, the Neuropsychiatric EEG-Based Assessment Aid (NEBA) system, which aids in diagnosing ADHD in patients ages 6 through 17.17

III. Key Clinical Studies – Pediatric, Adolescent, and Young Adult Populations

A 2007 Centers for Disease Control and Prevention (CDC) survey of parents of children with ADHD revealed that 2.7 million children ages 4-17 years old were actively taking stimulant medication for treatment.3 The following represents a few of the many studies conducted in the pediatric and adolescent populations, which sought to establish a statistically significant relationship between serious cardiac effects with stimulant medication use.

The Gould et al. study, sponsored by the National Institute of Mental Health (NIMH), analyzed the strength of association between immediate use of a stimulant (i.e., amphetamine, dextroamphetamine, methamphetamine or methylphenidate) prior to death and sudden unexplained death among deceased children and adolescents ages 7 through 19. In addition to the stimulant, patients may also have been taking tricyclic antidepressants (TCAs), selective serotonin-reuptake inhibitors (SSRIs) and/or clonidine. Interestingly, the comparison group consisted of deceased passengers of a motor vehicle accident because they were found not to be at greater risk for symptoms of hyperactivity, impulsivity, and inattention. The investigators matched 564 motor vehicle accident victims to 564 patient cases of sudden explained death...
by year of death (within three years), gender, and data source available. It was concluded that stimulant use, primarily methylphenidate, increased the odds of sudden unexplained death [odds ratio (OR), 7.4; 95% CI: 1.4-74.9; p=0.02]. Although there were several limitations to this retrospective case-control study, such as the exclusion of gross structural cardiac disease in autopsy results, the study highlighted the possibility of sudden death from stimulant use in a young patient population.

In a study conducted in Medicaid beneficiaries, ages 3 to 20 years old, there was a 20% and 21% increased risk of cardiac-related emergency room and physician office visits for cardiac symptoms, respectively, among newly diagnosed ADHD patients who were current users of stimulants. There was no increased risk in cardiac death or hospitalizations observed. In their secondary analysis, there was no statistical difference between the use of methylphenidate and amphetamine salt medication preparations. Even with a relatively large sample size of 55,383 patients (i.e., 124,932 person-years) the authors determined that they would need a sample size 16 times larger (i.e., 2,000,000 person-years) to determine a significant difference between stimulant use and nonuse groups. This study conflicts with the results of the Gould et al. study for the risk of cardiac death, but highlights an increase in need for immediate medical attention with stimulant use.

*Person-years represents the number of years that a patient has been affected by ADHD times the number of members in the study population (derived from Stedman Medical Dictionary).

The FDA and Agency for Healthcare Research and Quality (AHRQ) funded a matched cohort study that analyzed data collected over 20 years from more than 1.2 million beneficiaries of four national health plans. The inclusion criteria consisted of patients ages 2 to 24 years old who were stratified into groups of current users, former users or nonusers of an ADHD drug (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine salts, atomoxetine, or pemoline). There were 81 total serious cardiovascular events (33 sudden cardiac deaths, 9 acute myocardial infarctions, and 39 strokes) among the three groups of patients. The results showed that current use of an ADHD medication did not significantly increase the risk of a cardiovascular event [adjusted hazard ratio (HR), 0.75; 95% CI: 0.31 to 1.85], compared to nonusers and former users [adjusted HR, 0.70; 95% CI: 0.29 to 1.72]. An alternative analysis which included 7 patients with severe underlying cardiac disease, also found no increased risk of sudden cardiac death for current users. Although the point estimates of the relative risks for ADHD drugs did not demonstrate a statistical significance, because the upper limit of the 95% confidence intervals (1.85 for current users compared to nonusers and 1.72 for current users compared to former users) were approaching the value of 2.0, the authors suggested that a doubling of the risk of serious CV events could not be ruled out. The results of this study helped influence the FDA’s recommendations for ADHD treatment management in 2011 (see Table 1).16

### IV. Key Clinical Studies – Adult Population

For patients who begin treatment for ADHD as a child, most of those patients discontinue stimulant use because they either feel “well” or they fear the risk of having a decrease in height and/or weight with long-term use of stimulants. However, approximately 29.3% of those patients who prematurely discontinued ADHD treatment as a child continue to experience clinically significant symptoms into adulthood. For example, behaviors such as restlessness, impatience, disinhibition, and callousness which are perceived as personality issues, may more accurately be associated with ADHD. A 2013 epidemiologic study indicated that adults with childhood ADHD are at an increased risk of death from suicide, and 56.9% of those adults have more than one psychiatric disorder other than ADHD. Although evidence suggests that long-term treatment can relieve symptoms and improve quality of life, the following studies evaluate the risk of serious cardiovascular events in adults receiving stimulants, in the presence of age-related comorbidities.

Holick et al.’s population-based study compared the incidence of cerebrovascular attacks (CVA) (e.g., stroke) and transient ischemic attacks (TIA), which are associated with increases in blood pressure, in adults ages 18 years and older (including adults £65 years old) with the use of atomoxetine or an ADHD stimulant. With 21,606 patients matched to each treatment group, there were a total of 44 CVAs and 21 TIAs within a mean of 1.5 years follow-up. When compared to each other, there was no greater risk of stroke or TIA between the two ADHD treatment groups. However, when later compared to a general population cohort (n=42,993), atomoxetine and stimulants significantly increased the risk of TIA, but not stroke [HR, 3.44; 95% CI: 1.13-10.60]. The authors acknowledged that the study does not support an increased risk of cardiovascular events but stimulant use may increase risk of TIA in adults.

