MSHP Pharmascript

Volume 41, Issue No. 1
First Quarter

What's Inside This Issue?

Article Submission Deadlines for Upcoming Newsletters

March 17th, 2017 for the April 2017 Edition
June 16th, 2017 for the July 2017 Edition
September 15th, 2017 for the October 2017 Edition
December 15, 2017 for the January 2018 Edition

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.

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Medication Safety Corner:

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In 2004, The Maryland Hospital Safety Program (COMAR 10.07.06) was passed into legislation. This legislation outlines the steps that must be followed in the event of a preventable medical error that involved death or serious physical or psychological injury. A root cause analysis must be conducted for all level 1 and 2 adverse events within 60 days of the time that the hospital is notified of the event. A root cause analysis is a review process used to identify and analyze various factors that lead to an adverse event. The focus is typically not on the

actions of the individual that caused the error but on the systems in place that allowed the error to occur. A level 1 adverse event is an adverse event that is unrelated to the patient's illness that results in death or serious disability. An example of a level one adverse event is a patient receives a medication that is incorrectly dosed resulting in an overdose that leads to death. Level 1 adverse events must be reported to the Department of Health and Mental Hygiene within 5 days of the hospital's awareness of the event. A level 2 adverse event is an adverse event that requires a medical intervention to prevent death or serious disability. An example of a level 2 adverse event is if subsequent surgery is required to remove items left in a patient after a surgery. Once a root cause analysis is preformed, the hospital's designated medication safety committee is expected to develop and execute an action plan to prevent the sentinel event from occurring again.

The first step is to identify the sentinel event and provide care to the patient if able to do so. Hospitals are expected to have a reporting system for employees to report adverse events so that the patient safety committee may appropriately identify sentinel events. Once that has occurred the committee must analyze the event to determine why and how the event occurred. The resulting action plan should outline the expected oversight needed to execute the change required to reduce the probability a similar error will occur and a way to properly examine the efficacy of the action plan. For more information regarding the requirements of a patient safety program please refer to "COMAR 10.07.06: Hospital Patient Safety Program".
(http://dhmh.maryland.gov/ohcq/hos/docs/Patient%20Safety/Tool%20Kit/10.07.06.pdf)

Student's Perspectives on Pharmacist-Provided Home-Based Medication Management

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Home-based medication management (HBMM) is a unique program developed by a multidisciplinary team at The Johns Hopkins Hospital (JHH). Through this program, pharmacists see patients in the environment where the patient feels most comfortable – their own home. Patients are referred for a home visit during their hospitalization at JHH or Johns Hopkins Bayview Medical Center (JHBMC) or during a clinic visit at East Baltimore Medical Center (EBMC). The service is free for patients and completely voluntary. Referral reasons include: complex medication regimens, adherence issues, significant changes to medication regimens, or medication-related education needs that would be best addressed at home (e.g. inhaler technique, insulin administration teaching).[1]

Pharmacists are trained for HBMM by attending a service orientation and a safety class. The service orientation introduces the referral process, review of in-home visit procedures, and orientation to the electronic medical record. The safety class is provided by Johns Hopkins corporate security. The focus of the training is on in-home awareness, driving and parking safely, and service-specific safety precautions. Safety is a main priority of the home visit service. HBMM visits require two pharmacists/residents and/or student to attend the visit. If there is a last-minute cancellation among one of the two attendees, the visit must be rescheduled.[1]

Pharmacy students play a key role in making the home visit service successful. They not only serve as visit partners, as mentioned above but they also lead portions of the visit and prepare adherence tools for patients such as medication calendars and pillboxes. Below, two students share their perspectives on being involved in home visits:

> "Before my home-visit, I was nervous, not knowing what to expect in this patient's home. When my preceptor and I arrived at our patient's house we were welcomed into her living room. She had arranged all of her medication vials, inhalers, and pillboxes for us to review. We had brought her a typed calendar, showing her medications and what time of day she takes them, however she said that the font was too small for her to read. I observed the compassion of my preceptor as he took the time to handwrite each of her medications in a new calendar so that it was large enough for her to read. Additionally, while we were at her house, she received a phone call from her son. My preceptor was kind enough to talk to him for a few minutes and arrange a follow-up call so they could further discuss his mother's care.

