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Correction: An author of a July South Dakota Medicine article was misspelled. Kayla Riswold co-authored the article, “Physicians’ Use of Compliance Gaining.” We regret the error.
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President’s Comments

Excellence in Care and Commitment

By Tom Hermann, MD
SDSMA President

With the coming of September we have seen our young and college students return to school for another academic year – all of who will soon take up the rigors of studying, practicing and competing in fall sports, and in essence finding their way through life using their gifts to learn and grow. Parents and teachers will soon be back into the rhythms and routines of school schedules as well – a new academic year after a summer of nourishment, growth, fun, and family time. Where did the summer go?

The University of South Dakota Sanford School of Medicine (SSOM) recently held its white coat ceremony for incoming medical students. It was my privilege as your South Dakota State Medical Association (SDSMA) president to attend, welcome, and lead these first-year medical students in the Affirmation of the Physician. Among those in the audience were many proud parents – some of which were physicians – family members, and an amazing array of medical school faculty, representing both academic and clinical medicine. Our state is truly well served by the commitment of our medical school faculty, led by Dean Mary Nettlemann, MD, and by the ongoing supportive efforts of our South Dakota Legislature and Gov. Dennis Daugaard’s administrative team. I take pride in the fact that the SSOM also receives considerable support from our SDSMA and SDSMA Foundation through our legislative advocacy, medical student scholarships and low interest loans. Additionally, our journal, South Dakota Medicine, supports our medical school, its faculty and students through the publication of their medical research and educational guidance. If you have not contributed to the SDSMA Foundation or placed an ad in the journal, I would encourage you to consider doing so, as your contributions have a direct impact on the future of medicine in our state.

I would be remiss if I failed to mention the ongoing and extensive support of our health systems. Excellence in medical education is not only dependent on our students, faculty and university facilities but also by the commitment to medical education that is shown by our hospitals/health systems, community clinics, and the VA. This is inclusive of their commitment to all teaching programs in medicine including nursing, pharmacy and a variety of other ancillary care professionals, in undergraduate and graduate level education. May we share our gratitude to all those entities that make the provision of excellence in care of our patients possible.

This past year your SDSMA leadership team has guided us through a host of changes, some foreseen and some unexpected. Our national American Medical Association leadership continues to advocate on behalf of our physicians as we promote the well-being of our providers and patients. During our recent Executive Committee retreat at Sutton Bay in July, we were joined by several of our past presidents in a heartfelt discussion regarding the future of the SDSMA. In doing so, we discussed the past and the future, and our leadership team received recommendations and insights from those who have gone before us in leading the SDSMA. Over the course of those two days, we were time and again reminded of what really has not changed – the importance and commitment of the SDSMA to advocate for the art and science of medicine, to protect and improve the health of the public, and to advocate for the well-being of patients and the physician-patient relationship. As advocates, we can find common ground across all organizational systems to promote our profession and to advance the delivery of high-quality medicine. A special thanks to all who attended and shared stories of their lives in service to their patients and communities; our SDSMA is forever indebted to your leadership and commitment to our organization.

The value and strength of any organization begins with its mission and its membership, all of which begins with you – the members of the SDSMA – and your involvement in our district medical societies, Council, and Executive Committee. May this September find you mindful of your commitment to medical education and knowledge, professionalism and the ideals of medicine, and preserving the importance of the physician-patient relationship. Please consider renewing your commitment to each other by being part of our SDSMA.
According to the American Cancer Society, there are nearly 14.5 million cancer survivors in the U.S., many of whom face physical, psychological, practical, informational, and spiritual challenges after the completion of cancer treatment (Cancer Treatment & Survivorship Facts & Figures, 2014-2015). Primary care providers play a critical role in providing much-needed follow-up care for cancer survivors.

You can learn about caring for survivors of adult-onset cancers through the free cancer survivorship E-Learning Series. Continuing education credits are available at no cost.

Learn more at HTTP://TINYURL.COM/PCTRAINSD
Sanford School of Medicine (SSOM) at the University of South Dakota (USD) continues to achieve recognition as a leader in rural medical education. The class sizes continue to grow, as do the number of applications for admission. SSOM at USD clearly offers high quality medical training.

The research component of medical education, optional but highly important to a portion of the students, continues to be an area of concentration in SSOM. Physicians that understand evidence-based medicine are required in today’s medical environment. There is no better way to understand this approach to medicine than to actively participate in it. The Scholarship Pathways Program (SPP), now in its ninth year, provides research-oriented students with that opportunity. To date, about 15 medical students per year (113 in total) have participated in this program. Students gain admission to the program through a competitive application process, and may propose projects in the general areas of research, education, and service; a majority of projects are in the research area. Students work closely with mentors, who provide vital and important support for SPP participants. Throughout the program, they are supported by their mentors and the SPP administrative staff. After performing their project, the project is written up as a poster, an abstract (presented as part of this document), and as a manuscript. Most participants present their work in one or more medical venues. SPP participants report that, during residency interviews, there is considerable attention paid to and interest in the SPP project.

The annual Scholars Day Symposium, held in conjunction with graduation, is a venue where SPP participants display their posters. There are formal presentations as well. In this year’s Scholars Day, four presentations were featured. Allison Abitz (mentor: Matthew A. Barker, MD) examined the impact of FDA communications about the use of pelvic mesh. Using medical records from two local community hospitals, she found that mesh use decreased following the advisories from the FDA. Rebecka Bogue (mentors: Gene Hoyme, MD, and Amy Jacobson, EdD) created an elective for medical students to obtain training in international medicine. Using the Sanford International Clinics in Ghana, students were given the opportunity to have experience in these clinics, and the elective is now part of the SSOM curriculum. Kari Halvorson (mentor: H. Bruce Vogt, MD) examined the relationship of various maternal characteristics on birth weight of babies in the Caucasian and Native American communities of South Dakota using birth certificate data. She found that Native American race, gestational diabetes mellitus, overweight and obese BMI, and excessive gestational weight gain for BMI were the most significant maternal factors associated with high infant birth weight. Alexandra Higgins (mentor: Keith A. Hansen, MD) examined the incidence of screening for cystic fibrosis in couples with a family susceptibility for this condition. She found that the incidence of screening increased over time, and that decreased cost was an important factor in this increase, accounting for approximately 20 percent of the increased testing. It was a difficult job selecting oral presentations among the many exceptional projects in this 2016 SSOM class.

We are pleased to share this year’s Scholars Day Symposium abstracts and thank South Dakota Medicine for giving us this opportunity. If you would like to mentor a Scholarship Pathways student, please contact Candace Zeigler, MD, at candace.zeigler@usd.edu.
The Influence of Synthetic Mesh FDA Communications on the Practice Patterns of Physicians Performing Pelvic Reconstructive Surgeries

By Allison L. Abitz, MSIV
Mentor: Matthew A. Barker, MD

Background: With the introduction and increased usage of mesh as the treatment of pelvic organ prolapse and stress urinary incontinence, a subsequent increase in mesh-related complications were being reported to the U.S. Food and Drug Administration (FDA). Complications most commonly involved mesh erosion through vaginal epithelium and into adjacent structures. The FDA thus issued an initial public health notice on Oct. 20, 2008, and it subsequently stated in 2011 that complications could arise from such procedures. The aim of this research was to determine the magnitude of the impact of FDA statements regarding the use of mesh in gynecologic surgery on the utilization of mesh in two community hospital settings in Sioux Falls from 2005 to 2012.

Methods: We retrospectively reviewed CPT/ICD-9 codes, as well as purchasing data regarding transvaginal mesh for prolapse and urinary incontinence from community hospital systems in Sioux Falls from 2005 through 2012. Mesh products included the following: pelvic mesh products, pelvic organ prolapse products and stress urinary incontinence products. Exclusions of data included vague descriptions of billing and purchasing record data. No patient identifiers or links were included or recorded in the data analysis. Data was analyzed by looking at trends and determining outliers.

Results: There were 7,717 CPT/ICD-9 codes and purchasing data on 1,358 mesh purchases that were reviewed. Data from 2008 through 2012 showed that the FDA safety communications had contradictory impacts on pelvic organ prolapse (POP) with or without mesh use, pelvic mesh alone, and urinary incontinence during surgery at hospital System A (↓14 percent, ↓73.8 percent, ↓6.0 percent) versus System B (↑56.3 percent 2009 through 2012, no data, ↑204.6 percent). Purchasing data for POP and urinary incontinence products showed contradictory impacts as well for System A (↓18.6 percent, ↓11.5 percent) versus System B (↑155.6 percent, ↑167.4 percent). The 2008 through 2011 data was not negatively reactive until after the 2011 FDA safety communication.

Conclusion: Following FDA notifications, there was a decrease in overall mesh usage. Usage dropped perhaps due to physicians becoming more sensitive to the communications and the potential negative outcomes associated with mesh use. Overall, FDA statements had less impact on mesh utilization in System B with little change after 2008 and a slight decline after 2011. System A responded with noticeable decreases in use after 2008 and a substantial decrease in usage after 2011. The contradictory responses could be due to the volume of surgeries performed and System A having a more established program at the time.
The Structured International Health Elective through the University of South Dakota Sanford School of Medicine

By Rebecca Bogue, MSIV

Mentors: Gene Hoyme, MD; and Amy Jacobson, EdD

Background: As the world becomes more globalized, today’s physicians are expected to have a broader understanding of cultural medical practices, as well as knowledge of tropical diseases and emerging global infections. Medical schools are preparing for the future by offering an international health elective. Research shows that, although international health electives are offered at 25 percent of U.S. medical schools, there is little standardization in terms of clinical and cultural requirements. This project set up a structured international health elective by collaborating with Sanford International Clinics (SIC) for University of South Dakota Sanford School of Medicine students.

Project Description: In the summer of 2012, SIC opened three clinics in Ghana to bring health care to areas in need. These clinics provide communities with permanent, sustainable healthcare, which is central to developing a long-standing structured environment for an international medical elective. Clinics provide primary health care services, diagnosis, and treatments for children and adults. There is an on-site laboratory and pharmacy at each clinic. These sites offer medical students a structured, safe, and educational international elective and provide the medical school with its very first internal global elective.

Outcome: On-site evaluations were conducted in 2013 at three SIC locations in Ghana. Each site was evaluated quantitatively and qualitatively to determine if it would meet clinical requirements. Data gathered included average number of patients seen per day, National Health Insurance Scheme accreditation, patients’ main diagnosis, and number of physicians on site. Other information gathered was based on observations such as cross-cultural experience, living conditions, level of supervision, and personal safety. The results showed that Ghana would offer medical students a structured, safe primary care elective. The elective within the Department of Family Medicine was FAMP 890-08. This elective was designed and a syllabus with objectives was finalized along with a student evaluation to be completed by the Ghanaian attending physician. A pilot elective was completed in August 2015. During the elective, the primary preceptor gave daily feedback on the students’ performance, along with completing the required evaluation form and grading the student based upon Pillar 3 standards. The student kept a daily log of patient encounters. Upon arriving home, students held a debriefing session with faculty and SIC staff at Sanford Health.

