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What's Inside This Issue?

Article Submission Deadlines for Upcoming Newsletters

June 16th, 2017 for the July 2017 Edition
September 15th, 2017 for the October 2017 Edition
December 15, 2017 for the January 2018 Edition
March 16, 2018 for the April 2018 Edition

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Medication Safety Corner

Stop the Use of Codeine in Pediatric Patients

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Pain management in pediatrics can present challenges when considering the safety profile of agents such as codeine. On September 19th, 2016 the American Academy of Pediatrics (AAP) announced an updated "Codeine: Time to Say No" recommendation related to the use of codeine as an analgesic and antitussive in pediatric patients. AAP cited specifically the 2012 Food and Drug Administration (FDA) black box warning regarding variability in drug metabolism based on patient pharmacogenetics.[1] Codeine is an opioid used as an analgesic since the late 1800's. There has long been widespread belief among pediatric anesthetists in the US and UK that codeine was a safe opioid for outpatient treatment of acute pain.[2] However, as our understanding of pharmacogenomics increased, populations with a CYP2D6 mutation were found to be at increased risk for severe respiratory depression with use of codeine.

Codeine, a prodrug, must undergo metabolism in the liver, specifically by the enzyme CYP2D6.[3] The metabolite, morphine, provides the analgesic effect. In the absence of this metabolism, codeine possesses no analgesic properties. CYP2D6 enzyme activity varies significantly based on genetic polymorphisms. The level of enzyme activity can range from poor to normal to ultra-rapid. This altered CYP2D6 activity becomes problematic in ultra-rapid metabolizers, those with more than two functional alleles for CYP2D6, because these patients convert codeine to large amounts of morphine, even at recommended codeine doses. These higher doses of morphine have been associated with respiratory depression, apnea, and even death. The frequency of the ultra-rapid metabolizer genotype varies between different ethnic groups, from 4% in Caucasians to close to 30% of African and Ethiopian heritage.[1, 4-5]

The FDA completed a database search looking at Adverse Event Reporting System (AERS) data from 1969 to 2012 that revealed ten cases of pediatric deaths and three cases of respiratory depression. These cases were attributed to the use of codeine in patients age 21 months to 9 years.[6]

Continued on Page 2

Further analysis of these patients' CYP2D6 pharmacogenetics indicated four were ultra-rapid metabolizers and three were extensive metabolizers. An additional search of the FDA AERS database for children who received codeine or codeine-containing products between 1965 and 2015 resulted in 64 cases of severe respiratory depression and 24 codeine-related deaths. Of those deaths reported, 21 were in children less than 12 years of age. [7]

Codeine, once a readily used option as an analgesic, has fallen out of favor in the pediatric world. The European Medicines Agency (EMA), Health Canada (HC), and WHO, share AAP's viewpoint to stop the use of codeine in pediatric patients. In the last five years, these organizations have put out warnings regarding adverse responses associated with codeine.[1]

- In March 2011: WHO deleted codeine from its list of essential medications for children due to concerns of "efficacy and safety" and unpredictability in pediatric patients.
- February 2013: FDA added a black box warning to all codeine and codeine containing products advising health care providers to prescribe an alternative analgesic agent for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy procedures.
- June 2013: EMA recommended restriction of codeine for the treatment of pain to children older than 12 years and a contraindication to use in children younger than 18 years undergoing tonsillectomy and/or adenoidectomy.
- June 2013: HC recommended against use of codeine in children younger than 12 years.
- March 2015: EMA updated their warnings, recommending against use of codeine in patients between 12 and 18 years with history of breathing problems.

Based on these recommendations, the use of codeine in children should be avoided. A key for avoiding use will be the removal of codeine from pediatric hospital formularies and restriction of use to patients 18 years and older in all other hospitals.[8] When pain management warrants the use an opioid, it is pertinent for pharmacists to provide opioid alternatives. Morphine is considered the safest opioid alternative for pain management. Oxycodone may also be considered since its metabolism is handled through more than just the CYP2D6 pathway. Pharmacists can also offer alternatives such as acetaminophen or NSAIDs[1] in those patients who may experience pain relief from non-opioid therapy.