To date, the study by Habel et al. is the largest (n=443,198) retrospective, population-cohort study evaluating the cardiovascular effects of ADHD medications in adults. After adjusting for potential differences in cardiovascular disease in adults ages 25 through 64 years old, the risk of myocardial infarction (MI), sudden cardiac death (SCD), or stroke in current users of ADHD medication (i.e., methylphenidate, amphetamines, atomoxetine, or pemoline at baseline) was
no different from nonuse [adjusted rate ratio, 0.83; 95% CI: 0.72-0.96]. Among 107,322 person-years of current use (n=150,359; range 0.0-13.5 years per user), there was a crude incidence per 1000 person-years of 1.34 [95% CI: 1.14-1.57] for MI, 0.30 [95% CI: 0.20-0.42] for SCD, and 0.56 [95% CI: 0.43-0.72] for stroke. In a subanalysis in new users, who had not been exposed to ADHD medication for a year before the study began, for the composite end point of the risk of MI, SCD or stroke, there was an adjusted rate ratio of 0.77 [95% CI: 0.63-0.94] compared to use and nonuse of ADHD medications. Overall, this comprehensive study demonstrated that current or new use of ADHD medications was not associated with an increased risk of cardiovascular events, compared to nonuse or remote use in young to middle-aged adults.6,24

A nonrandomized cohort study in adults 18 years and older matched methylphenidate users (n=43,999) to nonusers (n=175,955) and found an increased risk of sudden death/ventricular arrhythmia among users versus nonusers [adjusted HR, 1.84; 95% CI: 1.33-2.55]. A secondary analysis showed a significantly increased risk of all-cause death for methylphenidate users [adjusted HR, 2.38; 95% CI: 2.20-2.56]. In contrast to sudden death/ventricular arrhythmia, there was an inverse association between high dose (≥20 mg methylphenidate) and low dose (<20 mg methylphenidate) and the risk of sudden death or ventricular arrhythmia, stroke, MI, or all-cause death. This study demonstrated that within 180 days of initiating methylphenidate in new users, the risk of developing sudden death/ventricular arrhythmia nearly doubled [adjusted HR, 1.92; 95% CI: 1.22-3.05], and that risk was also reflected in current users compared to nonusers.7

V. Conclusion
Although there is a myriad of data available evaluating the risk of cardiovascular effects associated with the use of stimulants for ADHD treatment; the results are inconclusive. It is important to note that a good proportion of these studies are retrospective, based on health records of patients with varying sociodemographics. Due to different methods of acquiring and statistically analyzing the data, the reliability of the results can be questioned. Until there is substantial data from ongoing prospective and well-designed clinical trials25, the FDA will most likely not move forward with issuing black box warnings regarding serious cardiovascular events for ADHD medications.

Regardless of statistical significance, the fact that a 14-year-old boy died presumably from treatment for ADHD is still of clinical significance. As pharmacists, we need to remind patients of the risks associated with ADHD medication use and abuse, and we need to
encourage patient recognition of symptoms that may require immediate medical attention (i.e., increased heart rate, elevated blood pressure, and chest pain). We can also collaborate with physicians to manage medications and to help determine which patients are at an increased risk of cardiovascular effects with stimulant medication (e.g., a patient with cardiovascular disease, preexisting cardiac structural abnormalities, or an elderly patient with psychiatric and cardiovascular comorbidities, in addition to reduced renal function). While stimulants and non-stimulants are considered well-tolerated and efficacious, careful monitoring and patient education could lead to safer use of these ADHD treatment medications.

References:
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. UAN: 0136-0000-13-052-H04-P and UAN: 0136-0000-13-052-H04-T Expiration Date 10/22/2016

Post Test
1) What are the symptoms of ADHD?
   A) inattention C) hyperactivity
   B) impulsivity D) All of the above

2) What is first-line pharmacotherapy for ADHD?
   A) beta-blockers C) antipsychotics
   B) central nervous system stimulants D) tricyclic antidepressants

3) The mechanism of action of stimulants results from an increase in neurotransmitter levels in the body due to
   A) inhibition of norepinephrine reuptake C) A and B
   B) inhibition of dopamine reuptake D) None of the above

4) Side effects of stimulant medications include
   A) decreased blood pressure and heart rate
   B) vasospasm C) QT prolongation
   D) B and C only

5) Stimulant medications have black box warnings for
   A) lethargy C) visual disturbances
   B) psychiatric effects (suicidal ideation)
   D) decreased heart rate

6) Guidance on stimulant use has been provided by which of the following groups
   A) Food and Drug Administration (FDA) C) American Academy of Pediatrics (AAP)
   B) American Heart Association (AHA)

7) Results from a national ambulatory audit published in 2013 showed that FDA public health advisories on stimulant use issued during 2005 to 2007
   A) did not have a statistically significant effect on stimulant prescribing habits
   B) led to an increase in stimulant prescribing
   C) caused practitioners to discontinue stimulant use
   D) resulted in a black box warning for cardiovascular effects

CE Assessment Answers
Passing Score is 70% or above
Please circle your answers (one answer per question)
1. A B C D 5. A B C D
2. A B C D 6. A B C D
3. A B C D 7. A B C D
4. 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

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

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Email ____________________________
Phone Number____________________ License No.__________
E-PID#______________________ Birth mm/date_________________
REGION 5 NEWS
By Alan “Scoop” Aronovitz, RPh, C.C.P.

