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Deadlines for Pharmascript Submissions

Submit articles for publication in the Fall Edition of Pharmascript by September 15, 2019
Submit articles for publication in the Winter Edition of Pharmascript by December 15, 2019

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MSHP Presidential Address-2019

Stacy Elder Dalpoas, PharmD, MPH, BCPS

The transition to a new academic year has provided the MSHP Board of Directors with opportunities for reflection on the tremendous work of the society over the last year, and preparation for the coming year. This is a pivotal year for MSHP, as we enter into the re-affiliation process with ASHP. Part of the work of MSHP is to advance the ASHP vision by fostering a collaborative relationship between the societies while ensuring that we serve the unique pharmacy needs of our state.

Over the summer, the MSHP leadership has thoroughly assessed our activities from the past 5 years and completed a strategic plan that promises to keep our work relevant to all constituents while advancing the initiatives of ASHP in our state for the coming year.

We have a rich history of pharmacy excellence and leadership in Maryland that has shaped the past work of MSHP. As we developed the reaffiliation report to ASHP, we highlighted some of our key initiatives from the past 5 years as best practices to share, including:

- Our strategy for advocacy surrounding legislation impacting health-system pharmacy in Maryland, particularly our role in forming the Maryland Pharmacy Coalition
- Our strategic planning process that supports ASHP practice standards
- Support for advancement of pharmacy technician roles in Maryland, specifically our most recent role in the Technician Training Consensus Conference and the outcomes of that effort
- MSHP new practitioner membership and discrete leadership opportunities for new practitioners
- Affiliation with student societies of health-system pharmacy and provision of student leadership programming in Maryland

As we look to the coming year, we have an ambitious and invigorating plan to build upon the strong foundations of the MSHP committees. A few of the key committee goals for the coming year include:

- Development of a new task force to explore the role of medication history legislation in other states and potential utility for Maryland
- Dissemination of the biennial membership needs assessment
- Facilitate activities to enhance resilience and well-being of our MSHP members
- Assessment of current state of accredited pharmacy technician training programs in relation to Pharmacy Technician Certification Board (PTCB) changes in requirements
- Investigation of opportunities to support dissemination of student research efforts
- Distribution of the biennial MSHP membership needs assessment

As we embark upon this year's journey to advance the goals of MSHP and our members, I encourage you to consider engaging in a project or committee. If any of the work mentioned here (or in any MSHP communication) interests you, please feel free to contact me directly at selder5@jhmi.edu.

MSHP aims to optimize medication outcomes while supporting the competence and well-being of the pharmacy workforce in all settings of care in Maryland. With your support, I look forward to engaging the society in these worthy endeavors for the coming year.

Medication Safety: Combining Opioids with Gabapentin or Pregabalin and the Risk of Opioid-Related Death

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Gabapentin and pregabalin are anticonvulsants commonly used as adjunct therapy for the treatment of chronic pain. Although both medications are widely perceived as safe, respiratory and central nervous system depression, as well as sedation have been described when they are used alone or in combination with other

medications. Additionally, the product monograph for gabapentin was amended in 2014 warning of possible respiratory depression when combined with opioids. Potential risk factors for gabapentin-related respiratory depression include advancing age, renal insufficiency, chronic lung disease, and dose.[2] The role of dose is particularly important in light of data indicating a 44% increase in systemic gabapentin exposure following its administration with morphine, likely reflecting increased drug absorption from diminished intestinal motility.[9] Recent findings demonstrate that concomitant opioid and gabapentin use is associated with opioid-related mortality, but it is also imperative to determine whether co-prescribing pregabalin with opioids poses similar risks.