Pharmacists must play an instrumental role in preventing use of codeine in pediatric patients without known CYP2D6 genetic profiles. Using this AAP stance as momentum, we call on all medical institutions to conduct formulary reviews and restrict/remove the option for use of codeine in children. Further, it is our responsibility to provide education to other health care providers and patients about these safety warnings. Taking these action steps, we work to ensure fewer patient complications, adverse drug events, and deaths caused by codeine.

Alternative Oral Opioid Analgesic Options

Morphine	0.05 – 0.2 mg/kg/dose every 4-6 hours
Oxycodone	<50 kg: initial dose: 0.1-0.2 mg/kg/dose every 4-6 hours as needed (max dose range 5-10mg) ≥50 kg: initial dose: 5-10 mg every 4-6 hours as needed (max dose 20mg/dose)

Alternative Oral Non-Opioid Analgesic Options

Acetaminophen	10-15 mg/kg/dose every 4-6 hours (max daily dose ≤75 mg/kg/day in ≤5 divided doses, do not exceed 4000mg/day)
Ibuprofen	10 mg/kg/dose every 6-8 hours (max 800mg/dose)

Opioid Dose Equivalence Charts*

Drug	Oral Dose (mg)
Morphine	30
Oxycodone	20
Codeine	200

*If pain controlled, reduce calculated dose by 50%
If pain is not controlled, reduce calculated dose by 20%

Continued on Page 3

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Congratulations to the 2017 MSHP Grant Recipients:

Student Research Grant:
Christine Nguyen

"Determining risk for pneumonia caused by drug resistant pathogens to improve empiric antibiotic therapy for patients presenting from the community."

Practitioner Grant:
Meera Vacchani

"Venous thromboembolism prophylaxis with unfractionated heparin for critically ill, obese patients."

Pharmascript

Volume 41, Issue No.2
Second Quarter

Statistics Review

Using the *p* value to interpret significant results – not the be-all end-all

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In biomedical literature, the use of *p* values to determine statistical significance of study results is ubiquitous. In fact, many believe that in order to produce scientifically sound and thus publishable results, the research must contain findings that demonstrate $p < 0.05$. These *p* values, however, are largely misinterpreted by the general reader, even to the point that the American Statistical Association (ASA) has released a position statement about their use. In their statement, the ASA write:

> "The *p* value was never intended to be a substitute for scientific reasoning…. Well-reasoned statistical arguments contain much more than the value of a single number and whether that number exceeds an arbitrary threshold…"[1, 2]

Ronal Fisher first introduced the concept of the *p* value in the early 1900s, by developing what we call the "null hypothesis."[3] The null hypothesis describes what the underlying data would look like if there were no true difference. For example, a null hypothesis may be: we assume there will be no difference in clinical cure rates among patients treated with antibiotic A compared to antibiotic B. The *p* value becomes a measure of how much the data you have collected/observed varies from this null hypothesis. The *p* value does not assess the difference between these two cohorts. In their 2016 *JAMA* article, "Understanding the Role of P Values and Hypothesis Tests in Clinical Research," Mark et al. define this as the "oomph" effect.[4] Do your data and findings support a largely enough difference in treatment oomph between comparators within a clinical study to actually be noteworthy? Would a subsequent sample of patients treated with antibiotic A versus antibiotic B produce similar results? As originally suggested by Fisher, the *p* value is meant to give an idea if the data were showing a meaningful pattern that diverges from what would be expected if the null hypothesis was correct upon multiple reiterations of the experiment. From its inception, the *p* value was never meant to be a one and done catch-all statistical product.

The *p* value is neither as reliable nor objective as most people assume.[5] If the same study, with the same metrics, is completed on separate datasets with different populations there is no guarantee that what you had assumed to be statistically (and thus clinical significant) will be so again. This lack of reproducibility may be surprising to some because they are assigning the *p* value a different meaning than it's actually intended. Again, Mark et al. provide examples of how relying solely on the *p* value allow you to miss the larger picture.[4] In one hypothetical study presented, a relative risk (RR) ratio is close to one (no difference). Based on the fact that the RR ≈ 1 we can conclude that the effect size is small, but we would need to look at the confidence in (in particular, 95% confidence interval) to determine the precision. Based on this precision of the underlying data, the 95% confidence interval may cross 1 and lead to a non-significant finding. Is a RR = 0.91 (95% CI 0.69 – 1.02) truly, significantly more important than RR = 0.91 (95% CI 0.75 – 0.98)? One of these can be associated with $p < 0.05$. On the other side of the coin, the *p* value is known to be sensitive to the sample size of the population under study. With a large enough patient population you will be able to reject the null hypothesis and determine statistical significance regardless of effect size.