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As we were talking with the patient, we identified potential barriers for her to remain adherent to her extensive medication regimen. We also discussed some options to help improve her medication adherence. At the end of the visit, our patient endorsed that she understood her medication regimen and she hugged us both in gratitude." - *Ashley Fan,* Pharmacy Student

"I have been fortunate enough to attend two home-visits within the last month. Both home-visits were with one community pharmacy resident. Additionally, both home-visits were a valuable and unique experience for a pharmacy student. The most recent visit required us to provide guidance and clarification on the indications for the medications a patient was taking. Of note, this specific patient had slight dementia with symptoms of forgetfulness and memory loss. We were welcomed by the patient into her living room and started to discuss the patient's daily routine in order to accurately assess what intervention would benefit the patient most. We had a friendly conversation with the patient and formulated a plan to help the patient with her medications. First, we went through all of her medications and sorted her multiple pillboxes. We soon realized the complexity of the medication regimen the patient had. We ultimately went through each medication, discussed the indication, simplified her medications in one pillbox rather than three pillboxes, and wrote notes around the house as reminders to take her medications in the morning and in the evening. Furthermore, we were able to properly connect her medical alert necklace to ensure her safety. We made additional recommendations encouraging her to keep a consistent routine, to take notes in a notebook so as to not forget them in the future, and to continue filling just one pill box vs. the multiple pill boxes she was filling before our visit. Throughout the entire visit, the patient expressed how happy she was to have us there with her.

There are not many instances where students have exposure to pharmacist provided home-based visits. These visits helped me gain insight to the other services that pharmacists could provide that will hopefully prevent admissions to hospitals and medication errors, all in the comfort of the patient's home." - *Erika Pineda*, Pharmacy Student

From a student's perspective, there are pros and cons in conducting home visits. First, being in the patient's home makes the patient feel comfortable and at ease to open up to the pharmacist about any medication issues they may have. Additionally, many patients may face transportation barriers that prevent access to adequate healthcare. With HBMM visits, this eliminates the barrier of having a lack of transportation for the patient in order to receive care. Furthermore, the pharmacist can gain better insight about the patient and enhanced perspective on the barriers the patient may be facing. Through this service, potential medication errors have been prevented. Some of the medication discrepancies found in the home include differences in dosing and frequency. The home is the ideal place to catch these discrepancies since patients usually come to clinic or to the pharmacy without their medications. Most importantly, this service provides continuity of optimal healthcare for transitions from hospital discharge to a patient's home or as a touch base between clinic visits.

On the other hand, there are a few limits and risks in conducting a pharmacist-provided HBMM visits. Home-based medication visits are time consuming. Each visit is scheduled for a one hour block in order for the pharmacists and residents and/or students to conduct the visit. However, this may limit how many patients a pharmacist can reach. In addition, safety is an issue for the pharmacists providing the service. As mentioned above, pharmacists always visit patients in teams of two and if they perceive the area to be a safety concern, they will opt to arrange for the patient to come to the pharmacy vs. going to the home.

The home visit service has demonstrated positive impact on patients and providers.. By visiting the patient in their home, there may be a greater appreciation of the pharmacist being a valued resource in regards to helping with their medications. In addition, this leads to a greater appreciation for pharmacist-provided services that are provided outside of a traditional community pharmacy setting. According to Pherson et al, a patient survey was conducted post-HBMM visit resulting in 98% of 50 patients agreeing the service provided help with their medications with 63% reporting a dramatic improvement in understanding of their medications. From a provider's perspective, this service may help prevent hospital readmission due to medications errors. From our involvement as students, we saw that primary care physicians appreciated the time and effort we had put into making sure the patient received optimal care. In the same study mentioned above, a mean of 2.5 recommendations were made to the provider per patient visit. These recommendations included dose adjustments, suggestion of laboratory monitoring, adding/discontinuing medications, refill notification, and medication formulation change. Overall, three educational interventions were made per patient including instructions on monitoring parameters (disease state and medication related), medication adherence reinforcement, therapeutic lifestyle changes, disposal of expired/discontinued medications, and medication administration instructions.[1]

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These data, along with our experiences in helping conduct the HBMM-visits, show that pharmacist home visits provide an important and valuable service. These visits help patients fully understand for the purpose and side effects of their medications. A home visit is an ideal option for patients who have physical barriers of transportation to a pharmacy. By visiting with the patient at home these pharmacy teams are putting patients in a position to be empowered and knowledgeable about their medications, while enjoying the comforts of their own homes.