A population-based, nested case-control study was conducted in Ontario, Canada to evaluate the risk of opioid-related death with gabapentinoids. Ontario residents eligible for public drug coverage who received prescription opioids between August 1, 1997 and December 31, 2016 were included in the observational study. Cases were patients who died of an opioid-related cause, excluding deaths from suicide or homicide, with the index date as the date of the opioid-related death. Each case patient was matched with control participants for age, sex, index year, history of chronic kidney disease, and the Charlson Comorbidity Score which served as a disease risk index.[1,2]

Design[1,2]		
	Study 1: Gabapentin	**Study 2: Pregabalin**
Patients	Cases: N = 1256 Controls: N = 4619	Cases = 1417 Controls = 5097
Primary Exposure Within the Last 120 days	Low dose: < 900 mg daily Moderate dose: 900-1799 mg daily High dose: ≥ 1800 mg daily	Low-moderate dose: < 300 mg daily High dose: > 300 mg daily
Comparison to Measure Specificity of Findings	NSAIDs	

Recent exposure to long-acting, higher doses of opioids as well as administration of benzodiazepines were variables adjusted to perform a statistical analysis of the results and draw appropriate conclusions.

It was found that co-prescription of opioids with gabapentin or pregabalin were associated with a significantly increased odds of opioid-related death compared to opioid prescriptions alone. Concomitant gabapentin and opioid exposure was associated with a 49% higher risk of dying from an opioid overdose. In the dose–response analysis, moderate-dose and high-dose gabapentin use was associated with a nearly 60% increase in the odds of opioid-related death relative to no concomitant gabapentin use. Higher odds of opioid-related death were associated with pregabalin exposure in the preceding 120 days (adjusted odds ratio, 1.68), overlapping gabapentinoid use and pregabalin overlapping index (adjusted odds ratio, 1.81), after matching on prior use of central nervous system depressants (adjusted odds ratio, 2.00), and both low/moderate dose and high dose pregabalin with higher doses corresponding to increased odds (odds ratios, 1.52 and 2.51, respectively).[1,2] There was no significant association between co-prescription of opioids and NSAIDs and opioid-related death as expected.[1]

Because this was an observational study, certain limitations associated with this study may be due to confounding bias, as there is potential of unmeasured variables.[2] However, this study is still pertinent. Gabapentin and pregabalin use has increased to support pain management, but their concomitant use with opioids may pose a significant risk with respect to respiratory depression, and ultimately death. Gabapentin has demonstrated analgesic effects in diabetic neuropathy, post-herpetic neuralgia, and neuropathic pain. The role of gabapentinoids are expanding for the use of perioperative pain: several meta-analyses reveal that perioperative gabapentin helps to produce a significant opioid-sparing effect and potentially decrease the postoperative pain score relative to the control group. Pregabalin has been shown to have efficacy of varying degree in neuropathic pain conditions such as postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia. Select studies suggest pregabalin to have effective sedative and opioid-sparing effects, and such clinical trials emphasize its effectiveness in acute pain control. Since safe postoperative pain control is necessary, the established role of pregabalin as an analgesic as a part of multimodal analgesia for acute pain control is in progress.[6,7,8] Therefore, it is apparent that the roles of gabapentin and pregabalin have expanded as analgesics, but it becomes a significant risk when these agents serve as adjunct therapy to opioids.

Based on the results of this study, it is evident that concomitant opioid use can increase the risk of respiratory depression, possibly leading to fatal events when these drugs are used together.[2] Clinicians should take caution when combining opioids with gabapentin or pregabalin.[2,4] Furthermore, patients treated with opioids and gabapentin or with opioids and pregabalin may need to have their doses adjusted to avoid potential drug overdose.[2,5]

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Pediatric Spotlight: New Indication for GATTEX® -- Now for Use in Pediatric Patients

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In May 2019, the FDA approved GATTEX® (teduglutide) 0.05 mg/kg/day, subcutaneous injection for use in children 1 year and older with parenteral nutrition-dependent short bowel syndrome (SBS). [1] Teduglutide is a human glucagon-like peptide 2 (GLP-2) analog. GLP-2 is secreted in the lower intestine with enteral intake. Patients with SBS have impaired secretion of GLP-2 due to insufficient intestinal length secondary to bowel resection, which leads to malabsorption of nutrition and fluids.[1]

SBS affects approximately 25 per 100,000 children. Complications of malabsorption can impact overall growth and brain development.[2] Common conditions leading to intestinal resection include necrotizing enterocolitis, Hirshprung's disease and congenital malformations. Current therapy for SBS is parenteral nutrition (PN). However PN-dependency is associated with complications including catheter-related infections, liver disease, and metabolic bone diseases.[3] Therefore, the treatment goal for SBS is to enhance nutrient absorption in the remaining intestine while minimizing chronic use of PN.