We are pleased to announce that Kruti Lodhavia has taken the postion of Chairperson of the Region 5 Membership Committee. Kruti is a USP PharmD graduate, class of 2002. Stepping up just at the right time, Kruti will act as the Region 5 liaison to the State Membership Committee as they prepare to debut several new and exciting initiatives. Locally, the Region 5 Membership Committee has plans in the works to hold a happy hour down the shore in the fall and begin working with the students at Stockton State College who are in the Ernest Mario School of Pharmacy matriculation program.

Anyone wishing to join the Membership Committee and help Kruti in her endeavors should contact Alan S. Aronovitz at ASAXPCS@aol.com.

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.

Academy of Disaster Management Pharmacists News (ADMP)

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

Congratulations to Stephen Brickman, ADMP President, who was recently appointed as a Clinical Pharmacist on the National Disaster Medical System’s (NDMS) Logistics Response Assistance Team (LRAT). The LRAT’s mission is to maintain and update team caches of equipment and medication used by federally deployed Disaster Medical Assistance Teams (DMAT) as well as surgical, veterinary, and mortuary teams. This includes resupply for deployed teams in the field, as well as refilling the caches as teams return to their home stations. According to Stephen, “It’s not as glamorous as being deployed to the field, but obviously necessary for mission success. It means being deployed to cache sites and working with my team to accomplish the mission. After over 20 years of being the customer, I will now be the supplier. It will probably entail more deployments annually compared to DMAT deployments, something I am actually looking forward to.” We wish him luck in this vital work that keeps us all safe during disasters.

On June 25th, ADMP President Steve Brickman and ADMP Vice-President Harold Bobrow took their road show south and again presented the lecture, “The Pharmacist’s Role In Disaster Preparedness” at Renault Winery in Egg Harbor, NJ for Region 5. The 1.5 hour credit lecture provided information to pharmacists and technicians on the resources available to successfully manage disasters. It reviewed some major events and discussed the pharmacist’s role in each event. Finally, they reviewed non-traditional roles that pharmacists and technicians can fill in the event of a disaster. The lecture was well attended and a lively question and answer session followed the talk.

The ADMP continues to recruit new members (request an NJPhA membership brochure with Academy information by sending an e-mail to ASAXPCS@aol.com or visiting the NJPhA website www.njpharmacist.org . click the Members tab on the top bar, and either Join now or Renew. Select ADMP as your academy choice when joining or renewing membership.) and encourages our members to join the Medical Reserve Corps (MRC) in their county. You can apply on line 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.
Phytosterols and Cardiovascular Health

Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio and J. Richard Wuest, R.Ph., PharmD, Professor Emeritus, University of Cincinnati, Cincinnati, Ohio

Provided by the Ohio Pharmacists Foundation

continuing education for pharmacists

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Dr. Thomas A. Gossel and Dr. J. Richard Wuest have no relevant financial relationships to disclose.

Goal. The goal of this lesson is to educate pharmacists on phytosterols (plant sterols), their mechanisms of action in reducing blood cholesterol levels, and implications for their use in promoting cardiovascular health.

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

1. define the term phytosterol and list specific types;
2. explain the mechanisms of action by which phytosterols act to reduce blood levels of low-density lipoprotein cholesterol;
3. identify natural dietary sources of phytosterols;
4. select the effective dose of phytosterols for reduction of cholesterol and avoidance of adverse effects; and
5. demonstrate an understanding of information and resources to convey to patients about phytosterols.

Throughout history, plants have been consumed by humans and animals. In addition to being rich in fiber and plant protein, our ancestors’ diets were also rich in phytosterols – plant-derived sterols similar to cholesterol in structure and function. Much evidence exists that reintroduction of plant foods that provide phytosterols into today’s diet can reduce the risk of cardiovascular disease (CVD) by decreasing blood cholesterol levels. The major manifestation of CVD is coronary heart disease (CHD), which remains the leading cause of death in the developed world. Atherosclerosis, which damages coronary arteries, is the primary pathology involved in CHD.

LDL-Cholesterol is a Major Cause of CHD

Sixty to 70 percent of the total cholesterol (TC) concentration in humans consists of low-density lipoprotein cholesterol (LDL-C). It is the primary atherogenic (atherosclerosis-causing) lipid and its reduction in the blood is the main target of total cholesterol-lowering strategies. Hypercholesterolemia is a prerequisite for atherogenesis.

Atherosclerosis progresses rapidly when LDL-C levels are high (160 to 189 mg/dL). At very high LDL-C levels (≥190 mg/dL), individuals can develop premature CHD, even in the absence of other risk factors. Those with high LDL-C levels can experience premature CHD when other risk factors, such as smoking, hypertension or family history, are present. This is true, even when absolute risk according to Framingham Risk Scores is <10 percent over 10 years.

