

Geriatric UPDATE

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SPRING 2016



From the Division of Geriatric Medicine



Message from the Chief

Our mission is to enhance the health of older adults by providing superb clinical care, training others to do the same, and conducting research to ensure that tomorrow's care is better than today's. To achieve these goals, we are focused on innovation in every aspect of our effort.

To care for our complex and often frail older patients, we annually handle more than 17,000 ambulatory visits, 1,000 admissions, and nearly 7,000 long-term care visits. The demands of such a practice challenge us all, especially when coupled with the evolution of health care delivery in the 21st century. Thus, to meet the growing need for both more effective and more efficient care, we are developing systems-based approaches, many of which incorporate new, IT-augmented techniques. The success we've had with our Acute Care and Transitions model at Magee-Womens Hospital of UPMC is just one of the ways in which we are re-engineering how we assess, manage, and care for older adults in the acute care setting.

In this issue of *Geriatric Update*, I'm pleased to share a number of our other initiatives to advance geriatric care. Many of them set the stage for, or have benefited from, our \$19 million award from the CMS Innovation Center. For instance, **Steven Handler, MD, PhD**, has made tremendous strides in developing, implementing, and measuring the use of telemedicine in skilled nursing facilities and also in devising innovative and effective approaches to prevent adverse drug events. In addition, he and his colleagues developed a tool approved by the Institute for Healthcare Improvement (IHI) which was recently used by the US Office of Inspector General to assess the impact of adverse drug events in SNFs. At the same time, **David Nace, MD, MPH** is leading efforts to enhance antibiotic stewardship through examining the current use of antibiotic medications in long-term care facilities, developing and testing new practice protocols, and packaging the results so that they can be applied in routine practice. The goal is to help reduce the consequences of inappropriate antibiotic use which leads to antibiotic resistance, side effects, and superinfections. **Susan Greenspan, MD** also continues to break new ground, not only in rethinking the approach to answering scientific questions in long-term care, but also in producing paradigm-challenging research in the areas of osteoporosis, falls, and fractures in frail elderly. And **Joe Hanlon, PharmD** and colleagues recently shared groundbreaking research on the long-term effects of anticholinergic medications in community-dwelling older adults. I think you'll also be intrigued by the capsule summaries of several of the division's other recent publications (pages 14-15).

We hope that you enjoy this issue. We also welcome your comments and suggestions. After all, we are all in this together. In the words of a wise person, "Aging is the only minority group of which — with luck — we will all become a member."

Kind Regards,

A handwritten signature in black ink that reads "Neil M. Resnick".

Neil M. Resnick, MD

Division Chief and Thomas Detre Professor of Medicine

Associate Director, Aging Institute of UPMC Senior Service and the University of Pittsburgh

Director, Hartford Center of Excellence in Geriatrics

Mitigating Adverse Drug Events and Transforming Patient Care Through Telemedicine



Steven M. Handler, MD, PhD, associate professor of geriatric medicine, and his colleagues in the Division of Geriatric Medicine are transforming the care of skilled nursing facility residents through targeted interventions to improve the quality and cost of care. Dr. Handler and his team have focused on detecting, monitoring, and responding to adverse drug events (ADEs), and decreasing unplanned hospital transfers and admissions from skilled nursing facilities. Their recent research and pilot programs have attracted significant funding from the Agency for Healthcare Reform and Quality (AHRQ), and the Centers for Medicare and Medicaid (CMS).

In addition to his primary appointment, Dr. Handler also holds faculty positions in biomedical informatics and clinical and translational research. He serves as director of geriatric telemedicine programs and is the chief medical informatics officer for the UPMC Community Provider Services division. Dr. Handler's primary investigative interests center on adverse drug events, biomedical informatics, and the use of telemedicine in the skilled nursing and other post-acute environments.

Reducing Adverse Drug Events in the Skilled Nursing Facility

There are approximately 15,700 skilled nursing facilities in the United States providing care to about 1.7 million residents, many of whom are frail and present with multiple comorbid conditions. The average nursing facility resident takes eight medications a day, and, "As many as 60% of residents are prescribed nine or more chronic medications — a definition used by CMS to define polypharmacy," says Dr. Handler. With so many residents taking so many medications, adverse drug events are a significant problem. "There are about two million ADEs occurring annually, with approximately 93,000 deaths. ADEs add about \$4 billion of excess health care related expenditures per year," says Dr. Handler.

Dr. Handler explains that it's difficult to predict who actually will have an adverse drug event. "There's no real way to do that in terms of the risk factors, except when polypharmacy is involved, because the more medications you use, the more likely you are to have an adverse drug event," he says, "But what we know from the literature is that about half of these events are preventable, and the majority are monitoring errors rather than prescribing errors."

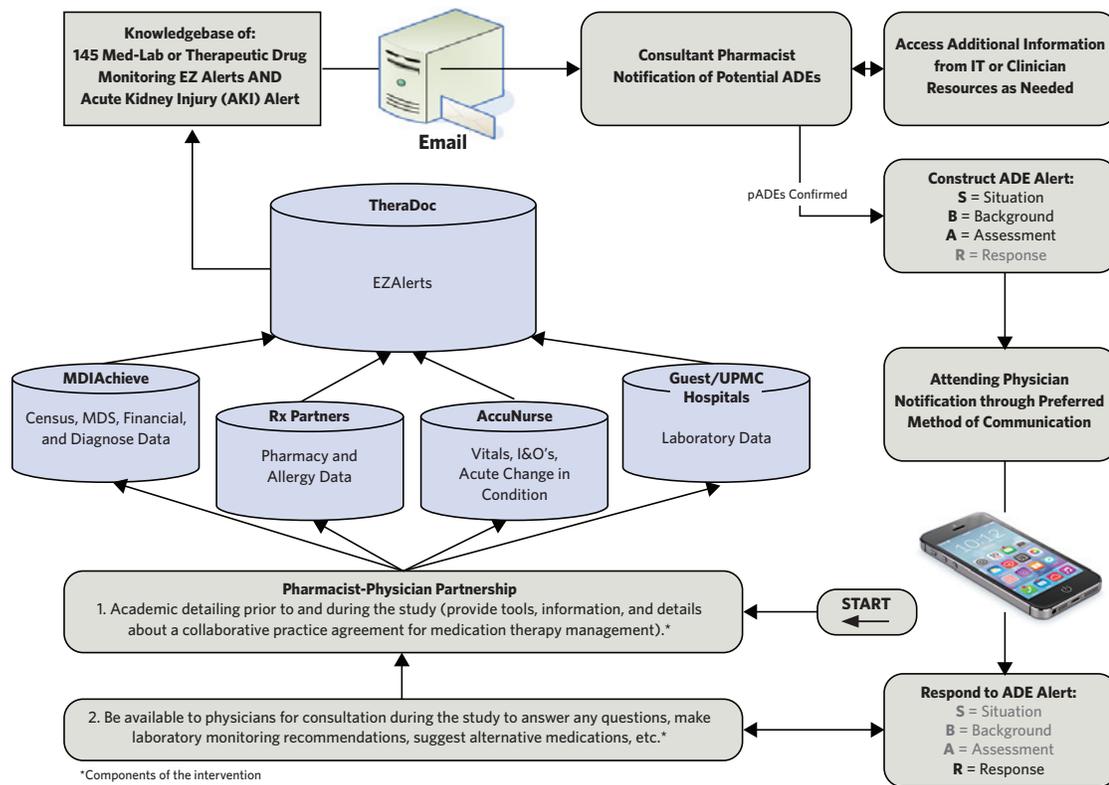
Dr. Handler and his colleagues' research and interventional approaches toward adverse drug events date back many years. "Our research was focused initially on developing a series of signals or agreed-upon consensus-based, laboratory, pharmacy, and minimum data sets, or MDS information, that can be used to detect these events

