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Utilization, Criteria and Outcomes

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IN THIS ISSUE

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Power in the palm of your hand: PDA's open window on pharmacy services

`We're better able to capture and quantify interventions'

Using a PDA-based system to document clinical interventions at a military treatment facility increased intervention reporting across all pharmacy points of service and yielded data pharmacy leadership could use to document the impact of pharmacist interventions on safety and quality of pharmacy care provided.

Such were the findings of a study by lead author **Stephen Ford**, PharmD, deputy director for clinical operations at Military Vaccine Agency in Falls Church, Va.[1] The study was conducted when he was director of the department of pharmacy at Evans Army Community Hospital, Fort Carson, CO. Ford tells *Drug Formulary Review* that PDAs have been used in other healthcare settings to document clinical interventions and his team wanted to see how well they would work in a military treatment facility.

"Before this experiment, the quality of pharmacy services was measured by waiting time," he tells DFR. "We wanted to document the impact of interventions in delivering care in terms of patient waiting time. But we also wanted to reinforce with the hospital leadership that pharmacy quality can't simply be measured by patient waiting time. We needed to be more concerned with the quality of pharmacy services."

The literature indicates that PDA-based intervention programs are broad in scope and serve to improve intervention documentation and analysis and in assessing the value of pharmacists' cognitive services. Also, some institutions have used medical information tracked through PDA-based programs for physician profiling and renewing privileges. Studies, the report says, have shown that PDA-based programs are both more effective and more efficient than paper documentation in compiling, tracking, and analyzing intervention data.

Ford writes that although their program was originally designed to simply improve collection and reporting of intervention data, it was expanded to include documenting the value of pharmacist interventions in improving the quality and safety of the medication use system,

compliance with approved clinical practice guidelines and related prescribing policies, and medication errors and adverse drug events. They also started a spin-off program for clinical pharmacists practicing in a disease management clinic.

The need for speed

Evans Army Community Hospital serves 145,000 eligible Department of Defense patients and beneficiaries living in the greater Colorado Springs area. The facility provides comprehensive inpatient and ambulatory clinic healthcare services. Ambulatory pharmacy services in the military go through three points of service: military treatment facility-based ambulatory pharmacies, a mail service pharmacy, and a network of community pharmacies. The Evans pharmacy is reported to be a high-volume ambulatory operation dispensing more than 2,000 new and refill prescriptions daily.

While most of the earlier clinical intervention studies used the Palm platform PDA, the Evans team chose the Dell Axim Pocket PC because of its reputation for sturdiness, storage capacity, and speed. All pharmacy interventions were documented in standard format using the Axim Pocket PC. A memory upgrade took place early in 2005 when the study team became aware that the 64 MB capacity of the PDAs was being taxed. The problem was solved by adding 128 MB compact flash memory cards to each PDA.

PDAs were synchronized and intervention data downloaded weekly to one computer. Elements of data collected included date of consult, clinic location, pharmacist location, patient's first and last names and Social Security number's last four digits, pharmacist name, healthcare provider, reason for intervention, drugs involved, suggested resolution, and whether the suggestion was accepted or rejected.

"Our presumption going into the project was that the number of reports would increase over the level documented using paper forms," the authors say. "But, we thought, as the pharmacy staff used documentation of their interventions to educate the professional staff, the number of interventions would plateau and perhaps even decline, medication errors would decrease and as a result, the quality of care would improve, with an associated increase in cost avoidance."

Future is improving outcomes

All pharmacists used their PDAs with the first iteration of software to record interventions for one month. The program underwent final design changes and then became the sole source for recording pharmacist interventions at Evans. Recognizing that the future of the pharmacy profession lies not in traditional distributive functions but rather in applying cognitive skills to improve patient outcomes, a pharmacy process action team was formed that included pharmacists, pharmacy technicians, and automation specialists. The team developed a time-phased plan to implement new PDA technology into pharmacist practice with the goal of using the technology to document clinical interventions. The team developed an implementation plan to prevent weakened resolve resulting from situations such as users becoming quickly overwhelmed.

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Editor: **John Hope**.
Senior Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Editorial Group Head: **Coles McKagen**, (404) 262-5420, (coles.mckagen@ahcmedia.com).
Managing Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Ami Sutaria**.

Editorial Questions

Questions or comments? Call **Gary Evans** at (706) 310-1727.

Ford and colleagues report that implementing a PDA-based system for documenting pharmacist interventions across all points of service within the department "dramatically increased reporting for the first six months following implementation (August 2004-February 2005)."

After initial fielding, he says, clinical pharmacists in advanced practice settings such as a disease management clinic and anticoagulation clinic recognized a need to tailor the program to their specific activities, resulting in a spin-off program unique to their practice roles.