There is little doubt that measures to lower LDL-C in persons with elevated levels can prevent atherogenesis. Using data from a large number of cohort studies, it has been shown that the benefits of blood cholesterol reduction are related to age. A 10 percent reduction in TC concentration attained at age 40 produces a reduction in CHD of 50 percent, 40 percent at age 50, 30 percent at age 60, and 20 percent at age 70. Some benefits can be realized right away, most after two years, and full benefit after five years.

The Framingham Heart Study and the Multiple Risk Factor Intervention Trial (MRFIT), along with the Lipid Research Clinical Trial, demonstrated a direct relationship between LDL-C (or TC) levels and the rate of onset of new CHD in both men and women who were previously free of the disease. A similar positive correlation can be shown for recurrent coronary events in persons with established CHD. The widespread prevalence of high LDL-C levels in persons living in the United States who consume a typical Western diet accounts in large part for their near-universal development of coronary atherosclerosis and their...
Atherogenesis. The development of atherosclerosis begins in adolescence as fatty-streak lipid deposits in arterial walls, and can be identified by gross pathological examination of coronary arteries. The streaks consist mainly of cholesterol-rich macrophages. The next phase embodies formation of fibrous plaque that is characterized by a layer of scar tissue overlying a lipid-rich core. Eventually, unstable plaque may rupture and form luminal thrombi, which are responsible for most acute coronary syndromes (unstable angina, myocardial infarction [MI], coronary death).

Elevated TC and LDL-C concentrations increase atherogenesis during the teenage years, with outcomes amplified by young adulthood, perhaps 20 to 30 years before coronary artery disease manifests clinically. Approximately 19 percent of men aged 30 to 34 years will have well-developed lesions in their left anterior descending coronary arteries. The significance of this early onset of atherosclerosis becomes even more apparent from observations of Klag and coworkers who showed that 22-year-old men with blood TC concentrations >5.45 mMol/L (approximately 209 mg/dL or higher) were 5.6 times more likely to develop coronary artery disease, six times more likely to experience an MI, and 9.6 times more likely to die during the next 40 years than men whose TC level was <4.45 mMol/L (approximately 171 mg/dL or lower).

The goal of therapy for all persons with elevated LDL-C levels is best achieved through an inclusive program that coordinates certain lifestyle changes along with drug therapies. Lifestyle therapy in clinical management, termed therapeutic lifestyle changes (TLC), is a four-step process that includes (1) reduced consumption of cholesterol and saturated fats, (2) dietary options employing phytosterols along with increased viscous fiber to enhance LDL reduction, (3) weight control, and (4) increased physical activity.

**Phytosterols**

Phytosterols are essential structural components of the lipid membrane of plants. Free phytosterols serve to stabilize the membranes of plant cells just as cholesterol does in animal cell membranes. In animals, cholesterol is most often the sole product of sterol synthesis. However, each plant species has its own characteristic distribution of phytosterols. More than 40 phytosterols have been identified in nature. The most abundant are beta-sitosterol (65 percent), campesterol (30 percent) and others, mainly stigmasterol, with much lower levels of brassicasterol. These compounds are structurally similar to cholesterol, but differ in their side chains.

Stanols are saturated sterols; that is, they have no double bonds in the sterol ring. Stanols are less abundant in nature than sterols, comprising only about 10 percent of total dietary phytosterols, and are produced by hydrogenating sterols. Stanols are more resistant to oxidation than sterols. The designation phytostanol is a collective term inclusive of both plant sterols and plant stanols.

Phytosterols are found in vegetables and vegetable oils, seeds, nuts, table spreads, and some fruits (Table 1). A major source of phytosterols is tall oil, also called liquid rosin or tallol. It is a viscous yellow-black odorous liquid which is derived from tall trees, such as pines, during the pulping process. Tall oil contains significant levels of sitosterol, campesterol, and the naturally occurring saturated (stanol) compounds, sitostanol and campestanol. Stigmasterol and other sterols are also found in lesser quantities. The phytosterols exist in nature in free, non-esterified forms.

Phytosterols can be present in Western diets in amounts almost equal to dietary cholesterol, with