in nursing homes," says Dr. Handler. This research with colleagues Joe Hanlon, PharmD, MS, and others, published in 2008, led to the development of a consensus list of signals to detect potential adverse drug events in nursing homes. Dr. Handler explains that the outcome of that research, "Essentially allowed us to be able to create a final list of 40 signals that were derived by consensus amongst major stakeholders in the nursing home setting — advanced practitioners, pharmacists, and physicians. Using that information, we developed an IHI-approved trigger tool, which is used by the Institute for Healthcare Improvement and was later used by the Office of Inspector General in their report on adverse drug events in nursing homes. The tool allows for a prioritization of an initial list of signals that can be included in paper, or computer-based methods for potential ADE detection."

Testing an Active Medication Monitoring System at the Bedside

To test the validity of the triggers, Dr. Handler and his research colleagues designed a study that used the triggers combined with a variety of medications that in conjunction are associated with adverse drug events. Their investigation was conducted at a 178-bed nursing facility within UPMC Senior Communities. The 15-week study enrolled all patients except those in hospice care. Dr. Handler indicates that the pilot study sought to determine, "The incidence and positive predictive values of signals specifically designed for use by an active medication monitoring system to detect ADEs in a nursing home setting."

Figure 1. **Multicomponent Active Medication Monitoring System Intervention: Pharmacist to Physician Notification**



While this pilot test was only conducted at one facility, the data captured and the predictive capabilities of the intervention were robust. “Our results showed an overall positive predictive value of 81%, and was the best performance of any previously reported clinical surveillance system with regard to detecting ADEs. We achieved this because we were able to derive a consensus list of alerts, combine multiple data sets, and perform the knowledge engineering linking labs and pharmacy information together,” says Dr. Handler. With the study’s results in hand, Dr. Handler and his colleagues were able to seek and obtain ROI funding from AHRQ for a randomized controlled trial to broadly test the predictive values of their system.

Enhancing the Detection and Management of Adverse Drug Events in the Nursing Home

A five-year study led by Dr. Handler that concluded in 2015 was the first large, well-controlled investigation of an active medication monitoring system in nursing homes (Figure 1). The trial sought to replicate the pilot study results on a larger scale to improve patient safety and, “Determine if nursing home patients managed by physicians who receive active medication monitoring

alerts have more ADEs detected, have a faster ADE management response time, and can result in more cost-savings from a societal perspective compared to usual care,” says Dr. Handler.

Their study included a randomized set of 36 skilled nursing physicians in four UPMC facilities over the course of 12 months. Dr. Handler says, “We used an updated production level system called TheraDoc, instead of a homegrown system. We also advanced our alerting by sending the alerts to a pharmacist who then adjudicated them and, when appropriate, provided them in a structured format to physicians using a communication technique called SBAR (Situation; Background; Assessment; Response). What was significant about the intervention was that the pharmacists actually made a suggestion or a plan and then they carried out that plan on behalf of the physician.”

Preliminary conclusions from the study showed significant findings, according to Dr. Handler. “During the study, a total of 1,350 potential ADE alerts were adjudicated, and the most common were for hypoglycemia, acute kidney injury, hypokalemia, and elevated INR. Overall, 41.2% of the potential ADE alerts were considered definitely or probably preventable, with prescribing as the most

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Mitigating Adverse Drug Events*Continued from Page 3*

common error detected (49.68%). The most common actions taken were: ordering labs, 50.16% (630 of 1,256); stopping drugs 14.73% (185 of 1,256); and changing dosages, 13.85% (174 of 1,256). Physicians in the intervention group responded to alerts much faster than in the usual care group; 50% of the time, the median response was less than two-and-a-half days for the intervention group and six days for the usual care group.

The Role of Telemedicine in the Skilled Nursing Facility

Dr. Handler has explored and evaluated the use of telemedicine in the nursing home setting on a number of fronts in the recent past. Beginning in 2012, a \$19 million Centers for Medicare and Medicaid Innovation Award, known as **Reduce Avoidable Hospitalizations Using Evidence-Based Interventions for Nursing Facility Residents** — or **RAVEN** — has allowed Dr. Handler and colleagues to work with 18 area nursing facilities to prevent and reduce unplanned admissions to the hospital, using a variety of interventions and education. In western Pennsylvania, potentially avoidable hospitalizations were reduced nearly 25%, while potentially avoidable emergency department visits were reduced more than 40%. The reduction in health care utilization led to a net savings to CMS of more than \$5 million. Along with the implementation of certified registered nurse practitioners (CRNPs) at each participating facility, the provision of advance care planning, tools for quality improvement, and enhanced communications surrounding changes in patient status, the use of telemedicine to

perform assessments and interventions on residents has led to significant reductions in readmission rates. Along with the other interventions of the project, “Telemedicine has helped patient care by offering increased access, which has had particularly great benefits for remote or rural facilities, or those with limited clinical capabilities,” says Dr. Handler.

Within each participating **RAVEN** facility, Telly — a customized telemedicine cart — has been implemented and is in use by the clinical staff. The telemedicine cart allows for a number of diagnostic tools to be used remotely, as well as face-to-face interactions with patients and onsite clinical staff. Since the carts were implemented at the program sites, 103 telemedicine consults and 1044 telephone consults have been conducted. “To date, 49% of the telemedicine consults have led to a perceived avoidance of a transfer to an emergency department or hospital admission, while only 16% of telephone calls led to similar avoidance,” says Dr. Handler.