Conclusion: Based on attending physicians, patient numbers, and variety of patients and cases seen, SIC in Ghana offers a structured learning environment for medical students. This elective has recently been approved as an elective for fourth-year medical students, FAMP 890-08. This provides students with exposure to atypical tropical diseases, enhances cultural perspectives, and teaches effective communication across cultural barriers. Research shows that medical students who have participated in an international clinical rotation often report a greater ability to recognize disease presentations, have more comprehensive physical exam skills, and have greater cultural sensitivity. There may also be a correlation between participating in an International Health Track and caring for the under-served populations following residency. We hope that this elective (FAMP 890-08) will expose medical students to global health issues and encourage students to enter primary care and serve in underserved locations.
Effects of L-Theanine on PTSD-induced Changes in Rat Brain Gene Expression

By George A. Ceremuga, MSIV
Mentor: Matthew A. Barker, MD

Background: Post-traumatic stress disorder (PTSD) is one of the most common and devastating injuries associated with war. PTSD is characterized by the occurrence of a traumatic event that is beyond the normal range of human experience, i.e., war zone stress. This event causes a level of stress that exceeds a person’s capacity to adapt. About 20 percent of service members returning from deployments meet the criteria for PTSD or major depressive disorder. The future of PTSD treatment may include medications specifically targeted for the molecular mechanisms of PTSD. It is of great importance to investigate new targets of pharmacotherapy to treat PTSD among service members and civilians. In the U.S., nearly one in five adults report taking herbal products to treat medical illness. L-theanine is the amino acid in green tea primarily responsible for its flavor and relaxation effects. L-theanine may attenuate anxiety by having a relaxing effect under resting conditions. When concomitantly administered with midazolam, L-theanine was shown to have a synergistic anxiolytic effect. There are no studies evaluating the potential therapeutic properties of herbal medications on gene expression in PTSD.

Methods: We evaluated gene expression in PTSD-induced changes in the amygdala and hippocampus of Sprague-Dawley rats. The rats were assigned to PTSD-stressed and nonstressed groups that received either saline, midazolam, L-theanine or L-theanine + midazolam. Amygdala and hippocampus tissue samples were harvested and sent to SABiosciences for gene analysis using the RT² Profiler PCR Array. One-way ANOVA was used to detect significant difference between groups in the amygdala and hippocampus.

Results: Of 88 genes examined, 17 had a large effect size greater than 0.138. Of these, three genes in the hippocampus and five genes in the amygdala were considered to be significant (p < 0.05) between the groups. We found a downregulation of the Erg1 gene in the PTSD-vehicle group compared to the PTSD-midazolam group. Erg1 is an early growth response nuclear transcription factor that plays a role in regulating the expression of genes required for learning and memory. Expression of the Maoa gene was decreased in the PTSD-vehicle group compared to the control group that received L-theanine and midazolam. Decreased Maoa enzymatic activity leads to increased levels of norepinephrine and serotonin and strong links to reactive social behaviors, including specific links to violence and aggression. The hippocampal genes related to long-term potentiation (Egr1), violence and aggression (Maoa), and major depressive and bipolar disorder (S100a10, serotonin receptors) were shown to be downregulated in PTSD animals and expression levels significantly changed. Other neurotransmitter genes Gabrb2 and Chrm2 were also modulated across treatment groups and warrant further exploration, as they are associated with depression related clinical conditions. Amygdalar genes that were changed across treatment groups also were related to psychological conditions such as depression (Drd2), stress enhanced fear learning (Gabra4), chronic mild stress (Drd1a), and anxiety, mood disorders, and psychoses (Htr3a). These findings taken together demonstrate a relationship of possible gene expression changes in important and known neurotransmitter system genes and associated clinical pathologies.

Conclusion: RT-PCR analysis revealed significant changes between groups in several genes implicated in a variety of disorders ranging from PTSD, anxiety, mood disorders and substance dependence. This study lays the foundation for future studies to interrogate and investigate the translation of these genes into proteins and the potential for these proteins to act as sites for pharmacologic therapeutic intervention.
A Mouse Model of Atp13a2: A Monogenic Cause of Early-onset Parkinson’s Disease

By Joshua M. Doorn, MSIV
Mentor: Michael C. Krue, MD

Background: Kufor-Rakeb syndrome (KRS) is a single gene cause of early-onset Parkinson’s disease (PD) that is due to a mutation in the gene ATP13A2 (PMID: 16964263). ATP13A2 encodes an ATPase of unknown function and is found in the membrane of endo-lysosomal structures (PMID: 19345671). KRS is inherited in an autosomal recessive manner (PMID: 16964263). KRS, which was first discovered in 1994, has been described in children under the age of 10 (PMID: 19345671). The goal of our study was to further understand the pathogenesis of this disease using a mouse model.

Methods: The Atp13a2 knock-out (KO) mouse was phenotypically assessed along with age-matched wild type (WT) mice to determine the presentation of KRS in the mouse. The mice were subjected to trials on the rotarod, Barnes maze, and open field testing. These tests allowed us to assess the mice’s motor abilities, cognitive function, and quality of movement. Then, the mice were sacrificed and immunohistochemistry (IHC) was performed on the mouse brains to determine neuropathological features of Atp13a2 KO mice. Glial fibrillary acidic protein (GFAP), autofluorescence, H&E staining, and calbindin staining were performed to characterize these neuronal changes. Contributions were made by Nadia Sahir, Lauren McBeth, Elizabeth Jones, Helen Magee, Marianna Madeo, Tyler N. Jepperson, Anna Yarrow, Chun-hung Chan, David Pearce, and Jon Cooper.

Results: WT mice consistently outperformed the Atp13a2 KO mice in the rotarod test. KO mice made more mistakes on the Barnes maze than WT mice. In an open field, KO mice traveled a shorter distance and ambulated more slowly than WT mice. IHC demonstrated increased GFAP staining in the KO mouse compared to the WT mouse. Calbindin staining showed decreased number of Purkinje cells in the cerebellum of the KO mouse. Finally, autofluorescence was increased in the KO mouse cortex when compared to the WT mouse cortex.

Conclusions: Mutation in the ATP13A2 gene presents as an early-onset autosomal recessive form of PD. The Atp13a2 KO mice showed a phenotype similar to that of KRS patients, with slowed movement, decreased cognitive performance, and impaired motor skills in our trials. IHC demonstrated changes that are consistent with neurodegeneration. Ubiquitin and alpha-synuclein stains did not show any abnormalities in the KO mouse. Our yeast and fibroblast experiments suggest defective autophagy, which could be the cause of the cellular changes we observe in vivo. Further studies using KRS cells may give additional insight into the mechanism of the observed neuronal changes in the brain.
Journal

Integrating Art Into Medical Education

By Emily E. Gaster, MSIV
Mentor: Stuart Inglis, PhD

Background: Medicine and art have a rich history of interdependence. At the origins of anatomical study, detailed drawing during dissection was necessary to document findings, while knowledge of musculature was integral to artists’ work. Often, physicians took it upon themselves to act as both artist and scientist in the lab. Engagement in art, such as drawing, may still be a pertinent exercise for medical students. Several medical schools have incorporated figure drawing into the curriculum as a way to supplement anatomy lessons, improve observational skills, increase comfort with the human form, and promote empathy and compassion. Offering a creative outlet and time for reflection may help reduce stress and improve emotional wellbeing. Empathy burnout and overall burnout is occurring ubiquitously and early on in medical education. Therefore, timely intervention of integrating art, such as figure drawing, into the curriculum may serve to positively cultivate the physician’s role as caregiver. Art may also facilitate learning. The act of drawing requires deeper engagement of the object or concept of study as well as greater attention to detail and nuance, which may improve comprehension.

Project Description: My project had two objectives. The first was to offer figure drawing sessions for medical students, residents, and physicians with the goal of providing a creative outlet, improving observational skills, and fostering empathy. I collaborated with the University of South Dakota and Augustana University Fine Art departments to create a mutually beneficial drawing program for both art and medical professionals. Three 2.5-hour figure drawing sessions were offered each semester in both Vermillion and Sioux Falls and instructed by graduate art students. The second project objective was to demonstrate the utility of art as a learning tool by personally composing a work of drawings to better understand dermatologic disease. Fortunately, dermatology’s visual nature lends itself well towards artistic representation. This work, entitled, “Skinscapes: Drawings for Understanding Dermatologic Disease,” contains detailed gross and pathologic representations of diseases affecting the skin.

Outcome: A total of 34 students, residents, and physicians took part in the drawing sessions. The response to the figure drawing sessions was overwhelmingly positive. Participants cited feeling refreshed and relaxed after attending sessions. Encouragingly, all participants expressed interest in attending future sessions. Drawing various dermatologic diseases led me to deeper questioning and understanding subtleties as I engaged the subject matter. As an aspiring dermatologist, this was an enjoyable, engaging way to increase my knowledge in this field. After completion of “Skinscapes,” I became more proficient and confident in my knowledge base.

Conclusion: Optional participation in figure drawing sessions adds a complementary dimension to medical students’ education. Additionally, individual student participation in drawing allows for deeper engagement during study. As in the past, art continues to inform medicine by improving observational skills, consolidating anatomical knowledge, and serving as a valuable instrument for learning. Engaging in a creative outlet may also help to reduce stress and promote empathy, which in turn enhances the physician’s role as caregiver and healer.
Great news: In 2015, 36.5% of our enrollees heard about QuitLine services from healthcare professionals. Even better, we’re introducing a new South Dakota QuitLine module on “PROF” (Program and Resource Online Facilitator) at dohprofso.org, where health professionals like you will learn even more about the effects of tobacco and the steps required to guide those addicted to seek help. You’ll also learn how to visit with patients about their tobacco use and how best to make a QuitLine referral.

The interactive online system tracks progress, so users can log in and out at their convenience and still maintain their place in the training. We encourage all health professionals and providers who interact with tobacco users to participate in this training.
The Impact of Maternal Diabetes, Obesity and Race on Infant Birth Weights in South Dakota

By Kari Halvorson, MS IV
Mentor: H. Bruce Vogt, MD
Co-authors: Lon Kightlinger, PhD; and Dennis Stevens, MD

Introduction: Maternal obesity, high gestational weight gain and diabetes mellitus (DM) during pregnancy are known risk factors that correlate with high infant birth weight and the mother's race. Previous studies have focused on low birth weight, prematurity and infant mortality. This study examined the interaction between race, maternal risk factors and high infant birth weights at the population level in South Dakota to identify factors contributing to the high Native American infant birth weights. We hypothesized that high infant birth weights were associated with maternal diabetes, obesity and high gestational weight gain, and that Native American infants' higher birth weights were related to the prevalence of diabetes and obesity.

Methods: De-identified birth certificate data was provided by the South Dakota Department of Health. We used data for live infant births to South Dakota resident mothers from 2006 through 2011. The mothers were categorized as Native American or white by the mother’s self-reported primary race. Infants were excluded from the study population for missing data, birth weight less than 350 g or gestational age less than 24 weeks or greater than 45 weeks. The study population included 11,416 Native American infants and 59,263 white infants for a total study population of 70,679 infants. Maternal variables (race, pre-pregnancy weight and body mass index [BMI], gestational weight gain, pre-pregnancy diabetes mellitus, gestational diabetes [GDM] and delivery BMI) and infant variables (gestational age and birth weight) were analyzed using SPSS software.

Results: The mean birth weight (BW) of Native American infants (3,377 g) was significantly greater than the mean BW of white infants (3,315 g) (p <0.001) even though NA infants had a younger mean gestational age (p = 0.006). More NA infants were categorized as high birth weight (HBW) (11.8 percent) than white infants (8.5 percent) (p < 0.001). Both DM and GDM were significantly more common among NA mothers (p < 0.001). Infants of Native American mothers with GDM had a higher mean BW than infants of white mothers with GDM (p < 0.001). There were more overweight and obese Native American mothers (p = 0.006). In each maternal BMI category, Native American infants had a higher mean BW. Mean BW was even higher for infants born to mothers with excessive gestational weight gain (GWG) for their BMI. The infants with the highest mean BW were born to obese Native American mothers with GDM and excessive GWG (3680 g). Multivariable linear regression showed that race was the most significant variable affecting infant BW (R² = 0.57, F = 692, p < 0.001). Pre-pregnancy BMI, GWG and excessive GWG were also significant. The most significant interaction variables were race and GDM and race and BMI.