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New Advancements in Artificial Pancreas Device Systems

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With the growing prevalence of diabetes amongst the population and the rapid advancements in treatment modalities, prescribers are increasingly turning to pharmacists to assist with diabetes management. The following article covers the most recent advances in artificial pancreas device systems (APDS) so that pharmacists can stay abreast of innovations in medical technology.

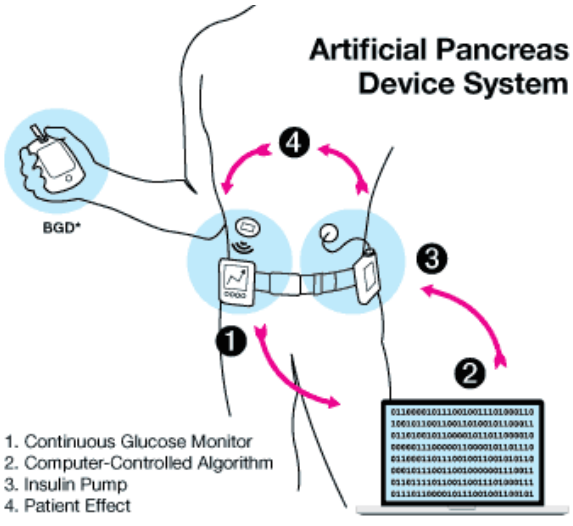
Background
Diabetes is a disease state often related to dysfunction with the pancreas. It is therefore logical that insulin based diabetes management has sought to mimic the glucose sensing and insulin release functions of the pancreas. As such, patients self-monitor blood glucose and self-administer insulin as a mainstay of treatment. While treatment has progressed in lockstep with advances in technology, moving from the 1970's archaic capillary based glucose monitors to futuristic continuous subcutaneous glucose monitors, the basic treatment algorithm for the average patient with diabetes has remained the same.

Artificial Pancreas Device Systems
Artificial pancreas device systems (APDS), specifically closed-loop systems, aim to take the next step in diabetes management by completely removing the patient from making decisions on insulin treatment. Figure 1 illustrates the basic components of a generic APDS.

APDS incorporate continuous glucose monitoring and insulin pump technologies that are already available on the market today. The differentiation with APDS is the inclusion of a computer algorithm either installed on a separate controller or, potentially, on a smartphone or similar device. This software is responsible for processing data collected from the glucose monitor to determine how much insulin to administer to maintain tight glucose control. Research has shown that this "closed-loop" between glucose monitor, computer algorithm and insulin pump has resulted in increased time within target blood glucose range, reduced frequency of hypoglycemia and better overnight control in comparison to an "open-loop" system that requires patient input.

Market Approval of First Hybrid Closed-Loop APDS On September 28th, 2016, the FDA announced market approval for the Medtronic's MiniMed ® 670G System, the first ever hybrid closed-loop APDS.[2] This system is indicated for Type 1 diabetic patients to monitor blood glucose and administer basal insulin. The hybrid designation is due to the limitation that patients will still need to carbohydrate count and administer bolus insulin. Even with this limitation, the pivotal trial used for market approval demonstrated trends towards a 0.5% improvement in A1C amongst 124 patients over a three-month period, with no DKA events or severe hypoglycemia.[3]

Figure 1 – APSD Components[2]



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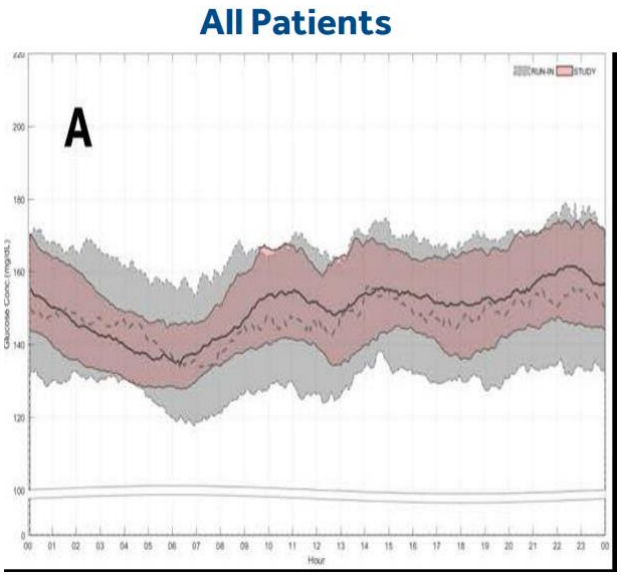
In addition, the most striking aspect of the trial, as illustrated in Figure 2, shows the reduction in glycemic variability throughout an average day. The grey shaded area in the graph shows a two-week run in time where patients utilized the glucose monitor and insulin pump in an "open-loop" manner, while the red shaded area shows a three-month period where patients utilized the system fully. As the graph demonstrates, the APDS is able to maintain significantly tighter glycemic control throughout the day.