Two randomized control trials have been conducted to evaluate the safety and efficacy for use of teduglutide in pediatric patients. Both studies also evaluated pharmacokinetic parameters to determine appropriate pediatric dosing.

Forty-two PN-dependent pediatric patients were enrolled in a 12-week phase 3 randomized control trial. Participants needed to have a history of SBS for ≥12 months and receive at least 30% of their caloric needs from PN. Patients in the treatment arm were randomized to teduglutide 0.0125 mg/kg/day (n=8), 0.025 mg/kg/day (n=14) and 0.05 mg/kg/day (n=15). The teduglutide 0.025 mg/kg/day and 0.05 mg/kg/day groups saw 41% and 25% reduction in PN volume and 45% and 52% reduction in PN calories respectively. Reductions in PN utilization first occurred at week 4 of treatment. Two patients in the treatment arm achieved autonomy from PN 4 weeks after treatment discontinuation.[4] Unfortunately this limited study was not powered to evaluate the differences in safety and efficacy outcomes. All participants in the study experienced at least one adverse event, the majority of which were gastrointestinal in nature (e.g., vomiting).

In a yet-to-be published trial of teduglutide, 18/26 (69%) PN-dependent pediatric patients in the 0.05 mg/kg/day treatment group met the study's primary outcome, a 20% reduction in PN use at 24-weeks. [5] The clinical significance of this percent reduction in PN use will need to be addressed in the final publication as PN-independence is most commonly the goal of care. Secondary outcomes such as change from baseline height and body mass index were larger in the treatment group than in the standard of care but statistical analysis has not yet been reported.

The most commonly reported adverse effects of teduglutide are abdominal pain (30%), injection site reaction (22.4%), nausea (18.2%), headache (15.9%), abdominal distension (13.8%), and upper respiratory tract infection (11.8%).[6] A medication guide is available for pharmacists to share with patients. The package insert includes important counseling information about reported cases of abnormal cell growth and the potential for increased absorption of concomitant oral medications.

Teduglutide comes in a single-use vial containing 5 mg lyophilized powder which should be reconstituted with a provided prefilled syringe of 0.5mL preservative-free sterile water. Kits can be dispensed to patients for home reconstitution. Teduglutide should be refrigerated at 2°C to 8°C (36°F to 46°F) before dispensing. Once dispensed to the patient, it can be stored at room temperature up to 25°C (77°F) for up to 90 days. Reconstituted teduglutide should always be clear, colorless, free of particulates and used within 3 hours of reconstitution. Any unused portion should be discarded. Of note, the single-use vial of 5mg GATTEX® has an AWP of $1,703.16.[1,6]

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Technician Corner: Error prevention in Compounding Sterile Products

Susan Daly CPhT, CSPT

Preventing medication errors is a top priority for the Pharmacy and other hospital staff. As Pharmacies begin to incorporate changes to their cleanrooms to meet new standards set by <USP> 797, error prevention in compounding sterile preparation is paramount in order to keep our patients safe along with the new standards. Studies have shown that simple compounds (those with two or less ingredients) had a 9% error rate prior to dispensing and more complex compounds (those with more than 2 ingredients) had especially high rates with 37% for manual preparation and 22% for partly automated preparation. [1]

In 2011, the Institute for Safe Medication Practice (ISMP) held a Sterile Preparation Compounding Safety Summit. The result of the summit was the publication of ISMP Guidelines for the Safe Preparation of Compounded Sterile Preparations.[1] The guideline covers a range of recommendations to help prevent medication errors, including the use of technology/automation and staff management (training).