Conclusions: Native American race, GDM, overweight and obese BMI, and excessive GWG for BMI were the most significant maternal factors associated with high infant BW. Mothers with any one risk factor gave birth to heavier infants. Mothers with all risk factors had infants with the highest mean birth weights in South Dakota. This large population-based study provides evidence that Native American mothers in South Dakota with GDM, overweight or obese BMI and excessive GWG are more likely to give birth to HBW infants. At-risk mothers should be educated regarding the risks and potential complications of HBW infants.
An Expanded Carrier Screening Tool Enhances Preconception Cystic Fibrosis Screening in Infertile Couples

By Alexandra Higgins, MSIV
Mentor: Keith A. Hansen, MD

Background: Cystic fibrosis (CF) is a progressive, multisystem disease. The carrier risk of CF in the non-Hispanic white population is approximately 4 percent and the disease incidence 0.04 percent, making it the most common life threatening autosomal recessive condition in this population. The American College of Obstetricians and Gynecologists recommends offering preconception and prenatal screening for CF while the American College of Medical Genetics also recommends offering screening for spinal muscular atrophy (SMA) to all couples. Both groups suggest specific screening if there is a family or personal history of a genetic disease or if the individual is from a high risk ethnic group. In 2007, only 2 percent of the patients evaluated for infertility at this Midwest infertility clinic elected to have preconception screening for CF. The purpose of this study was to determine whether availability of a more comprehensive, affordable genetic screening tool increased the number of patients choosing to have preconception screening for CF and other genetic diseases.

Methods: This was a retrospective chart review of new patients evaluated for infertility at Sanford Health Fertility and Reproductive Medicine between May 2010 and May 2013. A search of the electronic medical record was performed to identify all new infertility patients and a separate search was performed of the Counsyl dataset to identify all patients who submitted a sample for genetic testing. The two data sets were compared to ensure inclusion of all new patients. All identified records were reviewed and data abstracted. Those couples being evaluated for infertility had a detailed pedigree and were offered the Counsyl expanded carrier screening test after genetic counseling. The percentage of these patients choosing to undergo preconception genetic screening was determined as well as the carrier frequencies of CF and other genetic diseases.

Results: A total of 1,669 new infertility couples were offered Counsyl expanded carrier screening. Eight percent of the couples underwent screening of either one or both partners. Seventy-six percent of the tests were administered after the price reduction to $99 in May 2012. The carrier frequency for CF was 6.8 percent with 0 percent of the couples concordant heterozygotes. The carrier frequency for SMA was 2.51 percent with 0 percent of the couples concordant heterozygotes. Fragile X premutation was found in 2.78 percent.

Conclusion: With availability of the Counsyl screening test, the percentage of new infertility patients choosing to have preconception genetic screening increased from 2 to 8 percent. The largest increase (17.5 percent of new patients) in screening followed the reduction of out-of-pocket expenses. The carrier frequency for CF was found to be 6.8 percent in this study as compared with the anticipated 4 percent carrier risk before testing. Infertility patients are in a unique position to investigate their family history, discuss appropriate preconception genetic screening, and, if discovered to be at high risk of a genetic illness, review their reproductive options.
Background: In 2011, the Pediatric Infectious Disease Society released guidelines regarding the management of community-acquired pneumonia (CAP) for pediatric patients. These guidelines recommended not obtaining routine chest radiographs (CXR) for treatment of outpatient community-acquired pneumonia. However, historically, changes in medical practice are often difficult and require targeted interventions on provider behavior.

In order to aid in changing historic practice patterns, we examined the pediatric population presenting to the emergency department (ED) prior to release of the guidelines to determine if socioeconomic status impacted the use of routine chest radiographs for outpatient CAP.

Method: We conducted a retrospective study of de-identified patients from the Agency for Healthcare Research and Quality 2009 Nationwide Emergency Department Sample. Patients 18 years and younger were identified with a diagnosis of outpatient CAP through a validated ICD-9 coding algorithm. Outpatient status was based on discharge from facility following treatment. Socioeconomic status was based on the median household income quartiles for the patient’s ZIP code. Discharge weights from the American Hospital Association universe were used to obtain national estimates. Statistical analysis was conducted using STATA 12.1. Institutional Review Board approval was obtained prior to research study.

Results: There were 98,814 un-weighted observations representing an analyzed weighted population of 445,078 with a diagnosis of outpatient CAP. Of patients presenting to the ED and subsequently discharged with a diagnosis of CAP, 54.5 percent did not receive a CXR and 45.5 percent received a CXR. In comparing those receiving no CXR versus those receiving CXR: age (4.4 to 4.3 years of age, p = 0.05), gender (44.9 to 44.7 percent female, p = 0.71), weekend versus weekday (32.7 to 32.5 percent weekend, p = 0.57), number of diagnoses at discharge (2.1 to 2.1, p value 0.84), total ED charges ($1,516 to $1,486, p = 0.08) and median household income quartile (2.1 to 2.3, p < 0.001).

Conclusion: We found that pediatric patients presenting to the ED had a higher likelihood of receiving a CXR for outpatient CAP if they were from a wealthier ZIP code. This occurs despite no differences in age, gender, weekend versus weekday visit, number of diagnoses, or overall ED charges. Understanding the characteristics of those receiving possibly unnecessary CXR can be helpful to changing provider behavior towards meeting established guidelines.
Non-medical Vaccine Exemptions in a Western South Dakota School District, 2014-2015

By Heidi L. Moline, MSIV

Mentor: Jennifer L. Hsu

*Background:* Over the past 15 years, as social and personal beliefs about vaccination have shifted, the number of non-medical exemptions for early childhood immunizations have increased across the country. Interestingly, these changes in immunization practices are unique in demographic and geographic distribution. It is well established in the literature that parents who decline childhood vaccines are more likely to be white, well educated, and moderately affluent. As with most social metrics associated with demographic variability, low vaccination coverage and high exemption levels often cluster within communities. Unfortunately, these local clusters of high risk children, and the true exposure risk of non-immunized children, are lost within county and state-level immunization data.

*Methods:* The Rapid City Area School District (RCASD) maintains a record of the immunization status of over 13,800 children within the district, which is accessed primarily by school nurses. Through this database, the number of religious and medical exemptions were collected for each grade level in all RCASD schools between December 2014 and March 2015. A generalized linear model approach with a binomial link function and clustering by school was used to examine the data. Data were adjusted by race percentage, percentage taking free lunch, and student achievement score. Least-square means (adjusted by the fixed effects noted above) were computed, along with 95 percent confidence intervals for the means. Comparison of means (the proportions of cases in each grade who claimed an exemption from the vaccination requirement) was performed using designed contrasts.

*Results:* During the 2014-2015 school year, there were 127 children with non-medical exemptions in this district, for an overall rate of 0.9 percent (n=13,801). There is a statistically significant difference (p< 0.05) in the rate of exemptions across the district, with the highest school having a religious exemption rate of 3.5 percent and the lowest school with a religious exemption rate of just 0.3 percent. The highest rates of non-medical exemptions are seen in elementary schools, with nearly half of all non-medical exemptions (48.8 percent) occurring in children in third grade or younger.

*Conclusion:* Overall, the rates of school-entry vaccination coverage within RCASD are impressive. They are higher than both the state and national averages. The results of this analysis suggest that there is clustering among unimmunized children in public schools in Rapid City. This suggests that some schools are at a higher risk for a vaccine-preventable disease outbreak than others. The rates of religious exemptions are not equal across all schools, indicating there is local clustering occurring in this school district. Grade-level data indicates that more children are receiving religious exemptions than in the past, with most exemptions occurring in lower grade levels.
Investigation of Molecular Markers to Identify Pathways Involved in Polarization of Macrophages

By Robert Riggio, MSIV

Mentor: Peter Slivka, PhD

Background: Within the extra-cellular scaffolding lie cellular signals, which under the proper circumstances have been demonstrated to encourage replacement of damaged, non-functional tissue with functional tissue. The macrophage has been shown to be involved in this re-constructive process. A higher ratio of macrophage subtype 2 (M2)/macrophage subtype M1 (M1) is known to be associated with more functional tissue replacement, and a lower ratio associated with more scar tissue formation. The molecular pathways which the macrophage utilizes in order to become polarized towards an M1 or M2 phenotype have previously been investigated. This investigation looks at the pathways the extra-cellular scaffolding influences in order to drive the macrophage towards the M2 phenotype.

Methods: Using a Western blot with the cell lines HeLa (a human epithelial cervical cell line), CHME5s (a human microglial cell line), and Thp1s (a human monocytic cell line), the presence of STAT6 and phosphorylated STAT6 were measured. In the ELISA, the Thp1 cells were pre-incubated for six hours in the UBM and resup in order to measure the reduction or incretion of the secreted factors relative to the non-LPS/IFN-gamma treated controls known as a competition assay. A 4h time point was only used for the treatments of the TNF-alpha assay. Using the RT-PCR in the cell type Thp1 were exposed to 0.5mg/mL of UBM, 100ug/mL of IL4, 100ug/mL of LPS and 100ug/mL of IFN-gamma for 18 hours after pre-incubation with PMA (200nM) in order to push the monocytes to macrophages. The cells were then lysed with Trizol (1mL) and stored in -80 C for four weeks before the homogenate was thawed and the RNA purified.

Results: Using the Western blot, the IL4 treatment was the control and produced the predicted P-STAT6 response. In the lanes treated with UBM no P-STAT6 response was detected. STAT6 (inactivated) was found in each lane indicating that it is present, but inactivated. Rehydrated supernatant produced similar results. In the IL4 treated cells two bands were detected. This is due to the HeLa cell line used for this particular experiment was previously transiently transfected with STAT6, and the two STAT6-P bands are the endogenous and transfected versions of STAT6. In the ELISA to determine the TNF-Alpha, the LPS treated lane is the LPS treatment only. The 50X and 100X are the dilution factors of 1/50 and 1/100 respectively.

Conclusion: STAT6 is not a good molecular marker for M2 polarization with UBM based on our results. The UBM and resup do not activate STAT6 within the time points measured. IFN-gamma is a good candidate for future experiments to deduce the pathways involved with UBM polarization, due to the fact that there was significant contrast between UBM, resup, and the controls. In addition IL10 and PGE2 are good candidates for future experiments due to the fact that the controls were optimized. The controls for IL12 however had less contrast. RT-PCR showed the opposite of what was generally expected for both ferroportin and ceruloplasmin. Further investigation into this matter is ongoing.
Simulation Boot Camp – Preparing USD Medical Students for their Intern Year

By Rebekka Sneed, MSIV

Mentors: Jody Huber, MD; Gary Timmerman, MD; and Val Kozmenko, MD

Background: It is important to expose medical students to situations they will encounter in patient care, prior to their entrance into residency training. Training using simulation education is a relatively new approach. This area has developed over the past 10 years across the country, including South Dakota. Simulation allows healthcare students and professionals to be exposed to a variety of situations that closely mimic actual patient care. Although simulation education is often costly, many programs have found that the financial benefits of fully competent healthcare professionals substantially outweigh the cost of this type of education. Mistakes through simulation can be discussed and corrected without the risk of monetary cost or patient harm. The Sanford School of Medicine (SSOM) did not offer a simulation course for medical students despite having the Parry Center, a full simulation laboratory, on campus.