So, to summarize:

- The null hypothesis assumes there is no difference in the underlying data, and is almost always false because there is always some degree of heterogeneity present.
- The p value does not report the actual effect size or extent to which two cohorts under study are different.
- The cut-off of $p < 0.05$ is arbitrary and does not determine if the data presented is of clinical significance.
- Other statistical methods, such as likelihood ratios and confidence intervals must be used (either in conjunction or as a replacement) to provide a better interpretation of the data and there is no one catch-all test to determine significance.

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MSHP Pharmascript

Volume 41, Issue No.2
Second Quarter

Legislative Updates

New Legislation Affecting the Pharmacy Profession

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This past December, President Obama signed the 21st Century Cures Act into law. This bill attempts to accelerate the discovery, development, and delivery of innovative and advanced treatments for disease. This legislation will devote billions of dollars to funding organizations such as NIH, FDA, and state governments to stimulate research, advance disease treatment, move drugs and medical devices to patients faster while maintaining safety and efficacy, and improving programs dedicated to fighting the opioid abuse epidemic. Given the key role that medication therapy plays in the focus of this legislation, it is likely that this act will affect the pharmacy profession.
The 21st Century Cures Act has a large focus on mental health and substance use, particularly focusing on opioid abuse. The response to the opioid abuse epidemic is of particular importance to pharmacists due to the role pharmacists play in dispensing these medications. One billion dollars has been allocated for grants that will be awarded to the states with an incidence or prevalence of opioid use disorders that is substantially higher relative to other states. These grants are to be used by the state agency responsible for administering substance abuse and prevention programs. Activities that these funds may be utilized for include improving prescription drug monitoring programs (PDMPs), implementing effective prevention strategies, training health care practitioners in best practices for prescribing opioids, pain management, surveillance to identify cases of substance abuse, supporting access to health care services, and other public health-related activities the state determines appropriate. The greatest impact would undoubtedly be controlling the prescribing of these medications and pharmacists could play a role in this area. Another important role for pharmacists will be in interfacing with their state PDMPs. It will be important to make sure that the use of the PDMP is integrated seamlessly into the workflow of pharmacists. With increased funding for these efforts, pharmacists can help improve the PDMP within their state and make sure that both access and workflow are optimal for pharmacy practice.

Another important issue this legislation addresses are efforts to improve antimicrobial resistance. Within the next year, a report concerning the national and regional trends of antimicrobial resistance will be developed, summaries of state efforts in addressing antimicrobial resistance will be produced, and there will be enhanced coordination between the CDC and FDA with respect to the monitoring of antimicrobial resistance. The Secretary of Health and Human Services will also provide a mechanism for facilities to report data related to antimicrobial stewardship activities (including analyzing the outcomes of such activities) and evaluate resistance data as well as trends in the utilization of antimicrobials with respect to various patient populations. All of this information will be of great use to pharmacists in helping further their impact on antimicrobial stewardship. This information will allow antimicrobial stewardship programs to utilize the findings within the yearly report to their own program in order to combat resistance effectively. The most interesting aspect of the law states that the Secretary of Health and Human Services may approve an antimicrobial drug that is currently under investigation if the drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. In order for this to happen, the Secretary of Health and Human Services would need to receive a written request from the pharmaceutical manufacturer to approve the drug. After that, they will determine the safety and effectiveness of the antimicrobial drug by assessing the benefit-risk profile, severity, rarity, or prevalence of the infection and the availability of alternative treatment. Along with the annual resistance report, the Secretary of Health and Human Services will also issue draft guidance describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of these antimicrobial drugs that would be useful in limited populations within 18 months of the enactment of the Cures Act. In addition, a website will be established and maintained on the website of the FDA that contains a list of any appropriate new or updated susceptibility testing standards. All of this reported information will be useful to pharmacists and their respective programs to reduce resistance of microorganisms and overuse of antimicrobial drugs.