Before the change to PDA reporting, an average of 103 pharmacist interventions were reported each month. After the PDA effort was implemented, the mean increased to 268 reported interventions. More importantly, the authors say, the pharmacy leadership gained the capability of quantifying the time spent by pharmacists in patient-focused interventions to improve both the safety and quality of pharmaceutical care provided, in terms of number of prescribing errors, drug interactions, and contraindications.

During the first six months after implementation, a total of 417 hours of pharmacist time was spent in clinical intervention activities. That time was in addition to that spent in routine order evaluation, processing, and patient education/counseling activities. On average, the authors say, each intervention required about 15 minutes to complete, and 97% of suggested recommendations were accepted.

Interventions nearly tripled

Another important indicator to hospital leadership was the increase in interventions from 30 to 80 per month that resulted in a change in medication or was initiated to comply with an approved clinical practice guideline. Finally, they say, information obtained from documenting prescribing practices resulted in improved pharmacy-to-prescriber feedback on compliance with established formulary/prescribing policies and identification of potential risk management issues.

"Ideally," they say, "future program expansion will result in cost-avoidance estimates, medication-use evaluation data, and potentially a tool to use for billing purposes to charge for pharmacist services."

One of the side benefits of the program has been an improved quality of reporting, adds **Stan Illich**, BPharm, MHA, assistant director in the department of pharmacy, at Evans Army Community Hospital. He says the quality of reporting was poor with the legacy paper report system, but it's hard to track when it's not on a computer.

Another upside, according to Ford, was the ability to load reference software for pharmacists into the PDAs, which the pharmacists could use in educating providers.

Factors Ford and colleagues have identified for the success they have had include being able to overcome some initial resistance and have the program be part of an overall quality improvement initiative.

The program continues to be used at Evans, although the software may soon be changed along with the brand of PDAs. Until the changeover is complete, some pharmacists have had to return to manual reporting and the number of interventions has decreased, demonstrating again the program's value.

"We're better able to capture and quantify interventions," Mr. Illich says, "especially for medication errors. And we've been able to identify through physician profiles potential risk management issues and demonstrate an impact on compliance with local guidelines, which has produced improved outcomes and some cost-avoidance."

[Editor's note: Contact Mr. Ford at the Military Vaccine Agency in Falls Church, VA. Fax him at (703) 681-4692 or e-mail stephen.ford@us.army.mil.]

Reference

1. Ford S, Illich S, Smith Lisa, et al. Implementing Personal Digital Assistant Documentation of Pharmacist Interventions in a Military Treatment Facility. *Journal of the American Pharmacists Association* 2006;46(5):589-593. ■

Survey says: Pharmacists contribute to med safety

Troubling results: Adverse drug event reports fall

Pharmacists in hospitals and health systems continue to make significant contributions to the overall safety and effectiveness of medication therapy, according to results of the 2006 ASHP National Survey of Pharmacy Practice in Hospital Settings. The survey results, which were reported in the March 1, 2007, issue of the *American Journal*

of Health-System Pharmacy, focus on the role pharmacists play in managing and improving the medication use process.

The survey found that pharmacists regularly monitor medication therapy for patients in nearly all hospitals in the US (93.4%). Both the percentage of pharmacists' time spent monitoring medications and the percentage of patients monitored continue to increase, researchers said.

More hospitals are providing a technology infrastructure to augment medication therapy monitoring by pharmacists. Some 87% of hospitals provide computer access to laboratory data compared with 78% in 2003 and 74% in 2002. Nearly 60% of hospitals allow for transfer of electronic information between inpatient and outpatient settings compared with 45% in 2003.

"The survey results highlight encouraging trends that can greatly improve care in hospitals," said ASHP president **Cynthia Brennan**, Pharm.D. "Utilizing pharmacists in a patient care role capitalizes on their unique expertise and provides tremendous benefits to the safety, effectiveness and value of medication therapy.

Other survey highlights include:

Expanding Access to Patient Care: Increased use of technicians and automation are strategies many institutions are using to facilitate pharmacists' involvement in patient care. Some 46% of hospitals have expanded the responsibilities of pharmacy technicians to free up pharmacists' time, and 45% of hospitals have increased pharmacists' access to patient-specific data, while nearly 40% have implemented automated dispensing systems.

Patient Education & Counseling: Some 73% of hospitals provide medication education for up to one-quarter of their patients. However, only a small percentage of hospitals (7.3) provide patient medication education to 26% or more of their patients. Most hospitals select specific patients for medication counseling; only 4.5% of hospitals have pharmacists counsel all patients. Patients were most often selected for counseling because of physician orders (82.9%) or patient request (64.5%). Patients were also tapped for counseling if they were discharged on complex or high-risk medications (34.2%) or had a specific disease state (25.8%).