Project Description: The goal of this project was to design a two-week elective course for SSOM students during their fourth year that better prepared them for various surgical situations they will encounter during residency training. A survey of South Dakota residents assessed what types of tasks and techniques they felt needed to be focused on, and a pilot curriculum was developed. The curriculum also used modules from the American College of Surgeons’ Medical Student Simulation Based Surgical Skills Curriculum. In addition to the basic surgical skills, students had the opportunity to focus on certain skill sets that will be relevant to certain residency directions. A two-week elective course was designed.

Outcome: Several medical schools across the country have developed courses and electives focused on simulation education. By assessing the need for this type of program at the University of South Dakota (USD) we developed an elective opportunity that is enjoyable, informative, and specifically designed for South Dakota students interested in surgery. The course was piloted April 2014 with 11 USD medical students. The students were given pre- and post-course surveys to assess how they felt their knowledge was enhanced through this elective course. It was found that overall the students entering the Simulation Boot Camp course already had a relatively high level of knowledge when it came to basic surgical techniques needed for residency. Nevertheless, students’ competence and confidence increased in almost all areas addressed during the course.

Conclusions: It was found that South Dakota medical students participating in the Simulation Boot Camp pilot course already possessed a significant amount of knowledge necessary for beginning a surgical residency. Nevertheless, students felt that they gained competence and confidence during this elective course in areas of surgical technique, medical management, and patient care. The SSOM offers incredible training for medical students, and the addition of a simulation boot camp allows for an even more robust learning experience. The addition of a structured, well-designed simulation course is expected to enhance and deepen the skills of physicians at the start of their career.
Assessing a Primary Care Provider’s Knowledge of and Barriers to Addressing Childhood Obesity

By Molly Soholt, MSIV

Mentors: Jeffry Meyer, MD; and Karla Lester, MD

Background: Over one-third of our nation’s children aged 2 through 19 are overweight or obese, a rate that has tripled since 1980 (PMID: 23635310). Overweight or obese children are more likely to be overweight or obese as adults and to develop diseases such as cardiovascular disease and diabetes (PMID: 23710345). Current literature suggests that most physicians do not have adequate time to provide counseling on obesity and do not believe counseling is an effective strategy for change, although it has been shown to have positive outcomes in teenagers (PMID: 20083518). If physicians believe that obesity counseling results in actual change, they were more likely to discuss overweight and obesity (PMID: 23635310). Improving the manner in which physicians address overweight and obesity is likely to improve outcomes.

Methods: Teach a Kid to Fish is a non-profit organization whose mission is to prevent and reduce childhood obesity by encouraging healthy eating and physical activity. A survey was developed to determine what prevents primary care providers in South Dakota and Nebraska from counseling patients on obesity, nutrition and physical activity, and to understand how they view the effectiveness of their counseling. The survey was designed on SurveyMonkey and was distributed via e-mail and hard copy form to pediatricians and family practice physicians across Nebraska and South Dakota (n=46). Statistical analysis using ANOVA was performed to compare training effects on counseling efforts.

Results: Barriers preventing the counseling on overweight/obesity were examined. Frequently identified barriers included compliance by patient and family (21.4 percent), time (20.1 percent), compliance by patient (16.2 percent) and lack of community resources (14.3 percent). In assessing (on a 1-7 scale, 7 being total agreement) whether physician counseling would result in change, modest agreement was observed for obesity (mean: 4.04), nutrition (mean: 4.46) and physical activity (mean: 4.28). Barriers preventing providers from believing their counseling would be effective were examined. Physicians reported that a lack of referral resources in the community (26.1 percent), better reimbursement (13.9 percent), training on recommendations regarding the prevention, assessment, and treatment of overweight/obesity (13 percent) and lack of time (12.2 percent). Additional training in obesity counseling or motivational interviewing did not affect a physician’s confidence in their ability to provide information, motivate their patients, or support their patients in making lifestyle changes. Motivational interviewing training did affect a provider’s belief that counseling patients on physical activity would result in actual change for those trained (4.8 vs. 4 for those without additional training). This was not found for nutrition or physical activity.

Conclusion: The results demonstrate that time is a primary inhibiting factor preventing the counseling of patients. Future studies should focus on the effectiveness of obesity counseling, as this will increase the frequency of counseling (PMID: 23635310). Additional resources are needed for providers to assist in their management of child overweight and obesity. Physicians identify themselves as being confident to address key issues surrounding childhood overweight and obesity, and additional training did not further improve this level of confidence. However, current recommendations on management of childhood weight were not always used. These results should be considered in a comprehensive effort to improve management of childhood overweight and obesity.
Health Behavior Education of a Small Chinese Fishing Community

By: Na Smith, PhD, MSIV
Mentor: Richard Parent-Johnson, PhD

Background: The Chinese fishing village is 15 minutes away by ferry from mainland China. This community has been medically underserved for generations. The two-room clinic on the island provides basic medical needs and medications. The current clinic “doctor” was trained in a trade school after completing middle school education. Health education is lacking in this community.

Project Description: The project was approved by the Institutional Review Board (IRB) of the University of South Dakota and by the IRB of Shandong University QiLu Hospital in China, door-to-door face-to-face health behavior survey was conducted with 45 adult participants in the community. Data analysis identified several serious hazardous health behaviors. The most prominent ones were smoking, alcohol use and diet. Three educational posters targeting each of these areas were developed and sent to the community.

Outcome: The local community welcomed the help provided by this project. The local leaders provided assistance in conducting the survey and displaying the educational posters. The methods we were able to utilize to provide the education was very limited due to the educational level and the technology resources in the community. Health education targeting smoking, alcohol use and dietary change were provided via visually attractive posters. These posters are currently displayed on the walls of the local clinic.

Conclusions: This project identified several serious hazardous health behaviors that contribute to the rising health issues in the community. Health educational posters targeting the three most serious hazardous behaviors were sent to the island and displayed at the local clinic. Communication with the clinic provider indicated people were interested in reading the posters. Though no responses of viewers were collected, this project has planted seeds in the community to be mindful of their health behaviors in order to improve their health.
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Physicians have used the term “overactive bladder” for almost two decades. This terminology was not widely used by the medical community until 1997, when a pharmaceutical company-sponsored symposium promoted tolterodine. In the following year, the U.S. Food and Drug Administration (FDA) approved tolterodine to treat “symptoms of overactive bladder.” Although this terminology was originally used by a pharmaceutical company to attain commercial gain, identifying overactive bladder as a syndrome has encouraged many women to seek treatment from their doctors.

In spite of the increased use of overactive bladder syndrome (OAB) as a medical term and the high prevalence of OAB in the general population, one study found that less than one-fourth of patients with OAB had been properly recognized and evaluated. Possible reasons for under-treatment include lack of patient motivation to seek care, patient belief that OAB is part of the normal aging process, and primary care physicians’ unfamiliarity with diagnosing and treating this condition. There is also an observed lack of continuity between inquiring about OAB symptoms in the PQRI-CMS questionnaire before the appointment and follow up for positive responses during the appointment.

Untreated OAB has a profound impact on a patient’s quality of life. Although it is not a life-threatening condition, urinary urgency and frequency associated with this condition can limit travel and other daily activities, as the patient must be sure that a restroom is always within a short walking distance. Nocturia associated with OAB increases the risk of falls and fractures, especially in the elderly population.

The International Continence Society defines OAB by urinary urgency, urinary frequency, and small volume voids. These symptoms may or may not be accompanied by urge incontinence and nocturia. OAB is a condition in which there is no identifiable cause of these symptoms and all other potential causes have been ruled out. OAB affects more women than men, and some studies have shown that OAB affects up to 19.1 percent of elderly women in the U.S. OAB becomes more prevalent with increasing age and is estimated to affect 36 million people in U.S. Effective treatment of OAB not only requires the physician to take a systematic approach to the multiple therapies available for OAB, but also for the patient to be engaged in this process and to provide feedback on these therapies.

Pathophysiology

Under normal physiologic conditions, the bladder fills with urine and stretches to accommodate the increased volume. In a healthy individual, the bladder can accommodate 300 to 600 mL of fluid with minimal rise in pressure. As the volume of urine increases and the bladder stretches, the pressure in the bladder remains lower than the pressure in the urethra. As long as urethral resistance...
is greater than pressure in the bladder, continence is preserved. During micturition when the detrusor muscle is contracted to empty the bladder, urethral resistance decreases.¹

Micturition is regulated by the autonomic nervous system. The parasympathetic and sympathetic divisions of the autonomic nervous system modify bladder capacity through their actions on muscarinic, alpha, and beta receptors. The parasympathetic nervous system utilizes acetylcholine to activate muscarinic receptors to allow for bladder emptying, while the sympathetic nervous system utilizes norepinephrine to activate alpha and beta receptors to promote bladder filling.

Acetylcholine activates muscarinic M₃ receptors, which initiates a cascade of interactions that result in bladder contraction. When the M₃ receptor is stimulated, it activates G proteins to interact with phospholipase C. Phospholipase C generates inositol triphosphate, which releases calcium from the sarcoplasmic reticulum and causes contraction of the bladder.

Sympathetic nerves release norepinephrine at the neuromuscular junction. Norepinephrine acts on the beta-3 receptor to activate adenylate cyclase and cyclic AMP, which results in relaxation of the bladder muscle to allow for accommodation or filling of the bladder.

The pathophysiology of OAB is related to weakening of the pelvic floor muscles and idiopathic, involuntary contractions of the detrusor muscle. The contractions of the detrusor muscle increase the pressure within the bladder and result in urinary urgency with or without incontinence.¹

There are several risk factors implicated in the development of OAB. Increasing parity, body mass index, and age all increase the risk of developing OAB. Incidence of OAB rises significantly after age 60. Because removal of the uterus can alter the pressure dynamics of the bladder and urethra, women who have had a hysterectomy have an increased risk of developing OAB. Women are also predisposed to developing OAB if they experience stress urinary incontinence with the first pregnancy, recurrent UTIs, or fecal incontinence. Medications such as diuretics, caffeine, and estrogen increase the risk for OAB and exacerbate existing OAB.