This new push to develop and deliver new treatments at a faster rate while maintaining safety and efficacy will inevitably effect the way medication research is conducted. Within the Cures Act there is a section devoted to new trial design in order to develop evidence to support the approval of new indications for medications. This new trial design is vastly different from a standard randomized controlled trial and has an increased emphasis on using more robust sources of data. This section is an amendment to the Federal Food, Drug, and Cosmetic Act. A program will be established to evaluate the validity of data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials. Sources of more robust evidence will include ongoing safety surveillance, observational studies, registries, claims data, and patient-centered outcomes research activities. The programs framework would include information describing gaps in data collection activities, methodologies for collection and analysis of data, remaining challenges, and potential pilot opportunities that the program established.

Continued on Page 6

This program will be implemented within two years and at that time the Secretary of Health and Human Services will then guide the pharmaceutical industry on the circumstances under which sponsors of drugs may utilize alternative trial designs as well as the appropriate standards and methodologies for collection and analysis of that data. This new program will drastically change the way we evaluate the use of medications. This will have a big impact on how medications get approved for certain indications, particularly for drugs that are already on the market and have been used off-label for certain disease states. This program will allow manufacturers to obtain multiple indications for their new drugs and also enhance the need for continuing education in all health care professions.

There are many changes outlined in the 21st Century Cures Act that will affect all health care practitioners and researchers. I have defined some of the laws and amendments that were of particular interest to pharmacy and described how they could affect the profession. As of now, the top priorities include implementing programs to stop the progression of the opioid epidemic and advance the antimicrobial stewardships across the nation. This new legislation has provided the framework in order to develop programs that can be utilized to accomplish those goals.

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"The 21st Century Cures Act Fact Sheet." *U.S. House of Representatives*. Committee on Energy and Commerce. Web. 24 Mar. 2017.

Surviving Sepsis Campaign Guideline Update

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The Surviving Sepsis Campaign (SSC) recently released their highly anticipated 2016 International guidelines for the management of sepsis and septic shock.[1] Many of the recommendations remain unchanged, but a further, detailed explanation is provided in the 2016 update. The updated SSC guidelines define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock as a subset of sepsis with circulatory (vasopressors required to maintain mean arterial pressure [MAP]) and cellular/metabolic dysfunction (lactate greater than or equal to 2 mmol/L) which were first defined in Sepsis-3.[2] The phrase "severe sepsis" was removed from the guidelines as sepsis now incorporates organ dysfunction into its definition. Based on the 2014 landmark ARISE, ProCESS, and ProMISe trials, which showed no difference between early goal directed therapy (EGDT) compared to standard treatment, EGDT is no longer recommended. [3-5] Although EGDT did not reduce mortality, it was still safe and institutions that use this protocol may not need to abandon its use entirely.

Sepsis is a medical emergency and early recognition, treatment, and resuscitation remain essential. Initial fluid resuscitation with 30 mL/kg of crystalloid is the mainstay of treatment and providers should utilize dynamic (passive leg raise and stroke volume variation) rather than static variables (central venous pressure and central venous oxygen saturation) to predict fluid responsiveness and ultimately guide additional fluid resuscitation. There is increasing evidence that chloride-rich fluids may lead to worse clinical outcomes, but there have been no direct comparisons specifically in sepsis. Thus, no crystalloid is recommended over another, however avoiding hyperchloremia is recommended. Colloids are only recommended when patients require large amounts of crystalloid resuscitation.

A lactate level should also be drawn during the initial work-up. If the lactate is elevated, lactate-guided resuscitation is recommended to improve patient outcomes. In addition to early fluid administration, early administration (within one hour) of broad-spectrum parenteral antibiotics is recommended for the treatment of sepsis and septic shock with achievement of source control as soon as medically and logistically possible. Empiric antibiotic treatment should start out initially too broad rather than too narrow due to the high mortality associated with inappropriate empiric coverage.[6] The selection of the empiric treatment regimen should be based on the suspected source of infection and the local antibiogram. Following the lead from the IDSA hospital-acquired and ventilator-associated pneumonia guidelines, antibiotics are recommended to be dosed on pharmacokinetic/pharmacodynamics principles rather than package insert or FDA recommendations.[7] An example of these principles include administering beta lactams via extended infusion compared to a shorter, standard infusion.