Survey data from clinical users of the system points to the effectiveness of the technology, (see Figure 2 on Page 5) the program as a whole, and a number of other metrics. Dr. Handler says, “We’re measuring such things as, did the resident seem comfortable during the consult? Was the nurse comfortable communicating during the consult? Was the physician able to obtain an adequate patient record and conduct an adequate physical exam? These are all important variables, and the results speak to the quality of care being provided from the perspective of the clinicians on site.”



Figure 2. **Sample Metrics from Quality of Telemedicine Technology Survey.**

	strongly disagree	disagree	neutral	agree	strongly agree	Responses
The resident seemed comfortable communicating during the Telemedicine consult.	0 0.0%	0 0.0%	9 16.1%	22 39.3%	25 44.6%	56
I was able to obtain an adequate history of present illness, past medical history, and review of symptoms.	1 1.8%	1 1.8%	4 7.1%	25 44.6%	25 44.6%	56
The use of Telemedicine is an appropriate and effective use of my skillset and time.	3 5.4%	1 1.8%	2 3.6%	22 39.3%	28 50.0%	56

RAVEN: Phase Two

In 2015, CMS asked the RAVEN leadership to apply for a second round of funding that would expand upon the initial cohort of 18 facilities, adding approximately 20 additional sites, and provide for funding to implement some of the same measures that have borne results in the initial RAVEN intervention group.

Most aspects of the initial RAVEN grant will not automatically be provided to each new facility (nurse practitioners, telemedicine). The facilities will receive additional funding which they can choose to implement these and other measures deemed necessary by the participating locations. Dr. Handler indicates that each facility will receive funding for each resident, based on one of six qualifying medical conditions, for up to 10 days that are for the new onset or sudden worsening of these conditions. Residents also will be able to be seen either in person or through a telemedicine consult. “The unique aspect of this is that for the first time in nursing homes, you can see and receive payment for telemedicine services regardless of the location of the nursing home itself for one of the qualifying medical conditions. Prior to this, the facility had to be in a HRSA-qualified area, but that restriction has been lifted,” says Dr. Handler.

The intervention also will include payment reforms at the provider level for physicians and nurse practitioners, as well as a structure for advance care planning that can either occur annually or within two weeks of a qualifying major change in the resident’s condition. Dr. Handler indicates that a funding decision from CMS on the grant application will come out sometime in March or April 2016.

Addressing ADEs Through the Use of Telemedicine

As the role of telemedicine grows, and the body of evidence mounts showing its effectiveness in controlled situations, opportunities arise to leverage the technology to combat known issues in the nursing home and, within the entire health care arena. One such area is adverse drug events.

Dr. Handler is a co-investigator, along with primary investigator Sandra Kane-Gill, PharmD, MS, associate professor of pharmacy and therapeutics, University of Pittsburgh School of Pharmacy, on a recently funded AHRQ grant to study a telemedicine approach to prevent ADEs associated with high-risk

medications (diabetes agents, opioid pain relievers, and anticoagulants) in nursing homes. Their study seeks to use telemedicine to “Improve timely access to consultant pharmacists who can provide patient-centered medication regimen reviews (MRRs) when a high-risk drug is prescribed.” Their investigation also will assess the use of telemedicine “by the consultant pharmacist to directly interact with the resident and engage them in education to recognize and prevent ADEs associated with high-risk drugs.”

Telemedicine has helped patient care by offering increased access, which has had particularly great benefits for remote rural facilities or those with limited clinical capabilities.

Osteoporosis, Falls, and Fractures in the Older Adult



Susan L. Greenspan, MD, and colleagues in the Division of Geriatric Medicine, are investigating the detrimental effects of falls, osteoporosis, and fractures in the most at-risk patients — the frail elderly. Their investigations into the consequences of osteoporosis — frailty, falls, and fractures — and novel interventional models to detect and intervene in patients most at risk for poor outcomes, is reshaping care for the geriatric patient.

A Professor of Medicine, Dr. Greenspan is dually-trained in geriatrics and endocrinology and currently serves as director of the UPMC Osteoporosis Prevention and Treatment Center, director of the bone health program at Magee-Womens Hospital of UPMC, and as principal investigator of both the Pittsburgh Claude D. Pepper Older Americans Independence Center, and the Division's NIH-funded T32 Program in Research Training in geriatrics. Dr. Greenspan's research interest centers on the pathophysiology, evaluation, and treatment of osteoporosis.

Zoledronic Acid, Osteoporosis, and Fractures — The ZEST Study

In 2015, Dr. Greenspan and colleagues David Nace, MD and Neil Resnick, MD, published the findings of a new study on the use of zoledronic acid to treat osteoporosis. The study entitled "Efficacy and Safety of Single-dose Zoledronic Acid for Osteoporosis in Frail Elderly Women: A Randomized Clinical Trial" (*JAMA Intern Med.* 2015;175 (6):913-921.) sought to ascertain the effects of bisphosphonates, specifically zoledronic acid, in a controlled trial of frail, elderly women in a long-term care setting. "To our knowledge, this was the first randomized trial using an antiresorptive agent in a cohort of frail, elderly women," says Dr. Greenspan. From Dr. Greenspan's perspective little is known if these types of medications are beneficial for this group of institutionalized patients. "This cohort of patients has the highest risk, but they are not typically included in larger studies so our knowledge base is not comprehensive."

The zoledronic acid study was conducted with patients from UPMC skilled nursing and assisted-living facilities. Performing the study with institutionalized subjects allowed for a greater degree of monitoring. The study participants were women 65 years or older, with multiple comorbid conditions, considered to be frail based on data from several standard measurement scales, and "who were not receiving a bisphosphonate, and had either a history of vertebral or hip fracture, or a measured BMD below the treatment cutoff for osteoporosis." A total of 181 individuals were included in the study, 89 receiving the zoledronic acid and 92 in the control group.

"We found that, compared with calcium and vitamin D alone, adding a single dose of intravenous zoledronic acid significantly improved BMD of the hip and spine over two years. Furthermore, the medication was tolerated well," explains Dr. Greenspan. However, the study did not see a reduction in fractures, and they also observed an increase in falls in the active treatment group. As Dr. Greenspan explains, the study was not designed to examine fracture reduction. It is possible that in a frail older adult, the increase in bone mass from the zoledronic acid may not correlate with increased bone strength and ultimately fracture reduction, due to many underlying factors. The study suggested that a follow up investigation to look specifically at fracture reduction was needed.