Identifying Patients for Monitoring: More than 60% of hospitals have a list of specific medications that require daily monitoring. Patients were less likely than in 2003 (38% in 2006 vs. 48% in 2003) to be identified for monitoring based on their treatment in a specific medical or surgical service. Other methods for identifying patients include abnormal laboratory test values requiring dosage adjustments (72.5%), high-cost medications, (34.1%), and disease state (32.2%).

Medication Reconciliation: Some 72% of hospitals report having met the Joint Commission's National Patient Safety Goal on medication reconciliation— a significant increase compared to 2005 (44.8%).

Therapeutic Drug Monitoring: Therapeutic drug monitoring has increased since 2003. More than 87% of hospitals have pharmacists regularly monitor serum medication levels, also an increase since 2003.

Pharmacy Operations: The physical location of pharmacy departments often aids pharmacists' medication monitoring efforts. The survey found that 46.8% of pharmacy departments are located on a patient care floor of a hospital, which makes pharmacists readily available for consultations with physicians and nurses. However, nearly 43% of respondents noted that their current space allocations were inadequate for the level and types of services the department offered.

ASHP officials said a sobering finding from the survey shows a decrease in both internal and external reporting of adverse drug events (ADEs). Reporting of ADEs saw a substantial increase in 2003, most likely attributed to the influence of the Institute of Medicine's 1999 report, "To Err is Human: Building a Safer Health System." The decrease suggests that impact of the report is diminishing in hospitals and health systems, officials said.

"This is a troubling finding in an otherwise positive report," said Brennan. "Reporting of adverse drug events is a critical piece in the development of a fail-safe medication-use system. These reports help us gain a better understanding of why errors happen and allow practitioners to learn from the mistakes of others."

Survey respondents reported several methods to improve internal ADE reporting, including working to drive fear out of the workplace (76.9%); providing in-service education to promote voluntary reporting (64%); and sharing improvements resulting from events reported (60.1%).

ASHP said that monitoring and patient education are often shared responsibilities among the different healthcare disciplines. "The fact that pharmacists are not always involved in monitoring drug therapy or educating patients about medications does not mean that these activities are not being conducted in U.S. hospitals.

Nevertheless, if pharmacists were to assume a leadership role in improving the use of medications, it is important that they become involved." The survey was intended to determine the extent to which pharmacists are involved in monitoring and patient education activities and the percentage of patients who benefit from these services.

Data from the 2002 and 2003 surveys suggest that pharmacists continue to be very involved in monitoring and patient education activities. Interestingly, ASHP said, the percentage of patients being monitored increase, despite the fact that the time spent by pharmacists on monitoring activities did not increase. One explanation for this advanced by the paper is the increased use of technology, particularly electronic patient information, which improves monitoring efficiency. Another explanation is the increased transfer of patient information between inpatient and outpatient settings. An additional interesting finding was the increased autonomy granted to pharmacists to initiate orders for lab tests and make changes in drug therapy based on the results of these tests.

The role of pharmacists in patient education and counseling programs continues to be limited, ASHP said. Few hospitals reported having pharmacists provide medication education to patients during hospitalization and at discharge. "An unacceptably high percentage of hospitals had neither of these programs, the report said. "It is also discouraging to find that the percentage of hospitals that document patient education activities had declined."

Work force issues continued to be a source of concern among all healthcare disciplines, including pharmacy, in 2008. The rapid proliferation of chain drugstores with extended hours of service has exacerbated the shortage of pharmacists in many areas of the U.S. Therefore, it was surprising to find that the number of vacant pharmacy positions was as low as it was. The estimated number of vacancies was actually slightly lower than that reported in 2003. Therefore, ASHP says, this is even more surprising given the finding that the number of pharmacist positions per 100 beds continues to increase, perhaps because pharmacists find practicing in hospitals and health systems more professionally satisfying.

[Editor's note: More information is available online at http://www.ashp.org. Access the report at http://www.medscape.com/viewarticle/553700.]

Harmful errors most likely in perioperative setting

Some 12% of pediatric med errors result in harm

A study released by the United States Pharmacopeia (USP) says perioperative patients face an increased risk of harmful medication errors throughout the surgery process due to a lack of comprehensive oversight of medications. The seventh annual national Medmarx Data Report released by the USP studied medication errors in the perioperative setting — including outpatient surgery, the preoperative holding area, the operating room, and the post-anesthesia care unit.

The Medmarx report looked at more than 11,000 medication errors in the perioperative setting and found that 5% of the errors resulted in harm, including four deaths. USP says this percentage of harm is more than three times higher than the percentage of harm among all Medmarx records. Children are at higher risk for harm in the perioperative setting, with nearly 12% of pediatric medication errors resulting in harm.