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**Table 1**

Selected food sources and their total phytosterol content

<table>
<thead>
<tr>
<th>Food Sources</th>
<th>Total Sterol Content (mg/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oils</strong></td>
<td></td>
</tr>
<tr>
<td>Rice bran</td>
<td>1055</td>
</tr>
<tr>
<td>Corn</td>
<td>952</td>
</tr>
<tr>
<td>Wheat germ</td>
<td>553</td>
</tr>
<tr>
<td>Flax seed</td>
<td>338</td>
</tr>
<tr>
<td>Cottonseed</td>
<td>327</td>
</tr>
<tr>
<td>Soybean</td>
<td>221</td>
</tr>
<tr>
<td>Peanut</td>
<td>206</td>
</tr>
<tr>
<td>Olive</td>
<td>176</td>
</tr>
<tr>
<td>Coconut</td>
<td>91</td>
</tr>
<tr>
<td>Palm</td>
<td>49</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td></td>
</tr>
<tr>
<td>Beet root</td>
<td>25</td>
</tr>
<tr>
<td>Brussels sprout</td>
<td>24</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>18</td>
</tr>
<tr>
<td>Onion</td>
<td>15</td>
</tr>
<tr>
<td>Cabbage</td>
<td>11</td>
</tr>
<tr>
<td>Yam</td>
<td>10</td>
</tr>
<tr>
<td><strong>Fruits</strong></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>24</td>
</tr>
<tr>
<td>Banana</td>
<td>16</td>
</tr>
<tr>
<td>Apple</td>
<td>12</td>
</tr>
<tr>
<td>Cherry</td>
<td>12</td>
</tr>
<tr>
<td>Peach</td>
<td>10</td>
</tr>
<tr>
<td>Pear</td>
<td>8</td>
</tr>
<tr>
<td><strong>Nuts</strong></td>
<td></td>
</tr>
<tr>
<td>Cashew</td>
<td>158</td>
</tr>
<tr>
<td>Almond</td>
<td>143</td>
</tr>
<tr>
<td>Pecan</td>
<td>108</td>
</tr>
<tr>
<td>Pistachio</td>
<td>108</td>
</tr>
<tr>
<td>Walnut</td>
<td>108</td>
</tr>
<tr>
<td><strong>Legumes</strong></td>
<td></td>
</tr>
<tr>
<td>Pea</td>
<td>135</td>
</tr>
<tr>
<td>Kidney bean</td>
<td>127</td>
</tr>
<tr>
<td>Broad bean</td>
<td>124</td>
</tr>
<tr>
<td><strong>Table spreads</strong></td>
<td></td>
</tr>
<tr>
<td>Take Control® spread</td>
<td>100 mg free sterols per tablespoon (14g)</td>
</tr>
<tr>
<td>Benecon® spread</td>
<td>500 mg free stanols per tablespoon (14g)</td>
</tr>
</tbody>
</table>
was first demonstrated in 1951

The poor solubility of natural plant sterols and stanols in water and lipids can limit their usefulness in human applications and therapeutics. This problem has been partially overcome by esterifying them with mono- or polyunsaturated fatty acids. Esterification greatly increases their lipid solubility and ease of incorporation into food products such as table spreads and salad dressings. Following passage through the stomach, the esters undergo hydrolysis within the intestinal lumen as part of the normal digestive process, releasing free compounds.

**Phytosterols are Hypcholesterolemic.** The cholesterol-lowering property of phytosterols was first demonstrated in 1951 when Peterson fed plant sterols to chicks. Shortly thereafter, Pollak showed the same effect in humans by administering crude sitosterol at a dose of 5 to 10 g/day, over a span ranging from eight days to 14 months. He later observed that sitosterol was poorly absorbed from the intestine in rabbits, and when present in excess, blocked cholesterol absorption and ultimately prevented fatty streaking in coronary arteries.

Lees and Lees were among the first to speculate on the desirable therapeutic use of phytosterols. They used a preparation derived from soybean oil that consisted of 60 to 65 percent sitosterol with the remainder being mainly campesterol. Doses of 18 g/day lowered blood cholesterol, but resulted in marked increases in blood levels of the plant sterols, especially campesterol, which is better absorbed than sitosterol.

In another trial, investigators showed that ingestion of capsules of sitostanol dispersed in sunflower oil, at a dose of 12.5 g/day, lowered LDL-C by 15 percent in hypercholesterolemic adults. Two weeks after cessation of sitostanol administration, blood cholesterol returned to pretreatment levels.

On the basis of these reports and other data, Eli Lilly & Co. introduced the first plant sterol product, Cytellin, in the mid 1950s as a cholesterol-lowering pharmaceutical. It consisted predominately of beta-sitosterol. Due to its low water solubility and the resulting low bioavailability, a daily intake of 18 g/day of sitosterol was needed to achieve a reduction in serum cholesterol levels. Because the daily dosage was impractical, production of Cytellin was stopped.

In the early 1990s, researchers succeeded in the esterification of phytosterols by developing a process which considerably improved the water solubility of phytosterols. This process made it possible to greatly expand the market for phytosterols as dietary supplements, leading to a rapidly growing worldwide market.

The result is renewed interest in plant sterols as hypcholesterolemic agents to be used alone, or as agents to supplement drug therapy or phytosterol-enriched food. Combining phytosterols with an HMG-CoA reductase inhibitor (statin), for example, provides additional benefit on reducing LDL-C levels. The results of controlled clinical trials suggest that consumption of 2 to 3 g/day of plant sterols or stanols by individuals on statin therapy may result in an additional 7 to 11 percent reduction in LDL-C, an effect comparable to doubling the statin dose.

Results of well-designed clinical trials demonstrated that plant-derived stanol/sterol esters at dosages of 2 to 3 g/day lower LDL-C levels by 6 to 15 percent with little or no change in HDL-C or triglyceride levels. More recently, the Third Report of the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP:ATP III) recommended that maximal lowering of LDL-C occurs at intakes of phytosterol/stanol esters of 2 g/day. Despite potential advantages of stanols over sterols, a rigorous comparison of the two types had not been reported at the time of publication of the NCEP:ATP III. For this reason, NCEP:ATP III did not distinguish between them. LDL-C reductions are also noted in individuals with both hypercholesterolemia and type 2 diabetes (T2D), and in children with hypercholesterolemia.