An important limitation to this clinical trial is that the primary objective was to evaluate safety of the system with primary endpoints revolving around hypo- and hyper-glycemic episodes. The trial was not designed to determine efficacy of the system, and any improvement in clinical outcomes cannot be correlated to the device.[4]

Future Advancements in APDS

As noted previously, this first system approved is not a true closed-loop APDS. However there is ongoing development and research by other medical equipment companies to create a truly autonomous APDS as well as developing additional features to more fully mimic a biologic pancreas. Some examples of these features include ultra-rapid acting insulin and more responsive glucose sensors to react swiftly to changes in glucose levels and bi-hormonal systems that not only use insulin to control high glucose levels, but glucagon to control low glucose levels. In addition, APDS development is not only limited to outpatient and ambulatory sitesas inpatient systems are also being researched and developed.[5] Overall, it is an exciting time to be a practitioner as novel means to manage diabetes enter the market.

Figure 2 - Average glucose ranges during APDS safety clinical trial[3]



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MSHP Call for Speakers

We are seeking pharmacists and technicians to provide timely, relevant, and high-quality presentations for our bi-annual professional development seminars.

Our next session is the MSHP Spring Seminar on Friday, April 14, 2017.
DoubleTree by Hilton Hotel Annapolis
210 Holiday Ct, Annapolis, MD 21401

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Pharmascript

Volume 41, Issue No. 1
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Updates in Multiple Myeloma Treatment Options

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The landscape for multiple myeloma (MM) treatment is rapidly changing. Among other updates, the 2016 National Comprehensive Cancer Network (NCCN) MM treatment guidelines[1] now include an oral proteasome inhibitor, ixazomib, and two first-in-class agents, daratumumab and elotuzumab to therapy regimens. These new therapies can yield improvements in patient outcomes such as progression-free survival (PFS), overall survival (OS), tumor burden, and quality of life[2,3]. Given the expansive use of these agents, it is important that pharmacists in any health care setting are knowledgeable about agents' efficacy and toxicity profiles.

Daratumumab established itself as the first monoclonal antibody approved by the Food and Drug Administration (FDA) for treatment of MM. By targeting the CD38 transmembrane glycoprotein highly expressed on MM cells, daratumumab provides a novel mechanism to combat an incurable disease. It also has immunomodulatory effects, possibly offering a separate mechanism in combating MM. In the phase II SIRIUS trial[4] for patients with MM who had been treated with at least three prior lines of therapy or were refractory to both proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), daratumumab monotherapy conferred a 29.2%overall response rate (ORR) (95% CI, 20.8-38.9) with a median duration of response of 7.4 months. Median PFS was 3.7 months and 12-month overall survival was 64.8% (95% CI, 51.2 – 75.5). Consistent with the agent's favorable safety profile, there was no treatment discontinuation due to drug-related adverse effects or infusion related reactions in this trial. Optimistically, daratumumab seems to maintain its activity even in patients refractory to both IMiDs and PIs[4,5]. Daratumumab shows great synergy with other agents as well. It has been granted FDA breakthrough therapy designation in combination with lenalidomide/ dexamethasone (Rd) or bortezomib/dexamethasone (Vd) after at least only 1 previous therapy. In the CASTOR trial[6], patients who received 1-3 prior therapies were randomized to receive daratumumab with Vd or Vd alone. 1-year PFS was 60.7% (95% CI 51.2 – 69) in the daratumumab compared with 26.9% (95% CI, 17.1 – 37.5) in Vd alone. Expert Sagar Lonial, MD, writes "the hazard ratio of 0.39 is one of the best HRs seen in a randomized phase III trial for MM, and this could turn out to be one of the longest median PFS times seen in the context of relapsed MM.[7]" The ongoing POLLUX trial[8] is also demonstrating substantial PFS benefit in combination with an IMiD. Patients receiving daratumumab and Rd achieved 78% PFS at 18-months compared with 52% in patients receiving Rd alone, yielding a hazard ratio of 0.37 (95% CI, 0.27 – 0.52). Projected PFS is expected to reach 40 months for patients receiving daratumumab and Rd. Experts suggest that a broad range of agents may provide benefit in combination with daratumumab, comparing it with the use of rituximab in the treatment of lymphomas[7].