According to USP, what many people generally call "surgery" is actually a system of several different departments that patients move through to receive perioperative care, and each department is likely to have different teams of healthcare providers. "Even if located along a single hallway, these departments can be remarkably disconnected from one another," said USP Healthcare Quality Information vice president **Diane Cousins**, one of the report's authors. "The fragmented system creates a high risk for harmful medication errors."

The highest rate of harmful medication errors occurred in the operating room (7.3%). The post-anesthesia care unit had the next highest rate at 5.8%, followed by the outpatient surgery department at 3.3%, and the perioperative holding area at 2.8%.

To improve patient safety and reduce the risk of medication errors, USP recommends that hospitals and health systems dedicate pharmacists to the perioperative units so they can oversee the distribution of medications and that surgical staff better coordinate hand-offs.

Meanwhile, a special California Medication Errors Panel that spent a year taking testimony from experts in the field of medication errors says such errors are estimated to injure or kill 150,000

Californians each year and contribute to costs of more than $17 billion.

The in-depth report from the panel that was appointed by the legislature focuses on the causes of medication errors in the outpatient setting and recommends changing the healthcare system to protect consumers from errors associated with use of prescription and OTC medications.

"Not enough has been done in California to address this critical issue," said former state Sen. **Jackie Speier**, who introduced the legislation creating the panel. "The recommendations of the panel will save the lives of thousands of Californians and should be incorporated into legislation without delay."

In hearing from 32 invited speakers, the panel learned that:

• Medication errors are preventable and can occur at any point in the medication use process, including prescribing, transcribing, dispensing, using, and monitoring;

• Medication errors often are the result of problems associated with incorrect medication use by patients;

• Low health literacy is a significant contributing factor for many medication errors; and

• Using multiple medications increases a person's risk for experiencing a medication error, especially when they are prescribed by multiple providers and filled at multiple pharmacies.

The panel report contains 12 consensus recommendations for systemic change. Those recommendations are:

1. Improve legibility of handwritten prescriptions and establish a deadline for prescribers and pharmacies to use electronic prescribing;

2. Require that a medication's intended use by included on all prescriptions and require that the intended use of a medication be included on the medication label unless disapproved by the prescriber or patient;

3. Improve access to and awareness of language translation services by pharmacists at community pharmacies and encourage consumers to seek out pharmacists who speak their language and understand their cultural needs;

4. Promote development and use of medication packaging, dispensing systems, prescription container labels, and written supplemental materials that effectively communicate to consumers accurate, easy-to-understand information about the risks and benefits of their medication, and how and where to obtain medication consultation from a pharmacist;

5. Identify and disseminate information about best practices and effective methods for educating consumers about their role in reducing medication errors;

6. Establish an ongoing public education campaign to prevent medication errors, targeting outpatients and persons in community settings;

7. Develop and implement strategies to increase the involvement of public and private sector entities in educating consumers about improving medication safety and effectiveness;

8. Help ensure quality and consistency of medication consultation provided by pharmacists within and among pharmacies;

9. Establish standards for Medication Therapy Management programs and create incentives for their implementation and ongoing use by pharmacists and other healthcare providers;

10. Create training requirements for pharmacists and other healthcare professionals that address medication safety practices and related programs, including medication consultation and medication therapy management programs;

11. Establish and support efforts to collect data regarding the nature and prevalence of medication errors and prevention methods for reducing errors, especially focused on persons at high risk for medication errors and on community, ambulatory, and outpatient settings; and

12. Convene a panel of stakeholders to identify and propose specific actions and strategies to overcome barriers to qualified pharmacists being recognized and paid as healthcare providers. ■

[Editor's note: More information on the USP report is available online at http://www.usp.org. The California report is available online at http://www.pharmacyfoundation.org/medicationerrors.]

FDA starting drug safety audio broadcasts

The Food and Drug Administration has alerted health care professionals and consumers to

availability of audio broadcasts providing emerging drug safety information. The broadcasts, commonly known as "podcasts," can be transmitted to personal computers and personal audio players. Agency officials said the service is part of an ongoing effort to broaden and speed communications on the safety of marketed medications when unexpected adverse events are reported to FDA. They will be produced in addition to the existing print- and Web-based public health advisories. Anyone can subscribe to them at http://www.fda.gov/cder/drug/podcast/default.htm.

FDA said that since the service was launched in February 2007, it has alerted listeners to the potential hazards of skin-numbing products used in hair removal, the voluntary market withdrawals of drugs to treat the symptoms of Parkinson's disease and irritable bowel syndrome, and to serious adverse events associated with agents that reduce need for blood transfers in cancer patients. ■

Pharmacist's license revoked for fatal mistake

The Ohio Board of Pharmacy has revoked the license of a hospital pharmacist who failed to catch a technician's mistake that led to the death of a two-year-old girl at Cleveland's Rainbow Babies and Children's Hospital. The technician testified she warned pharmacist **Eric Cropp** that something wasn't right with a saline solution prepared for Emily Jerry. The little girl died March 1, 2006, three days after receiving a lethal dose of salt along with chemotherapy. Instead of a saline solution with 1% chloride, the girl received a mixture with concentrated sodium chloride, a 23.4% solution.