It has been proposed that phytosterol consumption of 2 g/day equivalents would reduce the risk for development of heart disease by 25 percent. Unfortunately, it is not feasible to conduct a clinical trial of adequate size and power to test this hypothesis. To test this assumption and prove effectiveness in reducing heart disease, a randomized clinical trial with CHD as the primary endpoint would be required. For such a trial to detect a 12 to 20 percent reduction in CHD incidence, 10,000 to 15,000 patients with CHD (and a greater number of persons without CHD to
serve as controls) would be needed. This is economically impractical, so current data must suffice.

**Mechanism(s) of Hypocholesterolemic Action**

Several mechanisms of action have been proposed for the cholesterol-lowering efficacy of phytosterols. As with cholesterol, phytosterols are incorporated into mixed micelles before they are taken up by enterocytes, cells that line the intestinal wall. Mixed micelles are mixtures of bile salts, lipids and sterols formed in the small intestine after a fat-containing meal is consumed. It is well documented that their action is primarily through reduced absorption of cholesterol as a result of its displacement from the micelles. Cholesterol displaced from the micelles is not absorbed and, thus, excreted in the feces. In response to decreased cholesterol absorption, tissue LDL-receptor expression is upregulated (more receptors are formed), which results in increased clearance of circulating LDL. Phytosterols can inhibit up to 50 percent of intestinal cholesterol absorption and increase fecal elimination of both dietary and biliary cholesterol, without causing a significant shift from larger to smaller, more atherogenic LDL particles in the blood.

Phytosterols also activate the adenosine triphosphate-binding cassette A1 (ABCA1) transporter and most likely ABCG5 and ABCG8 transporters in enterocytes. ABCG5 and ABCG8 each form one-half of a transporter that is responsible for the reverse transport of cholesterol and absorbed phytosterols from enterocytes back into the intestinal lumen. Phytosterols are secreted back into the intestine by ABCG5/G8 transporters at a much greater rate than cholesterol, which results in much lower intestinal absorption of dietary phytosterols than cholesterol.

Most clinical trials have investigated the effect of phytosterols ingested in two or, more commonly, three divided doses each day taken with meals. This regimen is based on the presumption that the compounds need to be present in the intestinal lumen postprandially to compete with cholesterol within mixed micelles and inhibit its absorption, thereby achieving an optimal hypocholesterolemic effect.

This hypothesis has been challenged, however. Plat and coworkers compared the effects of margarine-based stanol ester given in a single daily dose or three divided doses, and showed that the decrease in LDL-C in subjects on the single-dose regimen did not differ significantly from that in subjects on divided doses. The persistence of the single-dose hypocholesterolemic effect strongly supports the notion that stanols not only compete with cholesterol for micellar solubilization, but also have an additional, longer-lasting effect on intestinal mucosal cells.

**Selected Studies that Support Phytosterols’ Hypocholesterolemic Activity**

A number of controlled clinical trials have shown that phytosterols safely and effectively reduce blood levels of LDL-C and TC. The majority of these trials have used phytosterol-enriched food as a treatment choice. In terms of carriers, there is abundant evidence to support the beneficial LDL-C lowering efficacy of phytosterols either as plant sterols or stanols when incorporated into various foods, including yogurt, low-fat milk, orange juice, ground beef, mayonnaise, chocolate, cereal, snack bars and breads. In investigations that have compared plant sterols with plant stanols, no difference in LDL-C lowering effect has been demonstrated and the compounds can be considered to be comparable.

**Food Enrichment with Phytosterols.** One of the best-known studies is the year-long randomized, double-blind clinical trial undertaken by Miettinen and coworkers. One hundred-two hypercholesterolemic subjects consumed 1.8 or 2.6 g/day of sitostanol contained in margarine; 51 others consumed margarine without sitostanol. Subjects taking the higher dose exhibited a 14 percent decrease in LDL-C after 12 months, compared with a 1 percent increase in persons using the control spread. There were no significant adverse effects.

Hendriks et al evaluated the hypocholesterolemic effect of three different intake levels of esterified soybean sterols at doses of 0.83, 1.61 or 3.24 g/day incorporated into table spreads. In this randomized, double-blind, placebo-controlled trial, 100 healthy normocholesterolemic and mildly hypercholesterolemic volunteers consumed four table spreads (one of three treatment [sterol-enriched] concentrations or a control) with lunch and dinner, each for a period of 3.5 weeks. Compared to the control spread, the three relatively low dosages of phytosterols produced a significant cholesterol lowering effect in LDL-C by 6.7 to 9.9 percent and TC by 4.9 to 6.8 percent. The LDL/HDL ratio decreased by 6.5 to 7.9 percent. There was no significant difference in cholesterol lowering activity between the three dosages of phytosterols.

In an extensive meta-analysis of 23 clinical trials of plant sterol-enriched foods and 27 clinical trials of plant stanol-enriched foods, doses of 2 g/day of either plant sterols or stanols lowered LDL-C by about 10 percent. Higher doses did not improve the cholesterol lowering efficacy of either group. The results of numerous investigations hold that the minimum effective dose for lowering LDL-C is 0.8 g/day.