Fracture Reduction and the Frail Elderly

In late 2015, Dr. Greenspan and her colleagues received new RO1 funding to conduct a follow-up fracture reduction study, as well as another RO1 to support a study similar to the zoledronic acid research looking at the effects of the medication denosumab in an institutionalized population of both men and women.

"About 85% of frail women in long-term care facilities have osteoporosis. Their risk of a fracture is nearly 10 times that of a community dwelling older adult," says Dr. Greenspan. With such high incidence and likelihood, and the already precarious health of these individuals, a fracture from a fall can have dire consequences. Further, the benefits of increased bone mass from the zoledronic acid medication intervention (as seen in the ZEST study) may not actually be of any benefit in preventing a fracture. "While studies in younger individuals have shown significant reduction potential, we can't directly extrapolate those findings in the patient population we are studying," says Dr. Greenspan.

This new investigation, following the ZEST study, will be the first fracture reduction clinical trial using a potent intravenous agent such as zoledronic acid in an at-risk, long-term care cohort. Dr. Greenspan will enroll approximately 520 women over the age of 65 living in long-term care facilities who have comorbid conditions, frailty, and cognitive or functional deficits. The three-year study will measure, “incident fractures (new vertebral and non-vertebral), adverse events, safety, bone mineral density, and trabecular bone structure.”

Dr. Greenspan will be conducting the study with a number of novel features. She and her colleagues will, “engage a mobile lab equipped with state-of-the-art assessment of vertebral fractures and bone density, implement an electronic surveillance system to collect adverse events, including falls — in real time — and explore the role of bone structure in translating increased BMD to potential fracture reduction.” “If the trial shows positive results, we’ll have the data and the ability to influence clinical practice, and another tool to prevent fractures in our fragile population,” says Dr. Greenspan.

A Different Approach

Along with colleagues David Nace, MD, and Neil Resnick, MD, Dr. Greenspan is pursuing a corollary study on a population of frail older adults (similar to those in the ZEST study), this time with the inclusion of men and with a different agent — denosumab — a non-bisphosphonate, antiresorptive RANK ligand inhibitor. “This is a similar pilot study along the lines of ZEST, albeit with a different agent,” says Dr. Greenspan.

Using a semiannual dose of denosumab, delivered subcutaneously, Dr. Greenspan’s study will examine the effects on bone density and trabecular microstructure over a two-year period in men and women over the age of 65, that meet the inclusion criteria for the study. As in Dr. Greenspan’s fracture reduction study, her team will perform various assessments using a mobile lab, collect bone densities and measure other parameters to determine the medications effects on the enrolled subjects. Dr. Greenspan says, “We’ll be able to gather point of care vertebral fracture images, assess trabecular microstructure, and deploy an alert system that is able to collect adverse events, including infection or hypocalcemia, which are two potential side effects associated with the use of denosumab.”

Preventing Falls — A National Priority

Dr. Greenspan, and the Pittsburgh Claude D. Pepper Older Americans Independence Center are part of a \$30 million multi-state, multi-year PCORI/NIA/NIH funded trial to determine the, “effectiveness of an



evidence-based, multifactorial, patient-centered intervention,” designed to mitigate the risk of falling, and associated injuries in older adults.

Funded in 2014, *Strategies to Reduce Injuries and Develop confidence in Elders (STRIDE)* is a collaborative, multisite study that involves the Pepper Centers, and other health care systems across the United States. As collaborators, the Pittsburgh Pepper Center will participate in all aspects of the study, including patient recruitment, trial implementation, data collection, and advisement on study aspects and the final analysis.

The Research Continues

Dr. Greenspan and her colleagues are in the final phase of a study begun several years ago investigating the role of bisphosphonates and the incidence of atypical femoral fractures that can occur with long-term use. “We are just finishing up a pilot study that examines the impact of an anabolic agent, parathyroid hormone, to improve healing with atypical fractures. Our study has been a cooperative effort with the UPMC Department of Orthopaedic Surgery. We hope to have the results

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and Fractures***Continued from Page 7*

available in about a year but believe it is one of the first randomized trials to look at this parathyroid hormone for healing of atypical fractures,” says Dr. Greenspan.

**Fracture Liaison Service —
Interventions for At-Risk Patients**

Although a fragility fracture occurs every 15 seconds in the United States, only about 23% of older women with a new fracture are treated. In 2014, UPMC was awarded pilot funding from the National Bone Health Alliance (NBHA), and the National Osteoporosis Foundation (NOF) for a study to examine the efficacy of a Fracture Liaison Service (FLS) in an open health care setting. The FLS, often coordinated by a nurse practitioner, is designed to identify fracture patients, investigate the causes, and initiate treatment. Dr. Greenspan served

as the lead for the pilot project at UPMC. “We were one of three institutions nationwide to receive a pilot grant to determine whether or not the FLS model could work in an open system with multiple payers, and physicians at an academic university hospital. A follow up project began in June 2015 supported by UPMC. In both the initial pilot and the project extension,

Karen Vujevich, MSN, CRNP assumed the role of fracture liaison coordinator,” says Dr. Greenspan.

The pilot study, and the continuing project have shown positive results, albeit in a small initial sample size. “We found that we can deliver this service in an open system but it presents a unique set of challenges. Many patients that we initially saw with a variety of low-trauma fractures were from very far away and in rural areas, not in close proximity to our main UPMC facilities. Sometimes they did not have UPMC physicians or insurance, but their fractures were complicated and their orthopaedic surgeons wanted them to be seen because of the quality of care that we provide,” says Ms. Vujevich.

Since the second phase of the FLS project began, Ms. Vujevich has consulted on over 100 cases, with approximately half of the follow-up occurring directly in her clinic. “The visits take about an hour, but there’s a lot of leg work trying to coordinate getting patients to the clinic with ambulance services, caregiver schedules, or skilled nursing facility transports. And then there’s the follow-up after,” says Ms. Vujevich.

The FLS program consultations include a number of components. Each patient receives a DXA scan and the results and their implications are carefully reviewed to ensure the patient comprehends the information. Treatment options are recommended and discussed, medications are prescribed if necessary, and direct follow-ups with patients occur several months after the initial visit. Ms. Vujevich says, “We talk about fall prevention and things they can do at home to decrease that risk. If they smoke, we talk about its impact on bone density and the various cessation programs available. I explain the vital importance of calcium and vitamin D. Patients have my contact information, along with an education packet so they can call me directly with any questions or concerns once they leave.”

In January 2016, the Fracture Liaison Service was integrated into the electronic medical record. This integration allows clinicians to order an FLS consult just as they would a pulmonary or cardiac consultation, at the click of a mouse. The electronic order facilitates the hospitals adherence to good clinical guidelines, helps reduce potential penalties, and most important, allows the clinicians to intervene early with at-risk patients to provide education, improve their overall health, and prevent future fractures or complications that could land them back in the hospital.