**Evaluation and Diagnosis**

Since OAB is a diagnosis of exclusion, several conditions must be ruled out before diagnosing a patient with OAB. The presenting symptoms of OAB are urinary frequency and urinary urgency, with or without nocturia and incontinence. These symptoms can also present in patients with recurrent UTIs or with interstitial cystitis, also known as bladder pain syndrome.⁴ Physicians should screen patients for UTIs and rule out urinary retention with a post-void residual straight catheter or with ultrasound. OAB-like symptoms can also be seen in diabetes mellitus and neurologic conditions such as Parkinsonism, multiple sclerosis, cerebrovascular incident, congenital defects and spinal cord defect (Table 1). In a patient with OAB symptoms, workup to exclude these pathologies is warranted.³

<table>
<thead>
<tr>
<th>Table 1. Mechanisms by Which Medical Conditions Can Affect Bladder Function</th>
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<tbody>
<tr>
<td>Impaired neuromuscular function or impaired tissue integrity</td>
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<tr>
<td>• Parity and vaginal birth</td>
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<tr>
<td>• Prior pelvic surgery</td>
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<tr>
<td>Impaired sensorimotor function</td>
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<tr>
<td>• Diabetes mellitus</td>
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<tr>
<td>• Neurologic disease (Parkinsonism, multiple sclerosis, spinal cord injury, congenital defect, cerebrovascular accident, congenital defect)</td>
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<tr>
<td>Abnormal stressors (volume, pressure)</td>
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<tr>
<td>• Congestive heart failure</td>
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<tr>
<td>• Chronic obstructive pulmonary disease</td>
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<tr>
<td>Cognitive impairment or failure of voluntary bladder control</td>
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<tr>
<td>• Dementia</td>
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<tr>
<td>• Psychiatric disease</td>
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**Treatment**

**First Line Treatment**

First line treatment for OAB involves non-invasive, non-pharmacologic techniques to decrease urinary frequency and urinary urgency. The two main approaches to first line treatment are lifestyle modifications and exercises to strengthen the pelvic floor muscles. Lifestyle changes include reducing caffeine consumption, reducing fluid intake, and delaying voiding through bladder training.⁵ Pelvic floor exercises, also known as Kegel exercises, involve pelvic floor muscle training (PFMT), which can increase urethral resistance and improve bladder control.² Physicians typically refer patients who may benefit from PFMT to physical therapists or continence nurses.⁸

The American College of Physicians (ACP) recommends a trial of nonpharmacologic options for all patients with OAB. Specifically, the ACP reported that pelvic floor muscle training is associated with decreased OAB symptoms and improved quality of life for most patients. For overweight or obese women who suffer from OAB, the
ACP found that weight loss results in improved urinary continence. By utilizing non-invasive methods first, patients avoid the cost and potential side effects of pharmacologic treatment for OAB.

If patients find that first line treatment has not improved their OAB symptoms, they should continue first line treatment and start pharmacologic management. Second line therapies can be used in conjunction with first line therapies, and this approach has been shown to improve outcomes more than second line therapy alone.9

Second Line Treatment
Medications are second line treatment for OAB. Antimuscarinic drugs facilitate bladder relaxation and are the first line drugs for OAB syndrome. This class of drugs competes with acetylcholine to bind to muscarinic receptors and block their activation. Antimuscarinics have come to replace older anticholinergics such as tricyclic antidepressants in the management of OAB. The antimuscarinic drugs most commonly prescribed to treat OAB are oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, and trospium. These drugs have been shown to be effective in managing OAB, specifically urgency, incontinence, and nocturia.7 No one drug has been shown to be more effective than the others in improving symptoms of OAB.10

Some of these medications have several modes of administration, including immediate release tablets, extended release tablets, and transdermal formulations. Extended release medications tend to have fewer side effects than immediate release formulations, but the extended release products are often more expensive. The increased cost is a limiting factor for many patients.

Beta-3 agonists are also used in the treatment of OAB, and the only FDA-approved beta-3 agonist is mirabegron. As a beta-3 receptor agonist, mirabegron stimulates the sympathetic nervous system and reduces bladder excitability. The American Urological Association conducted a meta-analysis comparing the efficacy of mirabegron and placebo at reducing symptoms in OAB patients. On average, mirabegron reduced incontinence episodes by 1.5 episodes per day and the number of voids by 1.75 voids per day.8 The outcomes did not change significantly when the dose of mirabegron was increased from 25 mg to 50 mg. Mirabegron may offer an alternative to antimuscarinics for the management of OAB, as mirabegron does not have antimuscarinic side effects.

Dry mouth, constipation and vision changes are the most common side effects observed with antimuscarinic
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In some clinical trials, approximately two thirds of patients on generic immediate-release oxybutynin experienced dry mouth. Other known side effects include urinary retention, gastroesophageal reflux, constipation and blurry vision.

Contraindications to antimuscarinic therapy include closed angle glaucoma and gastroparesis. Antimuscarinic medications should not be given to patients with these conditions unless the consulting ophthalmologist and/or gastroenterologist approve this treatment. Since antimuscarinics will exacerbate urinary retention, patients with urinary retention should not receive this class of drugs unless the patient is comfortable with self-catheterization.

Of the antimuscarinic drugs, only oxybutynin has been found to cause significant central nervous system deficits. The central nervous system side effects have a wide range of manifestations, including dementia, psychosis, personality disorders, compromised attention span, impaired memory, and dizziness. The risk factors that increase the likelihood of adverse side effects in the central nervous system are concurrent medications and age. Medications that put a patient at greater risk for central nervous system side effects are antiparkinsonian medications, tricyclic antidepressants, antihistamines, bronchodilators, antispasmodics, and antiarrhythmic medications. Elderly patients have a higher incidence of both OAB and dementia. Therefore caution should be taken in prescribing oxybutynin to this population since the effective dose of oxybutynin required to treat OAB increases with age.

In spite of the increased risk for central nervous system side effects and increased incidence of dry mouth, oxybutynin is often prescribed because it is inexpensive.
and effective. Trials have shown that oxybutynin and tolterodine are equally efficacious, but that tolterodine has fewer side effects. Because the lipophilicity of tolterodine is 350 times lower than that of oxybutynin, tolterodine does not cross the blood brain barrier as easily as oxybutynin. Trospium is another drug of this class that may cause fewer CNS side effects. Trospium is a quaternary amine, and its larger size prevents it from crossing the blood brain barrier (Table 2). Their respective properties make tolterodine and trospium more favorable for patients with risk factors for CNS side effects.

To manage OAB successfully, patients may need to remain on pharmacologic therapy for life. Lee et al. studied 558 patients in a prospective study to evaluate OAB symptoms after discontinuation of antimuscarinic therapy. They found that within three months of discontinuing the medication, patients experienced a return of urinary frequency, urgency, and incontinence episodes. Their study also found that 65 percent of the patients desired to restart antimuscarinic therapy at this time. Another study found that patient compliance to antimuscarinic therapy for OAB declined by 60 percent by six months, which suggests that either the adverse side effects resulted in discontinuation or that patients developed tolerance to the drugs. More research is necessary to determine if antimuscarinic therapy is effective at treating OAB for longer than six months.

Mirabegron can cause headache and a mild increase in blood pressure, and providers should therefore be cautious when prescribing mirabegron to a patient with existing hypertension. The prevalence of these adverse effects is low and is generally not increased when the dose of mirabegron is increased.

Physicians should educate patients about common side effects when prescribing one of the above medications. The physician may also treat these side effects prophylactically. Simple measures to prevent adverse side effects include eye drops for dry eyes, mouthwash for dry mouth and stool softeners for constipation.

Although some patients experience relief from their OAB symptoms with the first trial antimuscarinic therapy, other patients continue to experience urinary frequency, urgency, incontinence and nocturia. The primary care physician should employ several strategies with the medications before conceding to pharmacologic failure. Primary care physicians should ask patients to start a bladder diary at the start of antimuscarinic therapy to measure efficacy of the medication, and patients should expect to be on antimuscarinic therapy for several weeks before symptoms improve. In addition, pharmacologic failure is not considered until the patient has tried two to three medications of this class. Drake et al. suggests that before referring a patient who has failed pharmacologic therapy to a specialist, the primary care physician should determine if the cause of the failure was due to insufficient duration, insufficient dose, incorrect antimuscarinic agent, or discontinuation due to adverse side effects.

Antimuscarinic therapy has been found to improve the symptoms of overactive bladder by reducing frequency and urgency. However, Reynolds et al suggest that antimuscarinic therapy for OAB is limited and usually does not resolve OAB symptoms completely. Primary care physicians should therefore inform patients that pharmacologic therapy is a partial solution to OAB. For patients who continue to experience disruptive OAB symptoms after trials of pharmacologic therapy, referring them to a specialist for third-line therapy may be the next appropriate step.

**Third Line Treatment**

Third line therapies include intradetrusor onabotulinum toxin A injections, Interstim (sacral neuromodulation) and percutaneous tibial nerve stimulation. These measures are reserved for patients who have not responded to first or second line therapy and are almost exclusively performed and managed by a specialist in urogynecology. Third line therapies include measures that are more invasive and pose more potential risks to patients.

**Intradetrusor Onabotulinum Toxin A**

If a patient discontinues pharmacologic therapy citing side effect profile, drug inefficacy, or noncompliance, the patient may be a candidate for intradetrusor onabotulinum toxin A (IOTA) injections. IOTA may be a good option because it involves one set of bladder injections that last several months instead of a daily pill. This set of injections provides varying degrees of relief, and the relief depends on the patient and dose of onabotulinum toxin used.

The FDA approved intradetrusor onabotulinum toxin A injections for the treatment of overactive bladder in January 2013. Similar to injections of onabotulinum toxin A into facial muscles, the goal of introducing onabotulinum toxin A is to relax the detrusor muscle of the bladder. This should increase bladder capacity and reduce urinary frequency and urgency. Onabotulinum toxin A inhibits contraction of the detrusor muscle by blocking release of acetylcholine vesicles from the presynaptic nerve and into the synapse. This results in temporary loss of neural stimulation and relaxation of the muscle. The most common side effects

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**Primers in Medicine**

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following IOTA injections are urinary retention and urinary tract infections. Education is provided regarding self-catheterization in case the patient is unable to void spontaneously following the procedure.

The FDA approves administration of 100 units of onabotulinumtoxin A for this in-office procedure, but the literature is still not clear regarding the optimal technique, dose, and follow-up for IOTA. Areas of dissent include dose (ranging from 100-300 IU), the number of injections with each procedure (from 15 to 30), and whether the trigone of the bladder is injected. One study found that the prevalence of urinary retention increased from 13 to 43 percent when the IOTA dose increased from 100 units to 200 units. Because of the high rate of urinary retention in the group receiving 200 units, the trial was stopped and patients were not followed long-term. In the group that received 100 units, the need for self-catheterization decreased with time, with rates of 11 percent immediately after the procedure, 5 percent at two months, 3 percent at four months, and 1 percent at six months after the procedure.11

Fortunately, the reduction in OAB symptoms provided by IOTA lasts longer than the need for self-catheterization. Participants reported adequate control over OAB symptoms for an average of 8.8 months. Twelve months after injection, 38 percent of women reported adequate control over their OAB symptoms. Although this procedure is relatively new, experts are cautiously optimistic about the relief it can provide for those who suffer with pharmacologically resistant OAB.3

Visco et al. compared anticholinergic therapy to IOTA. This study found that the methods were equally efficacious at controlling symptoms, but that IOTA provided longer-lasting relief. One study followed two groups of OAB participants for six months, treating one group with antimuscarinic therapy and one with IOTA. Before intervention, participants reported an average of five episodes of urgency urinary incontinence per day. After six months of intervention, the antimuscarinic group had 3.4 fewer episodes and the IOTA group had 3.3 fewer episodes of urgency urinary incontinence per day. However, the IOTA group had a higher proportion of participants reporting complete resolution of OAB symptoms, with 27 percent of women in the IOTA group and 13 percent of women in the antimuscarinic group. IOTA is also associated with a lower rate of dry mouth than antimuscarinic therapy, with 10 percent of women on IOTA and 31 percent of women on anticholinergic agents reporting dry mouth.5

Sacral Neuromodulation
Sacral neuromodulation is an FDA-approved therapy for the treatment of OAB. Sacral neuromodulation involves surgical placement of an electrode stimulator. Since OAB may be caused by excessive neural input, the goal of sacral neuromodulation is to regulate neural excitation of the bladder. Several theories may explain the mechanism of sacral neuromodulation. Sacral neuromodulation may increase urethral sphincter tone and prevent leakage of urine by stimulation of motor axons innervating the external urethral sphincter. Stimulating these neurons may increase afferent signaling of the external urethral sphincter to the spinal cord. Stimulating afferent neurons from the bladder to the spinal cord result in sympathetic activation and relaxation of the bladder.12

Although the exact mechanism of sacral neuromodulation is not known, the outcomes are encouraging. In a study that examined outcomes five years after patients underwent sacral neuromodulation, half of the patients reported 50 percent or greater improvement of symptoms. Fifteen percent of patients reported that their symptoms remained completely resolved.13

Sacral neuromodulation involves placement of an electrode along the sacral nerve. Placement of the electrode is a surgical procedure that lasts about one hour, and the patient usually is discharged the same day of surgery. For the first part of the procedure, the patient remains conscious while the physician uses fluoroscopy to guide placement of the electrode along a sacral nerve. The patient remains conscious to demonstrate that he or she maintains sensation and motor control along the affected derm atome after the electrode is placed. The most effective nerve root in eliciting a motor response (a bellows-like contraction of the anus and plantar flexion of the hallux) at the lowest stimulation voltage is chosen, typically via the S3 foram en.