Technology/automation is not 100% effective in preventing medication errors. It has been shown, however, to significantly reduce errors when used consistently and correctly. ISMP believes that barcode scanning of base solutions and ingredients should now be considered the minimum requirement for Pharmacy IV admixture services. [1] However, there are other key components to preventing preparation errors in compounding.

Measuring the amount of ingredients is largely done based on visual inspection (volumetric) and what is measured can vary from person to person. The practice of using the “Pull back method”, pulling back the plunger on a syringe to the already injected amount for the Pharmacist to look at, should be eliminated from

the workflow process. The use of Gravimetric technology in the IV workflow process can greatly enhance quality control by confirming combined weight of both the base solution and additives for each IV made. Gravimetric analysis accomplishes this by using the specific gravity or density of each ingredient to confirm accuracy of the additives and base solution in an admixture base on its measured weight.[3] During each step of the process, the solution is weighed on an electronic balance, the results are compared to known values stored in the systems database.[3] If the solution fails to fall within the acceptable weight an error occurs and stops the continuation to the next step. It has been shown that the combination of barcode verification along with the use of gravimetric measurement can detect and prevent medication errors that would otherwise have gone unnoticed by traditional verification methods. Boston Children's Hospital found that 23% of errors detected by the system would have been undetectable by the previous verification practices, for example.[3] Combining technologies seems to help detect more potential errors by identifying either wrong volume, wrong drug or wrong base solution than the use of a single method.

Although technology/automation helps to decrease errors in compounding IV admixtures, the staff using the equipment also need to be properly trained. "Any program of pharmacy-based bar-code scanning should be accompanied by appropriate training, policies and procedures to promote and optimize safe use of the system…" [2] Pharmacy IV compounding personnel need to demonstrate proper use of all technology used in preparing admixtures along with a competency assessment on knowledge. Calculations, preparing complex sterile products and familiarity with all Standard Operating Procedures (SOP) and pharmacy policies regarding sterile compounding in the pharmacy are just some examples of appropriate competency assessments. ASHP has stated "…pharmacy-based bar-code scanning systems will only be beneficial if appropriately deployed."[2] Work-arounds, such as not scanning each vial needed to prepare a compound, scanning a universal base solution or bypassing barcode scanning due to workload should be discouraged. Barcodes that cannot be scanned, drugs without proper barcoding, are new or alternative drugs (different manufacturer) should be updated or corrected in the system quickly to avoid potential work-arounds.

It would also be beneficial for pharmacists and pharmacy technicians involved in preparing sterile compounds to participate in a certification program. Both the Pharmacy Technician Certification Board (PTCB) and American Society of Hospital Pharmacy (ASHP) have programs in sterile compounding. The PTCB offers a certification after passing a 75 questions exam and providing an attestation of competency in sterile preparation. The ASHP program offers a certificate, 29 hours of continuing education (CE) and will help prepare pharmacy technicians for the PTCB certification exam in sterile compounding. ASHP also offers a certificate and CE for pharmacists and a prep course for pharmacists who desire to be board certified in sterile compounding.

Sterile compounding is an area that is at high risk for medication errors. Implementation of technology/automation and staff management can help greatly reduce these errors. However, these two items are not mutually exclusive. The use of technology is only helpful in preventing errors in admixture preparation if pharmacy staff are competent in the use of the technology and there are SOPs and policies in place to help eliminate work-arounds. The technology must also be kept current with working barcodes with up-to-date information. Finally, technology used in tandem, such as, gravimetrics and barcode scanning as part of an IV workflow management system provide additional safeguards and error prevention in sterile compounding.