The importance of this kind of at-risk patient intervention is borne out by the statistics of those with osteoporosis. “Right now, one out of two women and one out of four men will have an osteoporotic fracture in their lifetime. There are huge costs associated with that. These individuals, once they have sustained a low-trauma fracture, have a 50% chance of having another fracture if we do not intervene. And what we’re really trying to prevent are hip fractures. 25% of individuals that sustain a hip fracture will not survive the first year,” says Ms. Vujevich. It is with such statistics in mind that Dr. Greenspan says, “Our goal is to eventually roll out the Fracture Liaison Service across the entire UPMC system, centralizing the service and extending our ability to reach many more patients that could greatly benefit from our interventions. Our motto is ‘make the first fracture the last’.”

About 85% of frail women in long-term care facilities have osteoporosis. Their risk of a fracture is nearly 10 times that of a community dwelling older adult.

The Case Against Long-Term Anticholinergic Medication Use in Older Adults



Joe Hanlon, PharmD, is a professor of medicine in the Division of Geriatric Medicine and Department of Pharmacy and Therapeutics. Dr. Hanlon also serves as a Health Scientist at the VA Pittsburgh Healthcare System Center for Health Equity Research and Promotion, and the Geriatric Research Education and Clinical Center (GRECC). In addition to his research interest in anticholinergic medications, he investigates what drugs or drug classes increase the risk for various geriatric-related conditions, including urinary incontinence, falls and fractures, and delirium. His work also has explored the consequences of adverse drug events and polypharmacy, as well as preventive interventions. Dr. Hanlon also helped revise the widely-used Beers list.

Dr. Hanlon and colleagues at the University of Pittsburgh, the National Institute on Aging (NIA), and the University of Washington have studied the use and effects of anticholinergic medications and published several papers in 2015 that have shed new light on the potential consequences and cumulative effects this class of medications has on older adults. Their research, while controversial, is among the most definitive on the subject to date, and has the potential to reshape clinical practice, prescribing rates, and future research.

Anticholinergic Medication Usage in Older Adults

While the general effects, side-effects, and risks of anticholinergic medications are fairly well known in the older adult population, the long-term and cumulative consequences are becoming more apparent. Dr. Hanlon explains, "Older adults are more susceptible to the effects and potential negative outcomes because as we age, our liver function degrades and the medications tend to linger and circulate in the blood for a longer period of time." As a natural consequence of the aging process, the blood-brain barrier becomes less able to block the medications once taken and it becomes more difficult to clear the agents once they have crossed the barrier.

Past studies have reliably shown a correlation between anticholinergic medications and acute cognitive impairments in older adults. "We know that they can cause delirium and other symptoms, and that when removed they resolve," says Dr. Hanlon. But he goes on to say, "In our recent study, what we found was that if you take a certain amount, over the course of time, you are at a significantly increased risk of developing an irreversible dementia."

With the prevalence of anticholinergic use in the older adult population ranging from 8% to 37%, this potentially puts at risk a significant number of individuals, many needlessly as medication alternatives without highly anticholinergic properties are available. And while Dr. Hanlon and his colleagues' studies examined their use specifically in an older adult population, there arises the natural questions about cumulative effects in the general population over a lifetime. This cumulative effect (if indeed one exists) will need to be studied further to tease out any possible additional risk increases or other health-related effects.



Cumulative Anticholinergic Use and the Increased Risk of Dementia

Published in March 2015 by Dr. Hanlon and colleagues their study "Cumulative Use of Strong Anticholinergic Medications and Incident Dementia", *JAMA Internal Medicine* (March 1; 175(3): 401-407) for the first time showed a strong correlation between sustained anticholinergic use and a significant risk increase for dementia. Their study looked at a population of older adults age 65 and older, with an examination of 10-year

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Anticholinergic Medication*Continued from Page 9*

cumulative anticholinergic use prior to and throughout the study. One of the critical elements that differentiated this study from past investigations is, “We were able to collect information about what people get over the counter in addition to what they were prescribed by their physician,” says Dr. Hanlon.

Along with Shelly Gray, PharmD, and colleagues, Dr. Hanlon explains, “We worked out the exposure analysis together. That’s a big difference between ours and previous studies that suggested there may be an association. Nobody else had pharmacy data. We came up with an innovative, clever way to actually have a combined variable for dose and duration over time, such that you can look at cumulative use. That’s rarely been done in the research.” To this, the research team worked to identify all the medications, their minimum effective doses, and standardize the doses to reflect a consistent approach across drugs within a class, and drugs across different classes.

Higher cumulative use of anticholinergic medications is associated with an increased risk for all-cause dementia and Alzheimer’s diseases (AD).

Dr. Hanlon and colleagues also worked to standardize the set of medications attributed to be highly anticholinergic in their effects (for this study these fall largely into first generation antihistamines, tertiary tricyclic antidepressants, bladder antimuscarinics, and others) by using the American Geriatric Society’s Beers criteria for highly anticholinergic

drugs, as well as additional research needed because of the timeframes involved with many of the study’s participants. Dr. Hanlon explains, “Our exposure could have gone back as far as into the 1980s. There are dozens of other drugs that were on the market but are no longer. We actually had to go back into old textbooks and reference sources to find what drugs were being used for things like depression, ulcers, or reflux disease. We had to look for things that we used for coughs, colds, and allergies, that are no longer used — first-generation antihistamines and such — as we had to consider them to make a complete list,” says Dr. Hanlon. Even after this exhaustive research and exploration, there were some medications in the study that only a handful of people used — old, discontinued drugs. “This provides an idea of the level of detail that we needed to bring to the analysis,” says Dr. Hanlon.

Adding Up the Risk

In the study, the group was able to conclude “Higher cumulative use of anticholinergic medications is associated with an increased risk for all-cause dementia and Alzheimer’s diseases (AD).” The adjusted-odds ratios from the study were 1.63 for Alzheimer’s disease, and 1.54 for all cause dementias over a four-year period. This means that the study showed a 63% and 54% risk increase, respectively, of developing AD or all cause dementia. “This is not an absolute risk because of the way we measured exposure and rolled it across time, but it is an adjusted risk,” explains Dr. Hanlon. The research also points to the risk persisting even after discontinuation of the medications.