After electrode placement, the patient is sedated for the second part of the procedure. In the second stage, the electrode is connected to a pulse generator by cables. The settings on the pulse generator can be adjusted by an external remote. Once the electrode is activated, it will send electrical pulses along the nerve that interfere with firing. The patient can adjust the settings according to the level of desired symptom relief.

Percutaneous Tibial Nerve Stimulation
Percutaneous tibial nerve stimulation (PTNS) is a procedure in which the tibial nerve is stimulated to relax the detrusor muscle. This is an office procedure in which
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DAKOTACARE’s exceptional distinction is its broad provider network. Patients can stay with their doctor, choose their hospital and go to the pharmacy of their choice.

~ E. Paul Amundson, MD, Chief Medical Officer for DAKOTACARE

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DAKOTACARE and the South Dakota State Medical Association have enjoyed a long history of cooperation and mutual trust over the years, with direct involvement of South Dakota Physicians. This is what sets DAKOTACARE apart.

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~ James A. Engelbrecht, MD, Associate Medical Director for DAKOTACARE

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a needle is inserted into the posterior tibial nerve for several minutes, weekly for 12 weeks and then as needed based upon symptom response. PTNS is based on animal research studies in which stimulation of the hind leg resulted in detrusor muscle relaxation. Several studies have sought to explain the mechanism of action of PTNS, but no definitive conclusions can be drawn. The studies show that PTNS may regulate bladder control by modifying neural input into the bladder or by modifying how the myocytes of the bladder respond to neuronal firing.14

Four randomized control trials have examined the efficacy of percutaneous tibial nerve stimulation in treating OAB. These studies have found that percutaneous tibial nerve stimulation improves the symptoms of OAB in 37 to 100 percent of patients. No adverse effects have been reported in the literature, although only one randomized controlled trial has studied PTNS patients for a full year after the procedure. Dr. Finazzi Agro’s study explored the possible placebo effect of PTNS in treating the symptoms of OAB. The study classified any patient whose symptoms improved by 50 percent or more as a “responder.” They found that 71 percent of the PTNS group were responders and 0 percent of the placebo group were responders, with a p-value <0.0001.14

Conclusion
Successful management of OAB involves physician directed systematic trials of therapies in conjunction with patient engagement and compliance. Since the pathophysiology of OAB is not completely understood, it is important that each patient with OAB symptoms be treated on an individual basis according to the severity of symptoms and comorbid illnesses.

REFERENCES

Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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SDSMA members have the opportunity to provide input on important issues facing the practice of medicine. The SDSMA wants to know about issues physicians are struggling with, or for which SDSMA action may be needed.

Issues are considered and discussed during an open forum. The next membership open forum is 10 a.m. November 4 at the RedRossa Italian Grille Highland/Hills meeting room in Pierre.

This is an opportunity to bring issues to the attention of the SDSMA, to discuss issues submitted by fellow physicians, and to get perspective on issues from physicians across South Dakota.

Please visit www.sdsm.org to submit a policy issue. Forms must be received by October 12 to be considered at the open forum.
A Primer on Diagnostic and Financial Implications of D-dimer Testing

By Kalyan Chakravarthy Potu, MD; Sujithasree Ketineni, MBBS; and Randall Lamfers, MD

Abstract
Given the high incidence of deep vein thrombosis/pulmonary embolism (DVT/PE) (300,000 to 600,000 per year in the U.S.) and the 30 percent mortality rate associated with undiagnosed PE, diagnostic evaluation is very important. One of the tools used to evaluate for DVT and PE is D-dimer testing. A negative D-dimer test, along with a low Wells clinical probability score, can safely rule out DVT/PE without the need for additional imaging. This approach can reduce cost; however, D-dimer testing is not indicated in all patients. D-dimers can be elevated in patients without DVT/PE, like the elderly. The consequences of over utilizing D-dimer testing can lead to excessive imaging, unnecessary contrast exposure, unnecessary exposure to radiation, and increased cost. In this primer, we provide a brief literature review of D-dimer testing for the diagnosis of DVT and PE. We also discuss the overutilization of D-dimer testing and its financial burden on the health care industry.

Introduction
Estimates of the number of people affected by DVT/PE ranges from 300,000 to 600,000 each year in the U.S. (on average, one to two per 1,000 and, in those over 80 years of age, as high as one in 100), per the Centers for Disease Control and Prevention. Untreated, pulmonary emboli have a mortality rate of 30 percent; however, if treated, the mortality rate decreases to 2 to 8 percent.1 There are several tools in existence to evaluate for DVT or PE. These include D-dimer testing, the venous duplex ultrasound, computed tomography (CT) angiography of the chest, and the ventilation/perfusion scan.

The purpose of this primer is to focus on the utility and proper use of D-dimer testing. We will explore how the D-dimer test is run, its interpretation, and when to use it. We will also discuss how overutilization of D-dimer testing is causing increasing health care expenditures. Excessive overutilization of D-dimer testing can lead to unnecessary imaging, unnecessary contrast exposure, unnecessary exposure to radiation, and financial wastefulness in terms of increased cost.

Physiology of D-Dimer Testing
The D-dimer antigen is a marker for fibrin degradation.1 In a review by Adam, Key, and Greenberg, they describe a sequence of events that leads to the formation of the D-dimer.3 First, the fibrinogen is broken into fibrin monomers by thrombin. These fibrin monomers then join with other monomers of fibrinogen to make larger polymers and eventually protofibrils. Then, through thrombin activation of factor VIII, crosslinks are formed at the D-domains. Plasmin eventually breaks the crosslinks and exposes the D-antigen. D-dimer testing uses monoclonal antibodies that identify D-dimer antigen epitopes. The assays are different, as they measure different D-dimer epitopes. This leads to varying reference ranges, sensitivity, and specificity.

Factors Affecting the D-Dimer Test
The D-dimer test is helpful for ruling out DVT/PE but not for making a diagnosis of either disorder. In a large meta-analysis, enzyme-linked immunosorbent assay (ELISA) D-dimer tests had a sensitivity of about 95 percent, excluding DVT and PE. This indicates that a negative ELISA D-dimer test is strong evidence against DVT or PE.4 D-dimer assay specificity is as follows for three age groups: less than 40 years – 70 percent; 40 to 60 years – 25 percent; and greater than 60 years – 5 percent.5 The low specificity means that a positive D-dimer is not diagnostic for DVT/PE. The reason for the low specificity is that the D-dimer can be increased by a number of different factors. In a multicenter, observational study of 4,346 patients who presented to emergency departments...
(ED) and had D-dimers drawn, D-dimers were increased in females, those of increased age, African-Americans, those who underwent surgery within the past four weeks, and those with cancer, immobility, connective tissue diseases, end-stage renal disease, sickle cell disease, and/or pregnancy (particularly the third trimester, where 96 percent of patients tested positive). The study authors further found that warfarin use was protective of an elevated D-dimer. In this study, 44 percent of ED patients had a positive D-dimer, but only 11 percent of those positive D-dimers were also positive for PE.

The reference concentration of D-dimers is less than 500 µg/L fibrinogen-equivalent units; however, D-dimer concentrations increase with age. This leads to a high proportion of older patients with D-dimer concentrations higher than the conventional cut-off value (500 µg/L). In a large, retrospective study, the age-adjusted cut-off value was defined as age (years) × 10 µg/L for patients aged over 50 years. For example, for a patient who is 69 years old, a D-dimer concentration below 690 µg/L would be considered normal. Given the low specificity of the D-dimer assay in the diagnosis of DVT/PE, the positive D-dimers can then lead to an additional increase in cost. In another retrospective study, they reviewed 220 patients with D-dimers drawn in the hospital. Of the 220 patients, 118 had positive D-dimers, but only five had PE. The positive D-dimers led to an additional 92 tests at a cost of more than $200,000.

**Clinical Utility of D-Dimer Testing**

A Wells clinical score for DVT/PE should determine further diagnostic investigations for DVT/PE. A higher Wells score in a patient suspected of having DVT/PE indicates a higher clinical probability of DVT/PE in that patient. Doppler ultrasonography is recommended in patients with high Wells scores, and D-dimer testing is recommended in patients with low scores. An unlikely Wells score (less than or equal to 1) combined with a negative D-dimer test result can safely exclude deep vein thrombosis, missing less than 2 percent of cases.

In a prospective study including 357 outpatients with clinical suspicion of DVT, an algorithm that ruled out DVT among patients with low Wells clinical probability with negative D-dimer was compared to traditional use of compression ultrasonography and/or contrast venography for all patients. At no significant difference in diagnostic efficacy the algorithm based approach was cost-effective.

Separate Wells scoring systems exist for the clinical probability assessment of DVT and PE, as shown in the tables.

### Table 1. Wells’ Criteria: Clinical Assessment for Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralysis, paresis or recent orthopedic casting of lower extremity</td>
<td>1.0</td>
</tr>
<tr>
<td>Recently bedridden (more than 3 days) or major surgery within past 4 weeks</td>
<td>1.0</td>
</tr>
<tr>
<td>Localized tenderness in deep vein system</td>
<td>1.0</td>
</tr>
<tr>
<td>Swelling of entire leg</td>
<td>1.0</td>
</tr>
<tr>
<td>Calf swelling 3 cm greater than other leg (measured 10 cm below the tibial tuberosity)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pitting edema greater in the symptomatic leg</td>
<td>1.0</td>
</tr>
<tr>
<td>Collateral non varicose superficial veins</td>
<td>1.0</td>
</tr>
<tr>
<td>Active cancer or cancer treated within 6 months</td>
<td>1.0</td>
</tr>
<tr>
<td>Alternative diagnosis more likely than DVT (Baker’s cyst, cellulitis, muscle damage, superficial venous thrombosis, post phlebitic syndrome, inguinal lymphadenopathy, external venous compression)</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

### Table 2. Wells’ Criteria and Modified Wells’ Criteria: Clinical Assessment for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms of DVT (leg swelling, pain with palpation)</td>
<td>3.0</td>
</tr>
<tr>
<td>Other diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (≥ 3 days) or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

#### Probability

<table>
<thead>
<tr>
<th>Probability</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>3.0 to 8.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.0 to 2.0</td>
</tr>
<tr>
<td>Low</td>
<td>-2.0 to 0</td>
</tr>
</tbody>
</table>

#### Traditional Clinical Probability Assessment (Wells’ Criteria)

<table>
<thead>
<tr>
<th>Probability</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.0 to 6.0</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 4.0</td>
</tr>
</tbody>
</table>

#### Simplified Clinical Probability Assessment (Modified Wells’ Criteria)

<table>
<thead>
<tr>
<th>Probability</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE likely</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>PE unlikely</td>
<td>&lt; or = 4.0</td>
</tr>
</tbody>
</table>
Table 3. Algorithm for Diagnosis of PE

Clinical suspicion for acute pulmonary embolism
   - Perform clinical probability assessment (use Wells scoring)
      - Hemodynamically stable
         - Low clinical probability
            - Perform D-dimer assay
               - Normal
                  - Perform multidetector CT Scan
                     - Negative
                        - Pulmonary embolism excluded
                     - Positive
                        - Pulmonary embolism confirmed
         - Hemodynamically unstable
            - Intermediate/high clinical probability
            - Not critically ill
            - Critically ill and high clinical probability

Table 4. Algorithm for Diagnosis of DVT

Clinical suspicion for DVT
   - Determine clinical probability (use Wells scoring)
      - Low
      - Intermediate or high
         - Perform D-dimer assay
            - Negative
               - DVT excluded
            - Positive or not available
               - Perform compression ultrasonography
                  - Negative
                     - DVT excluded
                  - Positive
                     - DVT confirmed
         - Perform compression ultrasonography
            - Negative
               - Repeat compression ultrasonography in 1 week
                  - Negative
                     - DVT excluded
                  - Positive
                     - DVT confirmed
Concluding Summary

D-dimer testing has good sensitivity in diagnosing DVT/PE but does not have great specificity. Other factors can cause elevated D-dimers, such as being female, elderly, and/or African-American. Having recent surgery, active cancer, connective tissue diseases, end-stage renal disease, and/or pregnancy can also elevate D-dimers. Radiologic testing for DVT or PE with every D-dimer elevation can lead to increased costs.