Elotuzumab was approved just two weeks after daratumumab by the FDA. Though not shown to have anti-myeloma activity as a single agent, Elotuzumab has shown improved response rates when combined with other anti-myeloma agents. Elotuzumab targets SLAMF7, which is highly expressed in normal plasma, MM, and natural killer (NK) cells. The mechanisms of action include mediating antibody-dependent cell-mediated cytotoxicity (ADCC), enhancing NK cell cytotoxicity, and disrupting MM cell adhesion to bone marrow stromal cells. The ELOQUENT-2 study compared elotuzumab plus Rd with Rd alone for relapsed/refractory multiple myeloma (RRMM)[9]. The overall response rate (ORR) in the elotuzumab group was 79% (95% CI, 74 – 83) compared with 66% (95% CI 60 – 71) for the control. The PFS rate was 68% (95% CI, 63 – 73) vs. 57% (95%, CI 51 – 62) for the elotuzumab and control groups at 1 year; this improvement persisted after a 3-year follow up period. Notably, the addition of elotuzumab increased the time to next therapy by almost 12 months. The elotuzumab group had a higher rate of lymphocytopenias, and with mandatory premedication, infusion reaction occurrence was 10%. However, patients older than 65 years responded similarly to younger patients, indicating good overall tolerance. Clinical trials are further investigating the efficacy of elotuzumab in monotherapy and with IMiD or PI combinations in both untreated and RRMM.

Ixazomib is an oral, reversible PI with higher tissue distribution and a shorter dissociation half-life than bortezomib[10]. TOURMALINE-MM1[11] demonstrated that in patients who had received 1-3 previous lines of therapy, ixazomib's combination with Rd yielded median PFS of 20.6 months compared with 14.7 months with Rd alone, and the hazard ratio for disease progression or death was 0.74 (95% CI, 0.59 – 0.94). ORR was 78.3% compared with 71.5% (P = 0.04) in the Rd group. Serious side effect rates did not differ dramatically between ixazomib (47%) and placebo (49%). This new therapy in combination with Rd allows for an entirely oral triple therapy regimen for patients who have received at least one prior therapy.

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Panobinostat is a potent histone deacetylase inhibitor (HDAC) that damages DNA and upregulates proteins that promote apoptosis and cell-cycle arrest in MM cells. The PANORAMA-1 study compared panobinostat in combination with Vd with Vd alone in patients who had received prior treatment with an IMiD and bortezomib[12]. The results showed 12 months PFS compared with 8.1 months ($P < 0.0001$). However, study investigators found no OS difference between the groups; patients more commonly discontinued treatment because of adverse events in the panobinostat group (34% vs. 17%). PANORAMA-2 was a phase II trial that demonstrated an ORR of 34.5% and a median PFS of 5.4 months in patients with the same combination therapy.[13]

As the options to treat patients with MM optimistically expand, healthcare practitioners can expect to see more of these medications, in various combinations, in practice. Given the nature of the incurable malignancy, patients will be exposed to many of these regimens, given the incurable, progressive nature of the malignancy.[14] Given the incidence of this malignancy and the outpatient nature of treatment paradigms, pharmacists can play pivotal roles in assisting with therapeutic decision making as well as provide and patient education.