Cropp cried as he testified before the board that "it was a bad day, the computer was down, and the technicians were way behind. It was nuts…. I should have caught it…. I wish I could go back in time and fix it. I wish it were me instead of her. I'll have to live with this the rest of my life." The hospital fired Cropp one week after the incident and the technician resigned. There have been calls for legislation in Ohio to regulate pharmacy technicians. ■

Patient cost-sharing cuts statin adherence

Requiring patients to partially pay for their statin medications has a negative effect on adherence to the cholesterol-lowering therapy, according to a new Harvard Medical School study published in the April 10, 2007 issue of Circulation. Lead investigator Sebastian Schneeweiss told Heartline that although treatment guidelines and health plan performance measures recommend statin therapy after acute myocardial infarction, adherence to therapy is often less than 60% six months after initiation, even among patients with comprehensive drug plans.

Researchers studied 51,561 patients who initiated statin therapy in the Canadian province of British Columbia. The provincial health plan had provided full coverage for the elderly until January 2002, when a $25 (Canadian) co-payment was implemented ($10 for low-income seniors). In May 2003, the co-payment was replaced with a 25% coinsurance, in which patients pay a percentage of the cost, plus an income-based deductible policy. The changes in payment policies allowed researchers to study the effect of the different cost-sharing interventions on adherence to and initiation of statin therapy after a heart attack.

Relative to full-coverage policies, adherence to new statin therapy, measured after nine months of follow-up, was reduced 5.4% under a fixed co-payment policy and 5.4% under the coinsurance policy. The proportion of new heart attack patients starting statin therapy increased steadily over the study period, similar to a Pennsylvania control population with full coverage.

"It is known, and frequently described, that

COMING IN FUTURE MONTHS

- Pharmacists providing pain management
- Assessing adverse events in a tertiary care medical center
- Drug-related hospitalizations
- Survey of collaborative drug therapy management
- Using bar-code technology and medication observation
- Telepharmacy at a critical access hospital

medication cost-sharing by patients out of pocket is associated with less drug use and sometimes adverse health outcomes," Schneeweiss said. "We wanted to specifically look at statins because statins are a preventive medication, and we're not treating symptoms that patients feel, making the adherence issue worse with statins than with other medications. Also, statins are expensive, so paying 25% of the cost out-of-pocket is quite a bit for these drugs. With fixed cost-sharing and coinsurance, we saw a 5% reduction in adherence, in the proper use of these medications. Adherence is already bad with statins, but if you reduce this further, we end up with only about 50% of people taking their medication. This is quite poor and will result in many outcomes that could have been avoided. Also, if you turn this around, if you think in terms of interventions on how to improve adherence, this costs a lot of money to boost adherence by 5%." ■

ESA safety information is strengthened

FDA has issued a public health advisory with new safety information, including revised product labeling, for erythropoiesis-stimulating agents (ESAs), used for treating anemia. The drugs involved are Amgen's Aranesp (darbepoetin alfa) and Epogen and Procrit (epoetin alfa). ESAs are genetically engineered forms of erythropoietin, a naturally-occurring human protein that is made by the kidney and increases the number of red blood cells.

FDA and Amgen agreed on revised product labeling with updated warnings, a new boxed warning, and modifications to the dosing instructions. The new boxed warning advises physicians to monitor hemoglobin levels and adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the risk of blood transfusions. Physicians and patients should carefully weigh the risks in using ESAs against the risk of blood transfusions, FDA says.

Recent studies have described an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure when ESAs were given at higher than recommended doses. In other studies, more rapid tumor growth occurred in patients with head and neck cancer who received higher doses of ESAs. In studies where ESAs were given at recommended doses, an increased risk of death was reported in cancer patients who were not receiving chemotherapy, and an increased risk of blood clots was observed in patients following orthopedic surgery.