To put the statistics into perspective, a person age 85 has roughly a 33% chance of acquiring AD, some of which might be due to anticholinergic drug use that may be avoidable. The nature of the conclusions derived from the study were bound to provoke dissent. “We did just about everything that we could think of to challenge the results. Let’s do the analysis this way, let’s do it that way. But we couldn’t make the effects seen go away. And so it was only then that we felt comfortable writing it up and sharing it. We’re not the first to show these associations, but I think we are the first that have very careful, comprehensive exposure data. Quite frankly we were, from a public health point of view, nervous about this. We sat on the results for a year,” says Dr. Hanlon.

However, as their findings show, further research is needed to develop a detailed understanding of the biochemical and neurological mechanisms at play in how anticholinergic medications function in adverse ways. Dr. Hanlon notes that there is some animal data, and data from Parkinson’s disease patients that show “brain structure changes,” but as of now no conclusive evidence is available.

Changing Behavior Will Require Education

From an awareness perspective, Dr. Hanlon sees a great need to educate not only clinicians prescribing these medications with anticholinergic properties, but patients themselves. “In the community, 18% of people are taking anticholinergic drugs. That’s a lot of people, especially when almost all of those drugs can be replaced by something else that is just as effective but without the anticholinergic properties. Educating prescribers is just part of the story. It also has to be about educating consumers so they understand what they are taking and the potential risks involved,” says Dr. Hanlon.

Improving Antibiotic Use in the Nursing Facility



David A. Nace, MD, MPH, is an associate professor of medicine, chief of medical affairs for UPMC Senior Communities, and director of long-term care and influenza programs. In addition, Dr. Nace is a co-medical director for an ongoing \$19 million Centers for Medicare and Medicaid (CMS) Innovation Award project —RAVEN or **R**educe **A**voidable Hospitalizations using **E**vidence-Based Interventions for **N**ursing Facilities — designed to reduce unplanned hospital admissions from skilled nursing facilities. Dr. Nace's research has covered a number of areas, but focuses primarily around infectious disease in the long-term care setting.

His current research includes three Agency for Healthcare Research and Quality (AHRQ)-funded studies centered around the use of, and best practices for, antibiotic medications in skilled nursing facilities. In the first project, he serves as a technical expert that is designing and testing a national antimicrobial stewardship toolkit. A second project seeks to implement an antimicrobial stewardship program which includes a Centers for Disease Control (CDC) recommended antibiotic "time out" process. A third study, funded in June 2015, is designed to update guidelines for urinary tract infection (UTI) management and develop a program to implement an improvement plan in a cohort of skilled nursing facilities in four geographic areas across the United States.

The Antibiotic Dilemma

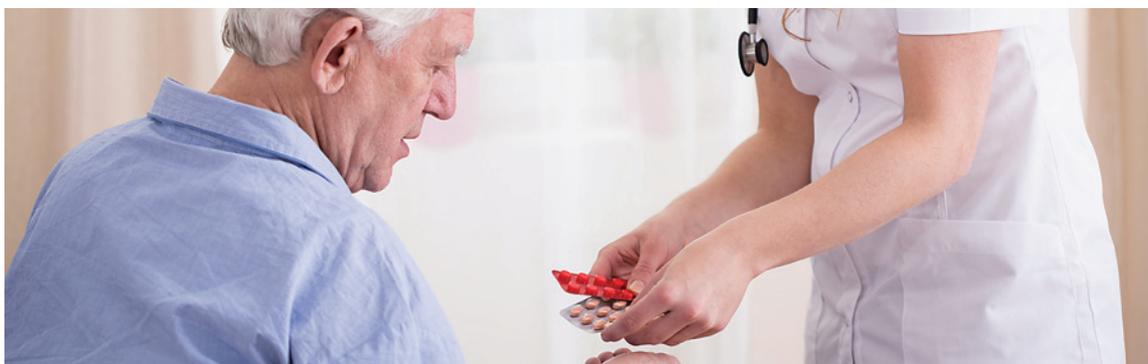
From Dr. Nace's perspective, there's a problem with antibiotic use in general in the United States, and in particular with older nursing home residents. Not only are antibiotics over-prescribed, they are now common in animals raised for food, and the number of new antibiotics in the pipeline has steadily decreased over the years. Together, this is leading to the rise of resistant strains of pathogens. "In the past, our whole philosophy was 'don't worry about it, we'll have a new antibiotic; the cavalry will come.' The cavalry is no longer coming, because there's just not that many new antibiotics in development. In the last year or so, there have been a few new antibiotics, but none of these are really novel, amazing classes of drugs that are going to reverse the problems of resistance," says Dr. Nace.

Dr. Nace further explains that without access to novel types of antibiotics we cannot be cavalier in prescribing them. As an example, the carbapenems — imipenem,

meropenem, doripenem — these antibiotics came out starting in the late 1990s and early 2000s, and substantial amounts of resistance are already being observed. "In ICU settings, in the nursing home setting, there's already a resistance to these brand new antibiotics. We have to be cautious," he says, "and we really have to think if it is necessary to use an antibiotic."

The problems go beyond just resistant organisms. Dr. Nace explains that the other issue at hand in prescribing an antibiotic to an older adult in the long-term care setting is, "You're giving a drug that has side effects that will, not if or could, but will potentially cause an adverse reaction. In nursing homes, 60% of people are on nine or more medications, and the chance of an adverse drug reaction is pretty high. Warfarin usage is common, and antibiotics such as Bactrim®, moxifloxacin, or ciprofloxacin all can interact with warfarin, leading to bleeding events and other complications."

Continued on Page 12



**Improving
Antibiotic Use***Continued from Page 11***The Trouble With Antibiotics
in Nursing Facilities**

In nursing homes, 75% of residents get an antibiotic in the course of one year. “The number of those antibiotics that are inappropriate can actually be up to 75%. Part of the reason is the environment: there’s not always a physician present on-site in the nursing home every day, and you’re dealing with people who are very frail with multiple medical problems. They can present with a condition in a variety of ways, and staff often have to make split-second treatment decisions,” says Dr. Nace.

A typical nursing facility does not have the same testing capabilities that exist at hospitals. Influenza tests, for example, is a classic situation where a facility might not have access to polymerase chain reaction — the gold standard test for flu. “For a variety of reasons — sick patients, lack of clinicians on site, the unavailability of timely, accurate diagnostic testing — a fairly significant number of antibiotics are started for sub-optimal reasons and if we had carefully looked at the person, we might have been able to avoid starting an antibiotic in the first place. And by treating the wrong thing, we miss treating the right thing,” says Dr. Nace.

Older adults in general present atypically for most conditions. But relying on nursing staff who may not fully appreciate how an infection presents in an older adult or the likely trajectory of the infection, coupled with inadequate diagnostic or laboratory capabilities, the chance of misdiagnosis can be great, which leads to unnecessary or incorrect antibiotic usage.