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The Fight against LDL Cholesterol Heats up: A Review of the Updated 2018 ACC/AHA Blood Cholesterol Guidelines

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High-density lipoprotein cholesterol (HDL-C), has been widely linked to protection against heart disease and stroke. Conversely, evidence indicates that low-density lipoprotein cholesterol (LDL-C), is associated with increased atherosclerotic cardiovascular disease (ASCVD).[1-5] In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines moved away from treating patients to specific LDL-C targets due to a lack of randomized controlled trials (RCTs). Instead, the writing committee recommended four treatment groups that would benefit from statin therapy based on 10-year risk of ASCVD events (coronary heart disease, nonfatal myocardial infarction, or stroke) [Table 1].[6] Although this strategy acknowledged the benefits of ASCVD risk reduction to absolute LDL-C lowering, subsequent RCTs revealed a correlation of decreased cardiovascular (CV) events when lowering LDL to targeted thresholds.[7] The release of the 2018 ACC/AHA guidelines has continued to recommend the four treatment groups. However, the updated guidelines sought to utilize new RCTs in their recommendations for the use of lipid-lowering non-statin therapies as adjuncts to statin regimens along with re-introducing LDL-C threshold values.[8]

Statin therapy: In addition to lifestyle modifications, statin therapy is the cornerstone of lipid-lowering regimens. This is because statins primarily work by reducing the amount of LDL-C circulating in the body via inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme. Statins are separated into two main groups representing how well they can reduce LDL-C levels from baseline [Table 1]. The 2018 ACC/AHA guidelines have continued to recommend statins based on ASCVD risk and LDL-C levels, remaining unchanged from the 2013 ACC/AHA guidelines.[6,8]

Table 1: Intensity of statin therapy, corresponding percentage of LDL-C lowering, and the four major recommended indications

Statin grouping (% LDL reduction from baseline)	Therapy	Indications for use
High-intensity (≥50%)	• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg	• Clinical ASCVD age <75 • LDL-C ≥190 mg/dL • Diabetics aged 40-75 with LDL-C 70-189 mg/dL with 10-year ASCVD risk ≥7.5%

Moderate-intensity (30-49%)	• Atorvastatin 10-20 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg • Pravastatin 40-80 mg • Lovastatin 40 mg • Fluvastatin 80 mg • Pitavastatin 2-4 mg	• Clinical ASCVD age ≥75 • LDL-C ≥190 mg/dL (if unable to tolerate high-intensity statin) • Diabetics aged 40-75 with LDL-C 70-189 mg/dL with 10-year ASCVD risk ≤7.5% • Non-diabetics aged 40-75 with LDL-C 70-189 mg/dL with 10-year ASCVD risk ≥7.5%

Non-statin lipid-lowering agents: Since the publication of the 2013 ACC/AHA cholesterol guidelines, new RCTs have found a role for ezetimibe along with ushering in the latest class of lipid-lowering agents known as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Both agents are limited to secondary prevention of ASCVD events in very-high risk patients.[8]

Although bile-acid sequestrants reduce LDL-C by 15-30%, ezetimibe is more commonly used due to being better tolerated and more affordable.[8] Despite evidence of ezetimibe's lipid-lowering effect, its use was not studied in lowering ASCVD events and questions remained on its clinical benefits. The SHARP trial opened the door to ezetimibe in combination with a statin to reduce CV events.[9] However, it was unclear if ezetimibe was the sole reason to CV event reduction. Based on the landmark IMPROVE-IT trial, ezetimibe lowered LDL-C by 13-20% when used as an adjunct to statin therapy, equating to a significant 2% lowered risk of CV events over statin monotherapy.[10] The addition of ezetimibe is therefore recommended for patients with clinical ASCVD with continued LDL-C ≥70 mg/dL on maximally tolerated statin therapy. ACC/AHA has further suggested that there is no added risk in how low LDL-C can go.[8]