NEW AGENTS	Daratumumab (DARZALEX)[15]	Elotuzumab (EMPLICITI)[16]	Ixazomib (NINLARO)[17]	Panobinostat (FARYDAK)[18]
Drug Class	CD38-directed monoclonal antibody	SLAMF7 monoclonal antibody	Proteasome inhibitor (PI)	Histone deacetylase inhibitor (HDAC)
Mechanism of Action	IgG1-kappa human monoclonal antibody that binds to CD38 transmembrane glycoprotein on tumor cells and induces apoptosis through Fc mediated cross-linking; and immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis.	Humanized IgG1 monoclonal antibody targeting the SLAMF7 protein mediating destruction of myeloma cells via antibody-dependent cellular toxicity (ADCC) through direct activation of NK cells and facilitation of interaction of MM cells with NK cells	Reversible proteasome inhibitor that induces apoptosis of MM cells.	Inhibits removal of acetyl groups from lysine residues of proteins resulting in relaxation of chromatin and transcriptional activation. Ultimately induces cell cycle arrest or apoptosis, with an affinity for tumor cells
NCCN Guidelines[1] Place in Therapy	Monotherapy, with bortezomib/dexamethasone, or with lenalidomide/dexamethasone after prior therapy	With lenalidomide/ dexamethasone or bortezomib/ dexamethasone after prior therapy	With lenalidomide/ dexamethasone as primary therapy or after prior therapy or with dexamethasone after prior therapy	With bortezomib/ dexamethasone or carfilzomib after prior therapy
Dosing and Administration	16mg/kg **IV** weekly x eight weeks → every two weeks x sixteen weeks → every four weeks until disease progression	10mg/kg **IV** every week for two twenty-eight day cycles → every two weeks until disease progression	Starting dose of 4mg **PO** on days 1, 8, and 15 of a twenty-eight day cycle	20mg **PO** on days 1, 3, 5, 8, 10, and 12 of weeks one and two of each twenty-one day cycle for eight cycles. Consider continuing treatment for an additional eight cycles for patients with clinical benefit.
Cost of first year of treatment based on Wholesale Acquisition Price from RED BOOK®)	~$115,000 (based on 70kg patient) for 52 weeks of treatment	~$124,350 (based on 70kg patient) for 52 weeks of treatment	$112,710 for 13 four-week cycles (52 weeks of treatment)	~$117,312 for 16 twenty-one-day cycles (48 weeks of treatment)

SLAMF7 = Signaling Lymphocytic Activation Molecule Family member 7; NK = Natural Killer; MM = Multiple Myeloma; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group

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NEW AGENTS	Daratumumab (DARZALEX)[15]	Elotuzumab (EMPLICITI)[16]	Ixazomib (NINLARO)[17]	Panobinostat (FARYDAK)[18]
Serious Side Effects	Anemia, lymphocytopenia, neutropenia, thrombocytopenia, pneumonia, infusion reaction, herpes zoster reactivation	Skin cancer, anemia, leukopenia, lymphocytopenia, malignant tumor of lymphoid hematopoietic and related tissue, thrombocytopenia, hepatotoxicity, herpes zoster, mycosis, opportunistic infection, acute renal failure, pneumonia, pulmonary embolism, respiratory tract infection, cancer, fever, infection disease, infusion reaction	Neutropenia, Thrombocytopenia, thrombotic thrombocytopenic purpura, cholestatic hepatitis, hepatocellular liver damage, hepatotoxicity, injury of liver, steatosis of liver	• BOX WARNING: severe diarrhea and cardiac toxicities Cardiac dysrhythmia, T-wave abnormalities, hemorrhage, myocardial ischemia, ST segment depression, diarrhea, anemia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia, abnormal liver enzymes, infection disease
Common side effects	Nausea, anemia, lymphocytopenia, neutropenia, thrombocytopenia, backache, cough, upper respiratory infection, fatigue, fever	Constipation, decreased appetite, diarrhea, asthenia, peripheral nerve disease, cough, nasopharyngitis, upper respiratory infection	Peripheral edema, constipation, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, backache, peripheral nerve disease, disorder of eye	Anemia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia, fatigue
Dose adjustments	None	None	• Moderate/severe hepatic impairment: reduce initial dose to 3mg • Severe renal impairment or ESRD on dialysis: reduce initial dose to 3mg	• NCI-ODWG mild hepatic impairment: reduce starting dose to 15mg • NCI-ODWG moderate hepatic impairment: reduce starting dose to 10mg • Avoid in patients with severe hepatic impairment
Counseling/ Clinical Pearls	• Infusion reactions can be delayed up to 4 hours • Corticosteroid, antipyretic and antihistamine pre-medications recommended • Corticosteroid post-medication recommended • Interferes with cross-matching and red blood cell antibody screening	• Infusion reactions can be delayed up to 24 hours • Dexamethasone, diphenhydramine, ranitidine, and acetaminophen pre-medications recommended	• Effective contraception is required during` and 90 days following treatment. • Contact with contents of capsule should be avoided • Take on an empty stomach • Drug interactions with strong CYP450 inducers	• Communication plan Risk Evaluation and Mitigation Strategy (REMS) • Should not be used in patients with recent MI, unstable angina, QTC ≥ 450msec, or clinically significant ST-segment or T-wave abnormalities • Women should avoid pregnancy for at least three months following therapy, and men should not impregnate women for at least six months following therapy. • Drug interactions with strong CYP3A4 inhibitors and inducers, sensitive CYP2D6 substrates, and anti-arrhythmic/QT-prolonging drugs