D-dimer testing has excellent sensitivity and can rule out DVT/PE with a highly negative predictive value. A negative D-dimer test and a low Wells clinical probability score can safely rule out DVT/PE without the need for additional imaging. This approach can reduce costs. Low specificity means a D-dimer elevation cannot accurately rule in (i.e., diagnose) DVT/PE. Therefore, imaging is used instead of D-dimer testing to diagnose DVT/PE, if the Wells clinical probability scoring is intermediate to high.

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Randall Lamfers, MD, Assistant Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, South Dakota.
Introduction

Fluoroquinolones (FQs) are a widely prescribed class of antibiotics in the U.S., and currently include five systemic FQs: ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin. FQ prescribing rates have rapidly increased and accounted for approximately 32.8 million prescriptions in 2014. Ciprofloxacin is the most commonly prescribed FQ with the primary indication of urinary tract infection (UTI) (Table 1). However, it is estimated that approximately 53 percent of quinolone prescriptions are for off-label indications.

Currently known and well documented adverse effects associated with the three most commonly prescribed FQs (levofloxacin, ciprofloxacin, and moxifloxacin) are listed in Table 2. While most of these adverse effects are reported at very low frequencies, there are increasing direct patient reports and published case studies outlining severe adverse effects resulting in permanent disability.

FDA Reviews FQ Indications and Safety

The U.S. Food and Drug Administration (FDA) Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met in November of 2015 to review new FQ safety information and use of FQs in uncomplicated infections. The first part of the FDA review evaluated the effectiveness of antibiotic treatment, not specifically FQs, for acute bacterial sinusitis (ABS), uncomplicated UTI (uUTI), and acute bacterial exacerbation of chronic bronchitis (ABECB). The FDA literature evaluation of ABS included 20 placebo controlled trials and several meta-analyses. A meta-analysis of nine randomized trials consisting of 2,547 patients assessed whether certain symptomology could identify responders to antibiotic treatment. It concluded that no subset of patients could be identified based on a pattern of symptoms that responded to antibiotics, and antibiotic treatment may offer no benefit or have harmful effects. A 2012 Cochrane Review by Lemiere et al. on rhinosinusitis in adult patients concluded that antibiotics are not warranted in acute non-severe rhinosinusitis given antimicrobial resistance concerns and low incidence of severe complications. In comparison, a 2014 Cochrane Review by Ahoovuo-Salorana et al. on maxillary sinusitis in adult patients suggested moderate evidence for small benefit; however, 80 percent of patients improved with no antimicrobial treatment. Furthermore, the Infectious Disease Society of America (IDSA) 2012 guidelines state that 90 percent of ABS is of viral etiology and it is too difficult to differentiate between viral versus bacterial. The IDSA recommendation is to reserve treatment with antibiotics for those with severe symptomatology. Based off of all literature evaluated, the FDA concluded:

- Only a small number of trials demonstrated benefit from antimicrobial therapy.
- There was a high placebo-response rate.
- Differentiating between viral and bacterial etiology based on symptoms is not reliable.
- Antimicrobials should be reserved for those with severe symptoms.

Table 1. Fluoroquinolone Prescription Frequency and Indication

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Number of RXs*</th>
<th>Most Common DX**</th>
<th>2nd Most Common DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>17.9 million</td>
<td>43% UTI</td>
<td>4% prostatitis</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>9.5 million</td>
<td>22% pneumonia</td>
<td>13% UTI</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>1.8 million</td>
<td>22% bronchitis</td>
<td>19% pneumonia</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>119,000</td>
<td>90% bronchitis</td>
<td>NA</td>
</tr>
</tbody>
</table>

*RXs = Prescriptions **DX = Diagnosis
In the FDA’s review of ABECB, 15 placebo-controlled trials in varying levels of disease severity were included.1 The level of severity was poorly defined between studies but the FDA considered any patient who was treated as an outpatient as mild severity. Additionally, the committee reviewed several published guidelines and review articles regarding treatment of bronchitis in COPD.11-13 The publications had similar recommendations in that patients with mild symptoms are not recommended to receive antibiotic therapy, but that patients with moderate-to-severe symptoms warrant antibiotic treatment. The FDA’s summarized recommendations were as follows:1

- Antimicrobial treatment was beneficial for moderate-to-severe ABECB.
- For mild cases there was a small benefit from antimicrobial treatment from a patient’s perspective.
- In general, antimicrobial treatment was not recommended for mild ABECB.

The FDA reviewed five placebo-controlled trials of uUTI, primarily enrolling young women, and performed a meta-analysis on the data.14,15 Based on the FDA’s analysis there was a treatment effect over placebo.3 However, they also found that the placebo group had a 34 to 44 percent response rate for microbiologic clearing. The FDA also stated that untreated UTI course is poorly understood and has not been evaluated.1 The 2010 IDSA guidelines recommended antibiotic therapy and there is no alternative.19 However, they also emphasized that three-day regimens of FQs may foster the emergence of antimicrobial resistance and therefore should be considered as second line treatments. The FDA’s summary of evidence stated:1

- Antimicrobials provided treatment effect over placebo in terms of symptoms, microbiologic eradication, and responder assessment.

While the evaluation of these uncomplicated infections was not specific to treatment with FQs, the overall conclusion was uncomplicated infections do not always necessitate antibiotic treatment. The review may have provided more insight had it specifically evaluated fluoroquinolone use in these infections.

The second part of the review focused on safety. In addition to previously reported adverse events with FQs, the FDA also evaluated the incidence of fluoroquinolone-associated disability (FQAD). FQAD is defined as disability that persists beyond 30 days resulting from symptoms in two or more of the following systems: musculoskeletal, neuropsychiatric, peripheral nervous system, senses, skin or cardiovascular.1 The 2013 FDA Pharmacovigilance Review of FQs described irreversible peripheral neuropathy resulting in permanent disability which led to labeling changes in 2013. Of the reports in the 2013 review, 76 percent had two or more organ systems involved (number of reports not provided). Additionally, they reviewed two published case series describing FQ-related adverse effects resulting in disability. Cohen20 described 45 cases of FQ peripheral neuropathy reported from members of internet sites formed by people sustaining FQ-related adverse events. The cases were noted as being severe with 80 percent of events involving multiple organ systems and 58 percent of cases lasting more than one year. The most recent published case reports by Golomb et al.21 described four cases of serious, persistent, multi-symptom adverse events in previously healthy adults. Some of the symptoms included weakness, confusion, weight loss, sleep disturbances, mood alterations, and musculoskeletal symptoms that resulted in prolonged disability. All four cases were well documented and evaluated for other potential causes and ultimately were attributed to FQs. Proposed mechanisms for FQ adverse effects are oxidative stress and mitochondrial toxicity though other mechanisms may be involved.21

The FDA conducted an updated FDA Adverse Event Reporting System (FAERS) review for the time frame of Nov. 1, 1997 to May 30, 2015.1 FAERS can capture data from millions of users therefor capturing rare and serious

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Table 2. Fluoroquinolone Adverse Events3-6

<table>
<thead>
<tr>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (e.g., nausea, diarrhea, constipation)</td>
</tr>
<tr>
<td>Hepatotoxic</td>
</tr>
<tr>
<td>CNS (e.g., headache, dizziness)</td>
</tr>
<tr>
<td>Skin (rash)</td>
</tr>
<tr>
<td>Psychiatric (e.g., insomnia, anxiety)</td>
</tr>
<tr>
<td>Phototoxicity</td>
</tr>
<tr>
<td>Cardiovascular toxicity (e.g., prolonged QT interval)</td>
</tr>
<tr>
<td>Blood glucose disturbances</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders (e.g., arthropathy, tendinitis, tendon rupture)</td>
</tr>
<tr>
<td>Ocular toxicity (e.g., retinal detachment)</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>Exacerbation of myasthenia gravis</td>
</tr>
<tr>
<td>Bacterial resistance</td>
</tr>
</tbody>
</table>
Pharmacology Focus

events but the disadvantages include: underreporting, causality can be difficult to determine, and potentially insufficient information to properly evaluate events. In this review, the FDA found 85 percent of reports were direct reports from patients, compared to an average of only 2 to 6 percent with other medications. Events were only evaluated if they met the following criteria:

- The event resulted in disability.
- The event involved two or more body systems and a duration over 30 days.
- Event was only related to systemic FQ treatment of uUTI, uncomplicated ABS, or bronchitis.
- The report contained sufficient data and no confounding medications.

There were a total of 1,122 FQ related disability reports for treatment of uUTI, uABS, and ABECB identified but after limiting the reports to all the specified criteria, only 178 were included in the evaluation. The following is a summary of the events:

- Mean age: 48.1 years with 74 percent of cases between the ages of 30 and 59.
- 78 percent females.
- 48 percent symptom onset within one to two days of starting FQ.
- Mean duration of symptoms: 14 months (range: 30 days to nine years/unresolved).
- Musculoskeletal (97 percent), neuropsychiatric (68 percent) and CNS systems (63 percent) were most common, less frequent were senses, skin, and cardiovascular.
- No single FQ appeared to have a higher correlation with FQAD than others.

The FDA concluded that all of the individual adverse effects that make up FQAD are listed in FQ product labeling as potential side effects. However, the labeling does not specify the possibility that two or more of these

Figure 1.

Percentage of Disability Reports* Among all Serious Outcome Reports with Selected Antibiotics for Treatment of Uncomplicated Sinusitis, Bronchitis, and UTI

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin (32/103)</td>
<td>31.1%</td>
</tr>
<tr>
<td>Ciprofloxacin (358/1221)</td>
<td>29.3%</td>
</tr>
<tr>
<td>Levofloxacin (592/2201)</td>
<td>26.9%</td>
</tr>
<tr>
<td>Gemifloxacin (4/38)</td>
<td>10.5%</td>
</tr>
<tr>
<td>Moxifloxacin (136/1371)</td>
<td>9.9%</td>
</tr>
<tr>
<td>Cefdinir (2/29)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Nitrofurantoin (34/504)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Amoxicillin (6/100)</td>
<td>6.0%</td>
</tr>
<tr>
<td>Doxycycline (6/67)</td>
<td>6.0%</td>
</tr>
<tr>
<td>Amox/Clav (13/254)</td>
<td>5.1%</td>
</tr>
<tr>
<td>Clarithromycin (24/516)</td>
<td>4.6%</td>
</tr>
<tr>
<td>Cotrimoxazole (34/617)</td>
<td>4.2%</td>
</tr>
<tr>
<td>Cephalexin (2/73)</td>
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*Number of US reports reporting disability divided by the total number of US serious adverse event reports for oral dosage forms, from November 1, 1997 to May 30, 2015.