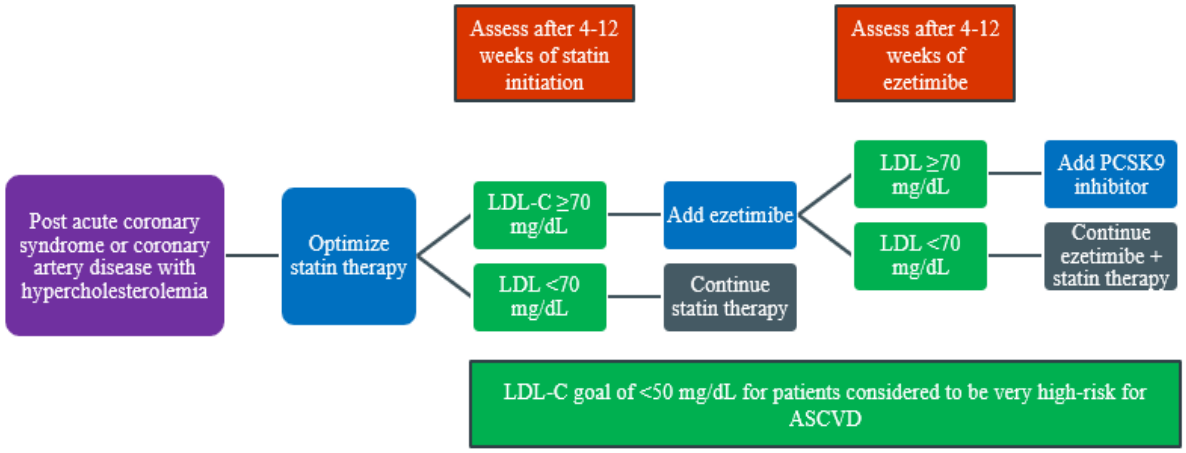
PCSK9 is a proprotein convertase that acts by eliminating LDL receptors in the liver and therefore results in reduced LDL clearance from the blood. PCSK9 inhibitors (alirocumab and evolocumab) are human monoclonal antibodies that block the activity of PCSK9 and thereby lower LDL-C levels by 43-64%. The 2018 ACC/AHA guidelines suggest adding a PCSK9 inhibitor to existing statin and/or ezetimibe therapy for patients with clinical ASCVD and continued LDL-C ≥70 mg/dL or a non-HDL level of ≥100 mg/dL. Due to their cost, despite PCSK9 inhibitors being well tolerated and reducing LDL-C levels significantly, their value per quality-adjusted life year (QALY) is low (>$150,000/QALY).[8]

What to expect in practice: The 2018 ACC/AHA guideline calls on pharmacist-led interventions to improve patient adherence through telephone/calendar reminders, education, and simplification of drug regimens. For pharmacists working in the community and ambulatory care settings, this may mean evaluating the appropriate dosage of lipid-lowering agents, monitoring for adherence and adverse events, and removing agents or simplifying dosing frequency where applicable.

For ambulatory care pharmacists, assessing LDL-C levels for response to therapy is an added component. The 2018 ACC/AHA guidelines suggest treating patients to a goal LDL-C <70 mg/dL. If the patient is considered very-high risk, an LDL goal of <50 mg/dL is recommended.[8] In addition, ambulatory care pharmacists may see ultra-low LDL-C levels as low as <10 mg/dL. Efficacy data suggests that LDL-C levels <10 mg/dL saw more than a 40% lower risk of CV events when compared to patients with LDL-C levels ≥100 mg/dL. There were no

significant adverse events associated with ultra-low LDL-C levels.[11] Lastly, pharmacists must be aware and able to recommend these new treatments that incorporate non-statin use [Figure 1].

Figure 1: Clinical Algorithm for Managing LDL-C[12]



Adapted from Rosenson RS, et al. *J Am Coll Cardiol.* 2018;72(3):314-29.

Conclusion: Aggressive lowering of LDL-C is receiving more attention as research suggests that ultra-low LDL-C levels may be safe to prevent CV events. Statin monotherapy may soon be a thing of the past as adjunct therapy with ezetimibe and PCSK9 inhibitors may become more prevalent. As the long-term safety and benefits of PCSK9 inhibitors continues to be elucidated, pharmacists must familiarize themselves with the indication, dosage, formulation, and storage of these new agents. This may be the dawn of a new era and pharmacists are well equipped to assist on the front line.

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