SLAMF7 = Signaling Lymphocytic Activation Molecule Family member 7; NK = Natural Killer; MM = Multiple Myeloma; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group

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MSHP Pharmascript

Volume 41, Issue No. 1
First Quarter

Re-Thinking Pharmacists' Roles in Transitions of Care

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Transitions of care may seem like a healthcare "buzz phrase," but it truly is an activity in which every care provider along the care continuum should engage. In general, one of the primary roles for pharmacists in transitions of care is medication reconciliation, but our involvement can, and should, go far beyond.

Transitions of care is the movement of a patient from one setting of care to another.[1] Examples include transitioning a patient from one level of care in the hospital to another and from the hospital to a long-term care facility. While seemingly simple, ineffective care transitions are not uncommon and have been shown to lead to adverse events for patients, increased costs for patients and hospital, and higher hospital readmission rates.[2] In 2012, The American College of Clinical Pharmacists (ACCP) published a white paper about current practices and future opportunities for pharmacists to improve transitions of care.[3] While many strategies were suggested, it seems that, in some institutions these suggestions were narrowed to just one solution: medication reconciliation. Today medication reconciliation is the most well-known form of pharmacist involvement in transitions of care.

Among the proposed benefits of medication reconciliation are a reduction in medication errors at admission and discharge, identification and prevention of adverse drug events, and minimization of patient confusion and/or enhancement of patient understanding about medication changes. Hundreds of studies have looked at these proposed benefits as study outcomes, and some have shown that medication reconciliation does make a significant difference in the outcomes of interest, whereas others have shown no difference between an established medication reconciliation process and standard of care. Therefore, it's important to understand the limitations of medication reconciliation as a transitions of care service. A major limitation seen with the studies published to date is the inability to translate medication reconciliation findings into clinically meaningful outcomes.

A multitude of studies featuring pharmacist-driven care transition activities beyond medication reconciliation have emerged over the past decade. These activities range from discharge prescription review for pediatric patients[4] to pharmacist-led efforts to discontinue stress ulcer prophylaxis and delirium therapy at the transition from an intensive care unit (ICU) to a step-down floor.[5] In addition to pharmacist-driven activities, other novel transition of care activities that have not incorporated a pharmacist may benefit from doing so. One such study described antimicrobial stewardship at the transition from the hospital to the community setting.[6] A brief description of each of these studies follows.

Discharge prescription review for pediatric patients[4]: Christensen and Morgan described a transitions of care initiative that aimed to determine if a pharmacist-provided discharge prescription review service enhanced the safety and accuracy of prescriptions written at an academic pediatric hospital. In this intervention, discharge prescriptions were written and faxed to the inpatient pharmacy and were then reviewed by a pediatric pharmacy clinical specialist. The pharmacists reviewed 74 prescriptions for 24 patients discharged during the 30-day study period, and from these 74 prescriptions, 81% contained at least one prescribing error. A total of 101 prescribing errors were detected, indicating that many prescriptions had more than one error. Approximately 50% of the pharmacists' interventions were for prescriptions that omitted the patient's date of birth and just over 15% of interventions were for both omission of the patient's weight or inappropriate weight-based dosing calculations. Interventions made by the pediatric clinical specialists may have prevented adverse drug events post-discharge.