Continued on Page 7

Microbiologic cultures are recommended before antibiotics are administered, with a suggestion of waiting 45 minutes, to not cause a delay in the initiation of antibiotics. A noticeable shift is the recommendation for combination antibiotic therapy in septic shock, but not for sepsis without shock, bacteremia, or neutropenia. However, if multi-drug resistance is suspected, then combination therapy should be considered for all patients. The recommended antibiotic treatment duration is 7-10 days, but longer or shorter courses may be appropriate based on clinical response and site of infection. There is a recognizable emphasis on antibiotic de-escalation throughout the 2016 SSC guidelines. Patients should be assessed daily for antibiotic de-escalation opportunities, empiric antibiotics should be narrowed based on pathogen identification and clinical improvement, and procalcitonin levels can be used to recommend antibiotic discontinuation.

Norepinephrine remains the first-line vasopressor for the treatment of hypotension refractory to fluid administration. The initial MAP target is greater than or equal to 65 mm Hg, but this target should be personalized based on patient-specific factors. For example, in patients with long-standing hypertension a higher MAP target may be necessary. If a second agent is needed they suggest either adding vasopressin (up to 0.03 units/min) to decrease norepinephrine requirements or vasopressin/epinephrine to help raise the MAP up to target. Epinephrine may increase aerobic lactate production, which would limit the use of lactate-guided resuscitation. Low-dose vasopressin should be thought of more as a treatment for relative vasopressin deficiency rather than a titratable vasopressor. The vasopressin dose recommendation is based on the VASST study, even though more recent study such as VANISH titrated vasopressin up to 0.06 units/min.[8, 9] If fluids and vasopressors do not achieve hemodynamic stability, IV hydrocortisone (200mg/day) is still suggested to achieve hemodynamic targets.

The 2016 SSC Guidelines also discuss recommendations for acute respiratory distress syndrome (ARDS), sedation and analgesia, glucose control and nutrition that are in line with guideline-recommended treatment. Appendix 2 in the 2016 SSC guidelines compare the 2012 and 2016 recommendations from 2012 to 2016, which is helpful because the reader can see the differences. In addition to the Appendix, the authors released a simultaneous users' guide to offer guidance for appropriate utilization.[10] The 2016 SSC guidelines are more transparent and offer the audience an in-depth view to the evidence behind the recommendations. In summary, early recognition in combination with intravenous fluids and broad-spectrum antibiotics remain the cornerstones of treatment.

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Pharmascript

Volume 41, Issue No.2
Second Quarter

Renewal Reminder

Individual members of MSHP are reminded to renew their memberships. Membership includes weekly updates, *Pharmascript* subscription (4 issues / year), discounts on MSHP programming, access to the MSHP online community, opportunities to volunteer on MSHP committees and more!

Call For Articles

The editors of *Pharmascript* are seeking articles related to ASHP recommended Practice Advancement Initiatives, student or resident research, MSHP committee updates, new drug updates and clinical reviews. Interested writers are encouraged to submit articles as a clinical review (1,000 words), a research project manuscript (2,000 words), or a new drug update (250 words). Other article topics will be considered. Articles should be submitted to Michael Armahizer (michaelarmahizer@umm.edu) or Vicki Leiman (victorialeiman@umm.edu) by March 17, 2017 to be published in the April edition of MSHP's *Pharmascript*. See the newsletter deadlines listed above for subsequent issues.

Call for Editors

The editors of *Pharmascript* are seeking content reviewers for upcoming editions. Interested Pharmacists, Residents and Students should contact Michael Armahizer (michaelarmahizer@umm.edu) or Vicki Leiman (victorialeiman@umm.edu). Reviewers should note specific areas of expertise or interest in their communications.

MSHP Pharmascript

Volume 41, Issue No.2
Second Quarter