It has been proposed, largely on theoretical grounds, that stanol esters derived from wood sources such as tall oil, which contain primarily sitostanol, might be more effective in inhibiting cholesterol absorption than stanol esters derived from vegetable sources, such as soybeans (up to 33 percent of which is campestanol). However, the results of three separate studies have shown that there is no significant difference in the LDL-C
lowering effect of sitostanol ester-rich versus campestanol ester-rich mixtures. Thus, the composition of stanol esters would appear to be irrelevant to their efficacy, the source being determined by market forces such as availability and cost.

Direct Oral Dosing. Most reports showing LDL-C lowering activity have involved phytosterols mixed into food. The question remains whether phytosterols administered in an oral dosage form would demonstrate similar properties. Pharmaceutical dosage forms, such as tablets and capsules, can be more convenient and flexible for the recommended long-term usage than the traditional food applications. In addition, these dosage forms of phytosterols are easier to incorporate into therapeutic regimens involving statins and other hypocholesterolemic drugs.

Woodgate and associates administered sitostanol ester in soft-gel capsules. Thirty hypercholesterolemic adults were supplemented with 1.6 g of free phytostanol equivalents as phytostanol ester (2.7 g stanol esters) or placebo, each day for 28 days in a randomized, double-blind, parallel study design. Subjects were instructed to maintain their regular eating habits and physical activity. Phytostanol supplementation resulted in a significant decrease in TC of 8 percent and LDL-C of 9 percent.

In another trial, Acuff et al studied the effect of plant sterol esters in soft-gel capsules. Sixteen subjects participated in a double-blind, placebo-controlled, sequential study with a four-week placebo phase followed by a two-week washout period and a four-week treatment phase. They were instructed to maintain their normal diet and exercise programs. Treatment consisted of doses of 1.3 g/day (equivalent to 0.8 g/day free sterol). Blood samples were collected at day 7, 21 and 28 of each phase. Primary measurements were change in blood TC, LDL-C and HDL-C between phases and within each phase. In comparison to placebo, LDL-C was significantly reduced by 7 percent and 4 percent at week 3 and week 4, respectively; HDL was significantly increased by 9 percent at week 3 of the treatment, but not at week 4; TC was not significantly different from placebo throughout the trial period.

Safety
An important question is whether it is safe to supplement the daily diet with phytosterols. They are virtually unabsorbed, and their consumption does not produce significant adverse effects. When adverse effects occur, they are usually mild and transient. The most frequently reported are of gastrointestinal origin (nausea, indigestion, diarrhea and constipation). In one study, individuals who consumed a plant sterol-enriched table spread providing 1.6 g/day for up to one year did not report more adverse effects than those consuming a control spread. In another, persons consuming a plant stanol-enriched spread providing 1.87 to 2.6 g/day for one year did not report any adverse effects. Consumption of up to 8.6 g/day of phytosterols in margarine for three to four weeks was well tolerated by healthy men and women, and did not adversely affect intestinal bacteria or female hormone levels. The debate regarding sterol versus stanol safety is centered on their differing intestinal absorptions and resulting plasma concentrations.

Beta-sitosterolemia. This is a rare autosomal inherited disorder that results from mutations in one or both of two adjacent genes, ABCG5 and ABCG8. As noted earlier, these genes encode transporters that regulate blood plant sterol levels by limiting the reverse transport of cholesterol and absorbed phytosterols from enterocytes back into the intestinal lumen. Although blood cholesterol levels may be normal or only slightly elevated, affected individuals (especially young men) are at high risk for premature atherosclerosis with CHD development, suggesting that high blood levels of phytosterols may be particularly atherogenic.

Because of concerns that increased absorption of plant sterols resulting from higher intakes may be pathogenic, some investigators have suggested that caution is needed in their recommendation. However, the degree of risk associated with high blood phytosterol levels in otherwise normal individuals is much below the risk of toxicity attained in patients with beta-sitosterolemia. Prudence dictates that persons with beta-sitosterolemia avoid excessive phytosterol ingestion.

Recommendations for Use of Phytosterols in Management of Hypercholesterolemia
The dosage recommendation of 0.8 to 1 g/day of free sterol and free sterol equivalents compares favorably with FDA’s proposed rule that recommends inclusion of 0.65 g of sterol esters per serving, twice per day, in table spreads, which is equivalent to 0.8 g/day of free sterol equivalents. On December 8, 2010, FDA recognized that the scientific literature supported expansion of the health claim to include free forms of plant sterols and stanols, and to approve of their use in a wider range of food products, including low-fat products. FDA further stated that there was sufficient evidence to recommend that the lowest effective daily intake of free phytosterols was 0.8 g/day. FDA has granted phytosterols GRAS (generally recognized as safe) status when used as food additives. The agency also tentatively approved the claim that doses of 0.8 g/day or more, expressed as the weight of free phytosterol, may reduce the risk of CHD.

TLC remains the cornerstone of treatment for patients with hyperlipidemia. The most powerful LDL-C lowering component of dietary therapy consists of adding phytosterols. Consumption from natural sources should be encouraged for all persons, following consultation with a clinician. Individuals who consume phytosterols regularly should also cut back on dietary fat
intake and increase physical activity. This same advice holds true for all individuals who consume a typical Western diet.