The three drugs are approved for treating anemia in patients with chronic kidney failure and in patients with cancer whose anemia is caused by chemotherapy. Epogen and Procrit also are approved for patients scheduled for major surgery to reduce potential blood transfusions and for treating anemia due to HIV treatment with zidovudine. ESAs are not approved for treating anemia symptoms in cancer patients, surgical patients, or those with HIV. ■

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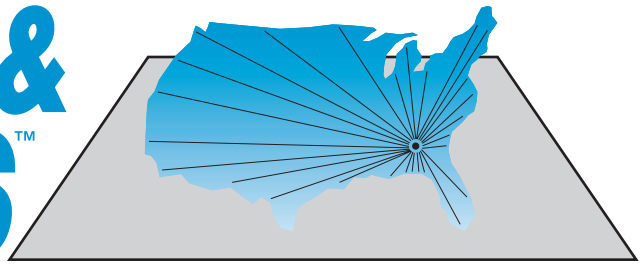

The eyes have it: Macular degeneration and the challenge of drug therapy

By **Leslie A. Davis**, Pharm. D. Candidate, Auburn (AL) University Harrison School of Pharmacy

It is projected that by 2025 the population of people in the United States over the age of 65 will be six times higher than it was in 1990. This is because of both the "baby boomer" population aging and overall life expectancy increasing. As patients age they may begin to experience a loss of vision via macular degeneration.

Macular degeneration is the leading cause of blindness in patients over the age of 65 and it is predicted that almost three million people will have symptoms associated with age-related macular degeneration (AMD) by the year 2020. Macular degeneration affects a part of the retina known as the macula, which is responsible for central vision and therefore patients experience problems performing daily tasks such as driving, reading, or writing. Severe cases may cause a decrease in mobility, poor orientation, and the patient may become unable to recognize faces of family and friends. Due to these manifestations, quality of life can be affected to the point at which it causes depression.[1,2,5]

A specific cause for macular degeneration is not known, but there are several risk factors. Age plays an important role in the development of the disease, and AMD also appears to be more prevalent in Caucasian females as well as patients with a family history of the disease. Studies indicate that smoking may also be a factor in the development of this disease and therefore it is deemed as the most modifiable risk factor associated with the disorder. There are other indefinite risk factors that may be associated with AMD, which include hypertension, obesity, light eye color, and overexposure to sunlight, but these have not been proven in clinical studies. The toxic effects of the antipsychotic drug class phenothiazines and the anti-malaria drug chloroquine also have the potential to induce macular degeneration.[1,2,3,6]

AMD is either 'wet' or 'dry'

AMD is divided into two subsets known as "dry" or non-neovascular form and "wet" or neovascular form. Dry macular degeneration is usually characterized by yellow deposits, known as drusen, which accumulate around the area of the macula. This is the mildest and most common form of the disease, and loss of vision occurs slowly. It is possible for the dry form of AMD to progress into the wet form.[1,2]

Wet AMD is characterized by the growth of new blood vessels beneath the retina. These new blood vessels that grow are not as stable as the original blood vessels and leak fluid and blood. This leakage causes the cells in the retina to die and this eventually leads to scarring and vision loss. Wet AMD can be further classified into two types known as classical or occult. Classical is associated with a more severe loss of vision. There is less leaking associated with the occult form of wet AMD and therefore there is less severe vision loss. With the wet form, vision loss usually occurs suddenly.[1,2]

While there is no cure, recently there has been increasing research centered on drugs to slow the progression of this devastating disease. Currently there are no therapies that are FDA approved for the treatment of dry AMD. Certain vitamins and nutrients have been implicated in protecting against the development of the disease or slowing its progression once a patient experiences

AMD. These include anti-oxidants, omega-3 fatty acids, leutein, zinc, zeaxanthin, and vitamins A, C, and E.[1]

Studies are currently underway to research these benefits. The age-related eye disease study was conducted in 2001 and involved 3,600 subjects. This study supported that vitamins C, E, zinc, and beta-carotene reduced patients risks of progressing to more advanced stages of dry AMD by about 28%. The patients who experienced these decreases were the ones who had high amounts of intermediate to large size drusen; patients with smaller drusen did not experience the same benefits. Due to study weaknesses, there is some controversy about the true effectiveness of these therapies among physicians, and therefore more studies need to be conducted in order to prove or disprove what is now considered to be a theory.[1]

New drug options coming on the market

Visudyne® (verteporfin) was the first drug that was FDA approved for the treatment of wet macular degeneration in the year 2000. Visudyne is administered intravenously over ten minutes, and is then activated by a laser being projected into the eye. Once Visudyne is activated, pathological blood vessels are destroyed by oxidative processes that cause vessel occlusion. It is indicated only for patients who have the classical form of wet AMD. The latest drug therapy that has been the focus of research are the vascular endothelial growth factor inhibitors. There are currently three on the market that are being used to treat AMD, two of which are FDA approved. The first was approved in December 2004 and is a murine monoclonal antibody known as pegaptanib sodium (Macugen®). Pegaptanib specifically targets the VEGF-165 isoform, and is administered as an intravitreal injection into the eye every six weeks for up to two years. The other two VEGF inhibitors are recombinant humanized monoclonal antibody fragments that act on all isoforms of VEGF. The clinical significance of the difference between binding capacity for VEGF between pegaptanib and the humanized monoclonal antibodies is unknown at this time. Animal studies have shown that these monoclonal antibodies are able to penetrate the membrane of the eye and enter into the retinal space.