**Suspected Urinary Tract Infections
and Antibiotic Usage**

Dr. Nace is the principal investigator for a \$1.5 million (\$500,000 annually for three years) AHRQ-funded cluster randomized controlled trial started in June 2015 to improve treatment and reduce antibiotic use in suspected urinary tract infections (UTI). For Dr. Nace, UTI (or suspected UTI) is the poster child for poor antibiotic use. “We know that older adults present atypically for a lot of changes in condition, sometimes for infection, but often for a lot of other diseases. The appreciation that infections can present atypically has, unfortunately, caused the pendulum to swing too far. We need to keep in mind that other, non-infection related conditions present this way as well and careful assessment of the resident is needed,” says Dr. Nace. Research indicates that many suspected UTIs are in fact instances of asymptomatic bacteriuria for which treatment with antibiotics is generally not needed and may in cases prove harmful.

The study, *Improving Outcomes of UTI in LTC Facilities: The IOU Study*, will be conducted at 40 nursing homes across the United States. “We decided we needed a broad representative sample, and we looked at where we thought there were a high proportion of nursing homes and a high proportion that we could reach. Pennsylvania was one area and represents the Northeast. We also have trial sites in North Carolina, Wisconsin, and Texas. This gives us four geographic regions, and because we know there’s geographic variability in prescribing patterns, our approach will take this into account” says Dr. Nace.

Dr. Nace’s long-term goal is to “Enhance the health of older nursing home residents with suspected UTI by increasing the appropriateness of antibiotic use through the dissemination of a multifaceted intervention,” he says. The importance of this study revolves around the creation of “an effective, multifaceted intervention that can be exported broadly to improve appropriateness of antibiotic use for UTI. This will lessen the risk of adverse drug events, help reduce the growing threat of antimicrobial resistance, and diminish the risk of *Clostridium difficile* infection.”

The guidelines that he and his study collaborators are developing will be rigorously vetted. “Oftentimes we hear that these types of guidelines are developed by people who don’t practice in long-term care. We are going back to the literature, pulling everything we can that is reasonable and pertinent to the nursing home environment, and running it past a panel of experts who practice in long-term care. These are physicians who can greatly inform the process because they are either certified in geriatric medicine, or certified in post-acute and long-term care medicine,” Dr. Nace says.

Another key component of the study is identifying what is appropriate treatment — something that hasn’t been done before. Dr. Nace explains, “Residents are often prescribed ciprofloxacin, but the resistance rate to ciprofloxacin is about 50%. So half the time you are picking the wrong antibiotic. We are trying to identify what are the reasonable empiric drugs, the ones that you should consider using before you get the culture results back.”

Education and educational components also are part of the study. “We want to target education to families and staff members, because a lot of them have been inappropriately trained to think ‘UTI’ the minute that there is any change in a resident’s condition. We are really targeting the prescribers and the physicians, but we’ll need an educational component for the facility staff, as well as the families to effect change,” says Dr. Nace.

Developing an Antimicrobial Stewardship Plan

Dr. Nace is involved as a technical expert, alongside primary investigator Elizabeth Frentzel, MPH, principal research scientist at the American Institutes for Research on an AHRQ-funded study to develop an antimicrobial stewardship toolkit for nursing facilities. The toolkit is being piloted at six nursing facilities in Pennsylvania, Maryland and Texas. "It's a relatively small study designed to test the materials we're developing and examine their overall usability. Our hope is that some of these tools can be adapted for the IOU study, says Dr. Nace."

Dr. Nace indicates that AHRQ has invested a lot of time and resources to develop tools for nursing homes. The antimicrobial stewardship toolkit organizes these existing tools logically and provides clear instructions to help facilities implement them. The toolkit includes standardized order sheets, sample antibiograms, and other communication tools that walk nursing staff through any number of scenarios. The toolkit will help nursing home staff to identify infections and which antibiotics are the most appropriate to prescribe, and for how long and at what dose. "We need to help the providers understand things like whether a resident is likely to have pneumonia, or whether it is appropriate to order a urine culture. At the end of the day we're providing standardized communication tools and order sets, and helping them put together antibiograms — collections of all the cultures in a facility — to see the different pathogens that grew out over the last 24 months and their resistance patterns. If you see 50% of isolates are resistant to ciprofloxacin, you can then talk to your prescribers and say 'don't use ciprofloxacin as a first choice because it's not going to work,'" says Dr. Nace.

Another part of the toolkit will be educational material for families and caregivers to help them understand what their family member is being treated for, and why. Dr. Nace indicates that right now, "We are in the pilot test. We did a beta test of just a couple facilities to get feedback on the tools, and now we're rolling out to additional locations. We've not yet completed gathering the six-month data for analysis, but that should be finished by mid-2016."

Antibiotic "Time Out" Measures

In a related study, Dr. Nace is collaborating with principal investigator Christopher Crnich, MD, PhD, associate professor, Department of Medicine – Infectious Disease, University of Wisconsin, to develop and implement a novel antibiotics stewardship program in nursing facilities. This study will involve 12 facilities,



six in Pennsylvania and six in Wisconsin. The goal of the study is to tailor an antibiotic stewardship program called the OASIS Program for specific nursing homes and their individual workflows.

"One of the things we're engineering into this program is what's called an antibiotic time out — a Centers for Disease Control and Prevention (CDC) best practice that has never been tested or implemented in a nursing home setting. Right now a resident may have what looks like an infection and an antibiotic gets started. Maybe a urine culture or an x-ray gets sent off, but the person just continues on the antibiotic. They may or may not even be seen by a physician. They will run the whole course of this antibiotic, and it will never get stopped, shortened, dose-altered, or changed. So what we're trying to do is engineer in a follow-up call in 48-72 hours that would address changes in condition," says Dr. Nace. These interventions may probe whether the patient's symptoms have resolved and the antibiotic can be stopped or whether the infection is resistant and a change in antibiotic is called for, or perhaps whether a more narrow-spectrum agent is appropriate.

For Dr. Nace the crux of the program is to reduce antibiotic burden: not just improve the use of antibiotics, but specifically cutting the burden of antibiotic exposure to the facility as a whole. For this project, a number of the materials have been developed and beta tested in the Wisconsin test locations. The research team has collected interviews and observations from the Pennsylvania facilities. The next phase of the project will be to begin baseline data collection followed by implementation of the program beginning in the second-half of 2016.

Recent Publications

Minster RL, Sanders JL, Singh J, Kammerer CM, et. al, and Newman AB. **Genome-Wide Association Study and Linkage Analysis of the Healthy Aging Index.** *J Gerontol A Biol Sci Med Sci.* 2015;70:1003-8.