Available at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM472655.pdf.
adverse effects can co-exist as a syndrome resulting in prolonged disability as defined by FQAD. Furthermore, the FDA stated in their conclusion, “The decrease in quality of life was described as being profound, and it affected both the patient and his/her family.”

On July 26, 2016 the FDA announced labeling changes will be required for systemic FQs including an updated boxed warning and revisions to the warnings and precautions section of the label regarding the risk of multiple disabling and potentially irreversible adverse reactions that can occur simultaneously. The label will also include verbiage stating FQs should be reserved for those who do not have alternative treatment options for uUTI, ABSS, and ABECB. Similarly, the mandatory patient medication guide will include the safety concerns with these medications and that FQs should be reserved as alternative treatment for uncomplicated infections.

Conclusion
FQs continue to be frequently prescribed with over 32 million prescriptions each year, and a large proportion are for uncomplicated infections. The FDA's review recognized that, in addition to previously known safety concerns, a constellation of FQ induced symptoms referred to as FQAD is rare but potentially irreversible. The FDA's evaluation of FQ use in uncomplicated infections is based off all antibiotic efficacy data, not specifically FQ efficacy data for these infections. The new labeling changes and prescribing restrictions are intended to curb unnecessary prescribing of FQs due to the risks outweighing benefits in uncomplicated infections. If FQ use is required, educate patients on potential risks and to report any serious adverse effects immediately. If serious side effects occur, complete a MedWatch report available at www.fda.gov/Safety/MedWatch/.

REFERENCES

About the Author:
Stacy Peters, PharmD, Associate Professor of Pharmacy Practice, College of Pharmacy, South Dakota State University; Clinical Pharmacist, Sanford Children’s Specialty Clinic.
Dear Participating Provider,

As a participating provider in the DAKOTACARE network, we value your partnership in delivering quality care to your patients.

On Monday, Aug. 22, DAKOTACARE received notice from Sanford Health that they would end their providers’ participation in the DAKOTACARE provider network effective Jan. 1, 2017.

DAKOTACARE has a 30-year history of maintaining a broad network of providers, and we value the relationships DAKOTACARE has built with physicians. Avera had hoped to continue negotiations with Sanford and is still open to collaborating with them.

Our top priority is our DAKOTACARE members. We will communicate with our employer groups and insureds to help them understand how Sanford’s decision impacts them.

For our members who are in certain active treatment plans with Sanford providers there will be provisions for continuity of care so they can conclude their care regimen. Our customer service representatives are available to assist you and any of your patients who may need to change providers in this transition as we approach the Jan. 1 effective date.

Our goal is to put patients first and find solutions to ensure DAKOTACARE groups and policyholders receive the access and coverage they need. Our commitment to our members and customers does not change.

We ask for your assistance and collaboration in transitioning patients, so they are impacted as little as possible and experience uninterrupted care.

Again, thank you for your partnership in providing quality care to the patients you serve. We will continue to communicate with you to keep you up to date with any new developments.

Sincerely,

E. Paul Amundson, MD
Chief Medical Officer

“DAKOTACARE Update” is a monthly feature sponsored by DAKOTACARE. For more information about DAKOTACARE, visit www.dakotacare.com
Board News is a monthly feature sponsored by the South Dakota Board of Medical and Osteopathic Examiners. For more information, contact the Board at SDBMOE@state.sd.us or write to SDBMOE, 101 N. Main Avenue, Suite 301, Sioux Falls, SD 57104.
**Quality Focus:**

**Beneficiary and Family Engagement**

By Stephan D. Schroeder, MD, Medical Director, South Dakota Foundation for Medical Care

Despite the universal concept that patients and their families or caregivers are the center of health care delivery, the actual involvement of those entities may become quite variable. The extremely complicated process of caring for patients across many providers and settings can be confusing and frustrating. Decisions that involve the level and extent of care as well as where and by whom it will be provided need the attention of not only the patients but their family as well. Cost, lifestyle changes, and complex medication regimens are also significant challenges in need of everyone's input.

Patient and family engagement is a strategy that hospitals, clinics, and care systems have chosen to help increase quality, safety, and health outcomes. Leadership in health care can use the experience and expertise of patients and their families to assist in this improvement. Focus groups with those who receive care offer a fresh perspective to assist providers with the always demanding goal of improving quality.

The scope and size of these groups, sometimes known as Beneficiary and Family Advisory Councils, can vary a great deal. Finding people with the time and commitment to become trained in this area and voice their opinion is a challenge. As our society ages along with a change in culture and linguistics, the need for patient involvement will only expand. The increase in diversity among both patients and providers will demand a resource to keep beneficiaries engaged. Health literacy among patients and their families offers another challenge to providers to assure adequate understanding of diagnoses and treatment.

The Centers for Medicare and Medicaid Services has undertaken the task of encouraging and, to a certain degree, demanding that families and caregivers become involved in all aspects of health care delivery. This may range from advocacy groups to governing board membership. South Dakota Foundation for Medical Care, as part of the Great Plains Quality Innovation Network, has established and is supporting a patient and family advisory board, Voices for Quality Healthcare (V4QH). V4QH hopes to represent the view of the patient and help our organization better understand issues that impact patient care.

Another example of patient involvement is Better Choices Better Health South Dakota, a program designed to encourage more involvement in understanding and coping with chronic disease and health conditions among these patients. There are also a number of commercial and public programs, such as the Partnership for Patients, which emphasize the importance of patients becoming more aware of their care.

The future delivery of health care will involve patients needing to become more involved whether it be as advisors to providers or becoming more active in their own disease management. Whenever and wherever quality of care improvements are being undertaken it is likely and probably necessary that patient and family advisors be part of the team. This is a great example of collaboration at its finest.

If you would like additional information, please feel free to contact me at stephan.schroeder@area-a.hcqis.org.

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**REFERENCES**

Partnering to improve quality and safety: a framework for working with patient and family advisors Health Research & Education Trust (March 2015).
It is not just poetry; it is almost a scientific fact to say that the eyes are the windows to the soul. To support that statement let's go to embryology class during the first years in med school, when you learn how the eyes develop in the embryo within the womb.

It is incredible how it works. The sperm joins with the egg; the cells duplicate and develop into a hollow ball of cells, which then elongates.

The first specialized nerve tissue becomes a darkening cord of special cells along the back of the tiny growing embryo. Next the neural cord thickens on one end, and this grows into the control tower of the brain. There, as the brain is expanding and convoluting like a miniature thunderhead into the command center, out pops two buds, which gradually mature into the eyes.

It is fascinating to realize that the eyes are truly an extension of the brain into the outside world. When you look into eyes of another individual, you are actually seeing the brain as it is gathering in the light energy around it. Of course, all of the senses are an extension of neural tissue. We listen, smell, taste, touch, and look so as to better understand the outside world and environment. But there is something about the looking, and that oh-so direct connection of the eyes to the brain that is so intriguing.

And with this almost naked exposure to the world comes the price of vulnerability. Despite the overhanging boney brow, the eyes are subject to easy destruction from stick and stone, or for that matter sparkler and bottle rocket.

Do we always have to lose a treasure before we cherish it enough to protect it? Bottom line: this special sense of sight needs protection lest we block out the windows to the soul.
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The SDSMA thanks its student membership sponsors. Through these generous donations, the new medical students at the University of South Dakota Sanford School of Medicine have their SDSMA and American Medical Association membership dues paid for all four years of medical school. Are you interested in sponsoring a student’s membership? Visit www.sdsma.org or email membership@sdsma.org.

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The SDSMA serves as your vehicle for advocacy for your patients and the art and science of medicine through lobbying at the state and federal levels, grassroots activity, and legal initiatives.

SDSMA PAC is your grassroots avenue that works to impact public policy decisions through bipartisan political participation. SDSMA PAC supports and elects pro-medicine candidates on the state level. Members of the SDSMA and their spouses can join SDSMA PAC.

The Association’s motto is “Values, Ethics, Advocacy.” We take our advocacy role to heart. With your help, SDSMA and SDSMA PAC have the opportunity to dramatically impact the political and legislative process to create meaningful changes in South Dakota’s current health care system:

• Improving health and access to care in rural areas;
• Increasing Medicaid reimbursement;
• Promoting Medicare physician payment reform and stopping reimbursement cuts;
• Working to improve clinical quality and patient safety;
• Partnering with state agencies to tackle regulatory, socioeconomic, public health and scientific policy issues;
• Advocating for public health immunizations;
• Promoting adequate funding for medical education;
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• Partnering with state agencies to tackle regulatory, socioeconomic, public health and scientific policy issues;
Seventy-one students are enrolled in this year’s incoming class at the University of South Dakota Sanford School of Medicine. They were selected from 859 applicants, the most in a decade.

There are 69 MD students and two enrolled in the MD-PhD program. Fifty-seven of the 71 are from South Dakota. The remainder come from Iowa, Minnesota, Wisconsin, Montana, Florida and New York.

SDSMA President Tom Hermann, MD, spoke to medical students about SDSMA membership and opportunities for involvement. Dr. Hermann also led the Affirmation of the Physician at the White Coat Ceremony at the Holiday Inn City Center in downtown Sioux Falls.

Four-year student memberships to the SDSMA are sponsored by member physicians.

Source: USD SSOM and SDSMA staff

Legal Brief Highlight: Physician Employment Agreements

When negotiating an employment agreement, physicians should be mindful of the length of the term of employment, the method and means of termination, how compensation will be determined and paid, the avoidance of conflicts of interest, and the terms of any possible restrictive covenant.

It is recommended that physicians establish goals for the employment relationship before starting contract negotiations with the potential employer. As stated in the preface to the American Medical Association’s (AMA) Annotated Model Physician Employment Agreement, “[t]he time to think about your future and to do something about it is before the contract is signed, preferably before negotiations begin. Know what you want and why you want it; then ask for it.” The SDSMA Center for Physician Resources at www.sdsma.org and the AMA at www.ama-assn.org have several resources available to physicians that can help in establishing goals and reasonable expectations, and potentially avoiding pitfalls as well.

For more information, download the SDSMA legal brief Physician Employment Agreements at www.sdsma.org. Through the SDSMA Center for Physician Resources, the SDSMA has developed more than 50 legal briefs that are available to members. In addition, the Center develops and delivers and programs for members in the area of practice management, leadership and health and wellness.

Source: SDSMA staff
SDSMA Meets with Congressional Delegates

SDSMA members met with Sen. John Thune and Rep. Kristi Noem during August Recess to discuss issues of importance to South Dakota patients and physicians – the national epidemic of opioid abuse, the VA’s proposal to allow advanced practice nurses to circumvent state law and practice indecently of a physician’s clinical oversight, and improvements needed concerning federal MACRA legislation.

“The Issue Is” is the SDSMA’s monthly update on key policy issues of importance to physicians.

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<td>Internal Medicine Grand Rounds: Advances in Prevention and Early Detection of GI Cancers</td>
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