In June of this year, ranibizumab (Lucentis®) was approved by the FDA for the treatment of AMD. It is dosed as an intravitreal injection monthly but if for some reason this is not feasible, the patient can receive injections every three months. Bevacizumab (Avastin®) is another monoclonal antibody with promising results for the treatment of AMD. It is FDA approved for the treatment of metastatic colorectal cancer and has recently been used to treat AMD as an "off label" use. There is some debate between physicians about which of these drugs should be first line for AMD patients since there are no competitive trials available comparing these medications. Avastin is the less expensive of the two drugs but since it is not approved for the treatment of AMD, insurance companies do not reimburse for its use. Medicare Part D does reimburse for the use of Lucentis but Avastin still may be more cost efficient even with the reimbursement. Both drugs are manufactured by Genentech, and they argue that Lucentis was specifically designed with smaller particles to penetrate the retina more efficiently than Avastin. Genentech has no plans of conducting trials on the use of Avastin as an AMD treatment because of their large financial investment in Lucentis; therefore, the government is currently conducting studies to determine Avastin's safety and efficacy compared with Lucentis. It is believed that this debate will be resolved once these trials have been completed and it is predicted that this may be as early as 2009.[1,4,5]

The treatment of AMD has recently become a hot topic in research and there are several new therapies currently being studied for both the dry and wet forms of the disease. Discovering treatment options for the dry form is important since it can progress to the more serious wet form. Another VEGF inhibitor called the "VEGF Trap" is being studied in addition to drugs and procedures that have other mechanisms such as a blood filtering system and implantable devices. With the aging population, more research will continue on the diseases and conditions that affect the elderly such as AMD. The elderly are a vital part of society and by preserving their sight, the patient will have a better quality of life and be able to serve their community more productively well into their retirement years.[1]

References

1. All About Vision. Update 3/2006. www.allaboutvision.com/conditions/amd.htm. Accessed 11/8/2006. National Eye Institute. Updated 11/2006. www.nei.nih.gov/health/maculardegen/armd_facts.asp. Accessed 11/10/2006.

3. The Eye Digest. http://www.agingeye.net/maculardegen/maculardegeninformation.php. Accessed 11/8/2006.

4. Arnold JJ, Sarks SH. Age related macular degeneration. *Brit Med Jrl*. 2000; 321: 741-744.

5. Bourla DA, Young TA. Age-Related Macular Degeneration: A Practical Approach to a Challenging Disease. *J Am Geriatr Soc*. 2006;54: 1130-1135.

6. Braunwald E, Fauci AS, Kasper DL, et al eds. *Harrison's Principles of Internal Medicine*, 15th ed. New York, NY: McGraw Hill Publishing; 2001. ■

Fluoroquinolones: Predator or prey for infections?

By **James Davis,** PharmD candidate, Auburn (AL) University Harrison School of Pharmacy

Fluoroquinolones, a broad class of antibacterial agents, were historically used in the treatment of gram negative infections; however, with the development of later generation quinolones, use for coverage of gram positive infections such as with *Streptococcus pneumoniae* has become commonplace.

Quinolones with this increased spectrum of activity are classified as "third" and "fourth" generation, or "respiratory" quinolones, and consist of Levaquin® (levofloxacin), Avelox® (moxifloxacin), and Tequin® (gatifloxacin). These later generation fluoroquinolones have increased in therapeutic importance since their initial development, particularly in treatment of penicillin and macrolide resistant pneumococcal infections.[1,2] Maintaining effective treatments for *S. pneumoniae* infections is of utmost importance since it is a common pathogen in a variety of bacterial illnesses including meningitis, bacteremia, pneumonia, and otitis media.[3] The formulary quinolone for Huntsville (AL) Hospital, Levaquin®, has maintained good coverage for *S. pneumoniae* infections throughout eleven years of use (percentage susceptibility of 99% to 100%, 2002 to 2005).[4]

The microbiological monitoring program, Tracking Resistance in the United States Today, or TRUST, reported results through 2002 suggesting that the occurrence of levofloxacin-resistant *S. pneumoniae* was 0.9% nationally, and regional data from Alabama, Kentucky, and Tennessee obtained through 2000 showed a 0.1% resistance rate.[2,5] Resistance rates for levofloxacin in the US appear to be increasing at a very gradual rate of approximately 0.1% per year.[2,6]

Current research is unclear regarding the exact mechanism of fluoroquinolone resistance with *S. pneumoniae*, but has shown trends regarding the quinolone resistance-determining region (QRDR) of its DNA. Specific mutations in this region include *parC*, which is highly associated with ciprofloxacin resistance. Mutations that occur in both *parC* and *gyrA* are frequently indicative of levofloxacin resistance; however, these mutations are not absolute and may not imply resistance to all respiratory quinolones.[7]