The Healthy Aging Index (HAI) was devised by Dr. Newman's group to measure the extent of health across multiple systems. In this study, they conducted genome-wide linkage analyses to map quantitative trait loci associated with the HAI in more than 3000 participants in the Long Life Family Study, a study of individuals selected for familial longevity. They tested their findings in two other cohorts, the Cardiovascular Health Study and the Framingham Heart Study. There were no genome-wide significant findings from the GWAS, although several single-nucleotide polymorphisms near ZNF704 on chromosome 8q21.13 were suggestively associated with the HAI in the Long Life Family Study and nominally replicated in the other two cohorts. Linkage results revealed significant evidence for a quantitative trait locus for mortality-optimized HAI in women on chromosome 9p24-p23 but fine-mapping studies did not implicate specific candidate genes within this region of interest. The authors conclude that ZNF704 is a potential candidate gene for studies of the genetic underpinnings of longevity.

Griffiths D, Clarkson B, Tadic SD, Resnick NM. **Brain Mechanisms Underlying Urge Incontinence and Its Response to Pelvic Floor Muscle Training.** *J Urol.* Published online March 28, 2015.

Urinary incontinence afflicts one-third of seniors, causes substantial morbidity, and costs tens of billions of dollars annually. Unfortunately, the cause of its most frequent form — urge incontinence — remains unknown and its treatment has improved little in the past 50 years. Drs. Resnick, Clarkson, and Griffiths decided to use the most commonly recommended treatment for UI (biofeedback) as a therapeutic probe to identify possible causes, reasoning that this approach could disentangle changes due to aging from those causing or contributing to incontinence. Their previous work focused on the lower urinary tract; this study explored the brain mechanisms governing bladder control. The investigators discovered two distinct patterns of brain activation and also found that these patterns predicted response or non-response to therapy. They also found that therapeutic response correlated with a change in brain activation among responders while there was no change in non-responders. These findings suggest that UI may comprise at least two phenotypes: one that responds to biofeedback by facilitating deactivation of the prefrontal cortex and one

that may respond much better to pharmacotherapy, a hypothesis they will explore next. These results, combined with findings from their ongoing studies that suggest a structural/functional correlation between white matter damage and brain activation, could lead to new insights into the brain's role in incontinence and suggest new therapeutic approaches.

Greenspan SL, Perera F, Nace DA, Resnick NM. **Efficacy and Safety of Single-Dose Zoledronic Acid for Osteoporosis In Frail Elderly Women: A Randomized Clinical Trial.** *JAMA Intern Med.* 2015;175(6):913-921.

Bisphosphonates are effective in preventing and treating osteoporosis in healthy elderly, but little is known about their efficacy or safety in frail elderly, the group at highest risk. This knowledge gap, combined with the high prevalence in frail elders of multimorbidity, polypharmacy, and impaired mobility, contributes to the infrequent use of bisphosphonates in this group. To address this problem, Greenspan and colleagues began by conducting a two-year, randomized, blinded, and placebo-controlled study to assess both bisphosphonate's safety and its impact on bone mass and markers of bone turnover. Results were mixed: the single dose of zoledronic acid was well-tolerated and led to sustained improvement in bone mass and bone turnover. Yet, the improvement was not associated with even a trend towards fracture reduction. Although the study was neither designed nor powered to assess fracture reduction, the results raise the important possibility that, in frail elders, an increase in bone mass may not correlate with an increase in bone strength. The data underscore the critical need for a followup study to assess the impact on fractures before recommending a change in nursing home practice.

Gray SL, Anderson ML, Dublin S, Hanlon JT, et al. **Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study.** *JAMA Intern Med* 2015; 175: 401-7.

Anticholinergic drugs are problematic for older adults in whom they can cause a variety of symptoms including delirium. Although symptoms generally abate once the drug is stopped, there is emerging concern that these agents may cause more long lasting problems, including dementia. Dr. Hanlon and colleagues recently examined data gathered prospectively from >3000 community-dwelling seniors. All were enrolled in a closed panel HMO for at least 10 years, were cognitively intact at baseline, and were screened biannually. The investigators found that use of a minimum effective geriatric anti-cholinergic dose for 3 years was associated with a 54%

increased risk of dementia, even after adjusting for other risk factors, comorbidities, and medications. Moreover, there was a dose response relationship and the association persisted even after excluding anticholinergic use for two years before a diagnosis of dementia. Although confirmation of the relationship is still required, these results add one more reason to be cautious in prescribing agents with anticholinergic side effects, especially for chronic conditions over several years.

Weiner DK, Fang M, Gentili A, Kochersberger G, Marcum ZA, Rossi MI, Semla TP, Shega J. Deconstructing Chronic Low Back Pain in the Older Adult — Step By Step Evidence and Expert-Based Recommendations for Evaluation and Treatment. Part I: Hip Osteoarthritis. *Pain Med.* 2015;16:886-97.

Although the prevalence of low back pain has doubled among older adults in the past decade, and use of advanced spinal imaging has skyrocketed, outcomes have not improved apace. One reason is that treatment has likely been misdirected, an hypothesis that Dr. Weiner is currently testing. She has begun by deconstructing the approach to back pain evaluation and management. This is critical because an approach that begins with spinal imaging identifies abnormalities in most older adults. Because older adults without back pain have similar pathology, it is not surprising that “treating the abnormality” often fails to relieve the pain, especially since such pathology may distract from evaluation that would have revealed the true cause — one that often lies

outside the spine. This article is the first in her important 12-part series which presents chronic low back pain (CLBP) as a syndrome, i.e., a final common pathway for the expression of multiple contributors, as opposed to a disease localized to the spine. Each article includes an innovative, evidence-based approach. In this article, Dr. Weiner et al demonstrate the connection between hip osteoarthritis and back pain and conclude that examination for hip OA must be included routinely in evaluating back pain so that appropriately targeted treatment can be delivered.

Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM, Zimmerman RK. Randomized, Controlled Trial of High Dose Influenza Vaccine Among Frail Residents of Long-Term Care Facilities. *J Infect Dis.* 2015; 211: 1915-1924.

As immune function declines with age, the incidence of infections increases substantially. Influenza is one of the most common of these infections and it causes much higher morbidity and mortality in older adults than in younger adults, especially those who reside in nursing homes — even among residents who have been vaccinated. This randomized, single-blinded, controlled trial compared high dose to standard dose influenza vaccines administered to some 200 frail, elderly nursing home residents during the 2011–2012 and 2012–13 seasons. Antibody responses were superior among those who received the high dose vaccine. These results applied across all strains with the possible exception of Influenza A (H1N1).

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