The sooner in life that treatment is begun to lower LDL-C levels, the greater the reduction in relative risk for development of CHD. Individuals should start early in life to slow the onset of atherogenesis, and lower their LDL-C levels when they are higher than normal. Some choose to downplay the importance of data on projected expansion of longevity based on epidemiological data. Investigation with HMG-CoA reductase inhibitors (statins), which are first line pharmaceutical treatment for reduction of LDL-C in most patients, indicates that a 1 percent reduction in LDL-C reduces risk of CHD by about 1 percent.

However, epidemiological studies across the globe strongly support the notion that maintaining lower blood cholesterol levels for periods beyond the duration of clinical trials yields a greater reduction in risk than is predicted from the trials, since clinical trials by their very nature are closed-ended. In populations that maintain very low cholesterol levels throughout life, the risk for CHD is much lower at any age than in populations that habitually maintain higher cholesterol levels. In contrast, in high-risk populations, the reduction in CHD attained with aggressive hypocholesterolemic therapy still leaves absolute CHD rates far above those in low-risk populations.

Importance of Patient Adherence to Therapy Instructions
Results from numerous studies have demonstrated that the variability in lipoprotein responsiveness to treatment is often due to poor compliance with therapy instructions. There is a strong likelihood that reported reductions in LDL-C recorded with doses of 0.8 g/day might be greater if full compliance with phytosterol dosage and instructions were assured. In studies where subjects were monitored closely to ensure full compliance with therapy, efficacy in LDL-C lowering with a 1.5 to 2 g/day dose ranged from 12 to 16 percent.

Patient counseling along with written instructions appears to have the greatest impact on improving short-term therapy adherence, but less impact on long-term regimens. A patient who admits to nonadherence with therapy means he or she is usually telling the truth. A patient who denies nonadherence with long-term therapy translates into his or her telling the truth about half the time. About one-third of patients will remain adherent with therapy just from having its importance stressed by a trusted healthcare professional. Fifteen to 25 percent will be nonadherent with therapy even with the most vigorous consultations. Interventions to improve adherence, then, are optimally aimed at the middle 50 percent of individuals who may adhere if given support and encouragement.

Summary and Conclusion
Therapeutic lifestyle changes remain an essential modality in clinical management of hypercholesterolemia. LDL-C reduction forms the basis to effectively reduce CHD. Plant sterols and stanols are safe and effective, well-tolerated hypocholesterolemic agents. At recommended intakes, food enriched with phytosterols, or oral products containing them with at least an 0.8 g/day equivalent dose, can help lower LDL-C without causing significant side effects. Oral administration of products containing phytosterols provides convenience in dose formulation and administration, and lower cost, compared to the use of conventional hypocholesterolemic drugs. The importance of patient adherence to dosing instructions cannot be overstated. The websites listed in Table 2 provide additional information on areas covered in this lesson.

The authors, 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 0129-0000-12-009-H01-P**
Release date: 9-15-12
Expiration date: 9-15-15
CE Hours: 1.5 (0.15 CEU)
Phytosterols and Cardiovascular Health

1. Sixty to 70 percent of the total cholesterol concentration in humans consists of:
   a. HDL-C.
   b. LDL-C.
   c. VLDL-C.

2. The Lipid Research Clinical Trial demonstrated a direct relationship between total cholesterol (TC) levels and the rate of onset of new coronary heart disease (CHD) in:
   a. both men and women.
   b. women but not men.
   c. men but not women.

3. Which of the following food sources has the highest total phytosterol content?
   a. Banana
   b. Cabbage
   c. Olive oil
   d. Walnut

4. The fatty-streak lipid deposits in arterial walls consist mainly of cholesterol-rich:
   a. apolipoproteins.
   b. cytokines.
   c. granulocytes.
   d. macrophages.

5. Elevated concentrations of which of the following sets of lipids increases atherogenesis during teenage years?
   a. HDL-C and TC
   b. LDL-C and VLDL-C
   c. HDL-C and VLDL-C
   d. LDL-C and TC

6. Approximately 19 percent of men aged 30 to 34 years will have well-developed lesions in which of the following areas of their coronary arteries?
   a. Left anterior ascending
   b. Right posterior ascending
   c. Left anterior descending
   d. Right posterior descending

7. The most abundant phytosterol in nature is:
   a. alpha-sitosterol.
   b. beta-sitosterol.
   c. gamma-sitosterol.
   d. delta-sitosterol.

Complete fill in the lettered box corresponding to your answer.
1. [a] [b] [c] 6. [a] [b] [c] [d] 11. [a] [b] [c] [d]
2. [a] [b] [c] 7. [a] [b] [c] [d] 12. [a] [b] [c] [d]
3. [a] [b] [c] [d] 8. [a] [b] 13. [a] [b]
4. [a] [b] [c] [d] 9. [a] [b] [c] [d] 14. [a] [b] [c] [d]
5. [a] [b] [c] [d] 10. [a] [b] 15. [a] [b] [c]

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2. Did it meet each of its objectives? □ yes □ no
   If no, list any unmet

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