Resistance appears to be most common for respiratory quinolones in patients > 65 years at 1.4% and is believed to be due to extensive use of these agents in this patient population.[8] Resistant rates for quinolones used in treatment of pneumococcal infections are relatively low despite findings in a 2002 study that suggest overall quinolone prescribing in adults had increased over a seven year period.[9]

Experience has shown that a judicial approach to antibacterial usage and prevention of bacterial illness are crucial in maintaining an effective arsenal in treatment of any bacterial disease. One approach to maintain judicious antibiotic usage is the adult pneumonia protocol, which is currently being refined at Huntsville Hospital. This protocol uses a guideline based approach, and will improve antibiotic selection and use.[10]

Another example that shows promise in limiting quinolone usage is the utilization of available pneumococcal vaccinations in children and elderly populations. These vaccinations can help in preventing the occurrence of different types of pneumococcal infections and reduce selection pressure imposed by various antibacterial treatments for these infections.

A recent study from Tennessee showed decreases in penicillin-resistant pneumococcus in children from 1999 to 2002 of 59.8% to 30.4% respectively after introduction of the conjugate pneumococcal vaccine (PCV 7).[11] There is, however, no exact correlation between penicillin and quinolone resistance observed with this study, but this does demonstrate that administration of pneumococcal vaccinations in children helps to maintain efficacy of primary antibacterial agents used in treatment of these infections.

In conclusion, it is clear that current rates of quinolone-resistant *S. pneumoniae* are relatively low. Fluoroquinolones maintain important utility in treatment of these infections, particularly

in light of increasing penicillin and macrolide resistance with these bacteria. Quinolone efficacy has been preserved for *S. pneumoniae* despite slow increases in resistance per year and high rates of overall usage. Improvements in judicious utilization of respiratory quinolones by guideline based protocols and prevention of pneumococcal illness via vaccination shows the most promise in maintaining quinolones as a " predator" in pneumococcus infections.

References

1. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis* [serial online] 2004 Mar Available at http://www.cdc.gov/ncidod/EID/vol10no3/03-0252.htm

2. Karlowski JA, Thornsberry C, Jones ME, et al. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST surveillance program (1998-2002). *CID*. 2003;36:963-70.

3. Siegel JD, Rhinehart E, Jackson M, et al. Management of multidrug-resistant organisms in healthcare settings, 2006. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf. Huntsville Hospital (US). Huntsville Hospital Antibiogram. Huntsville, Alabama; 2002-2005.

4. Thornsberry C, Sahm DF, Kelly LJ, et al. Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States: results from the TRUST surveillance program, 1999-200. *CID*. 2002;34(Suppl 1):S4-16.

5. Hoban DJ, Doern GV, Fluit AC, et al. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY antimicrobial surveillance program, 1997-1999. *CID*. 2001;32(Suppl 2):S81-93.

6. Richter SS, Heilmann KP, Beekmann SE, et al. The molecular epidemiology of *Streptococcus pneumoniae* with quinolone resistance mutations. *CID*. 2005;40:225-35.

7. Jones RN, Biedenbach DJ, Beach ML. Influence of patient age on the susceptibility patterns of *Streptococcus pneumoniae* isolates in North America (2000-2001): report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis*. 2003;46:77-80.

8. Linder JA, Huang ES, Steinman MA, et al. Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am J Med*. 2005;118:259-68.

9. Eiland, Ed (Speaker). 2007. Interview with J Davis. *Huntsville Hospital Pneumonia Protocol*. Huntsville Hospital, Huntsville, AL.

10. Talbot TR, Poehling KA, Hartert TV, et al. Reduction in high rates of antibiotic-nonsusceptible invasive pneumococcal disease in Tennessee after introduction of the pneumococcal conjugate vaccine. *CID*. 2004;39:641-8. ■

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21. "Wet" age-related macular degeneration (AMD) is characterized by the growth of what?

A. benign polyps
B. new blood vessels
C. yellow deposits known as drusen
D. none of the above

22. While there is no cure for wet AMD, there has been increasing research centered on drugs to slow the progression of this disease.

A. True
B. False

23. Which of the following was approved by the FDA for the treatment of metastatic colorectal cancer, but has recently been used to treat AMD as an "off label" use?

A. verteporfin
B. pegaptanib sodium
C. ranibizumab
D. bevacizumab

24. Maintaining effective treatments for *Streptococcus pneumoniae* infections is important since it is a common pathogen in a variety of bacterial illnesses, including:

A. meningitis
B. bacteremia
C. pneumonia
D. all of the above