Pharmacist-led efforts to discontinue medications at the transition from an ICU to a step-down floor[5]**:** Fujinaka and Louzon evaluated if pharmacist intervention during the transition from an ICU to a progressive care unit impacted days of unnecessary stress ulcer prophylaxis (SUP), delirium therapy, or ICU-restricted medications for patients admitted to a medical ICU.

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In this intervention, after a prescriber prepared the patient's medication list for transfer, a pharmacist would review the list for the therapies of interest using a checklist, clinically assess the need for continuation, and contact the prescriber if discontinuation of a medication was indicated. During the study period, pharmacists reviewed transfer orders for 184 patients and as a result of recommending the discontinuation of unnecessary SUP and ICU-restricted medications, 357 SUP and 52 ICU-restricted days of therapy were saved. 264 ICU-restricted medications were also discontinued with unnecessary sedation and vasopressors as the most frequently recommended discontinuations. Interventions made by the pharmacists likely prevented confusion with the medication list when the patient arrived to the floor from the ICU and also resulted in cost savings for the institution.

Antimicrobial stewardship at transition of care from hospital to community[6]: Shrestha and colleagues examined whether parenteral antimicrobial avoidance through stewardship efforts at discharge led to harm from inadequately treated infections for adult patients. The study looked at ED visits and readmissions for patients in whom outpatient IV therapy was approved vs. those in whom it was avoided. All patients to be discharged on IV antimicrobial therapy were evaluated by an ID staff physician who decided if the patient would receive IV or enteral discharge antibiotics, and the patient's clinical course was then followed for 30 days. During the study period, there were 244 consultations for outpatient IV therapy and for these patients, 72% were approved to receive outpatient IV therapy and in 28% outpatient IV therapy was avoided. For patients in whom outpatient IV therapy was approved, 26% had an ED visit or readmission to the hospital, and for patients in whom outpatient IV therapy was avoided, 39% had an ED visit or readmission to the hospital, which was a difference that trended towards but did not reach statistical significance (p=0.05). It's important to note that in this process, no pharmacist involvement is mentioned, but pharmacists who assist with discharge planning and/or infectious disease-trained pharmacists would be a valuable addition to any antimicrobial stewardship model. Furthermore, this study should lead us to ponder the need for pharmacist involvement in antimicrobial stewardship efforts post-discharge.

The studies described above are only a few examples of the expanded roles pharmacists may play in transitions of care services. Other opportunities for pharmacists may include pain management for patients as they transition from the hospital to a long-term care facility, medication management during the transition from an oncologist to a primary care provider after surviving cancer, and medication management for a young patient with a chronic illness as they transition from pediatric care to adult care. Like most medication reconciliation studies, these studies, and many others, report a mix of structure, process, and outcomes measures. As pharmacists continue to proactively develop and implement new transitions of care services for their patients (and we should!), it will be important to continue to assess and optimize these services using measures that accurately reflect clinically meaningful outcomes.

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Pharmascript

Volume 41, Issue No. 1
First Quarter

New Drug Update: Bezlotoxumab (Zinplava™)

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In October 2016, the Food and Drug Administration (FDA) approved bezlotoxumab (Zinplava™), a monoclonal antibody that is indicated to reduce recurrence of *Clostridium difficile* infection (CDI) in patients receiving antibacterial drug treatment for CDI at high risk for recurrence.[1,2] In 2011, the estimated incidence of CDI across the United States was 453,000 cases, which was associated with 29,000 deaths.[3] An estimated 20% of patients will develop recurrent CDI after their first episode, with an increased risk in the case of hypervirulent strains.[4] According to the 2010 Infectious Disease Society of America (IDSA) guidelines, first recurrence of CDI is usually treated with the same regimen as the initial episode, either metronidazole or oral vancomycin depending on severity.[5] In the case of a second recurrence, oral vancomycin should be used due to the risk of neurotoxicity with prolonged metronidazole use. Other options, albeit limited, for recurrent CDI, include oral vancomycin taper, rifaximin, fidaxomicin, and in extreme cases a fecal transplant or colectomy.[5,6] It is important to note that these guidelines are in the process of being updated and additional guidance may be available in the coming year regarding these additional options. The lack of a well-defined treatment strategy has warranted the development of novel agents, such as bezlotoxumab, which acts by binding to *Clostridium difficile* toxin B thereby neutralizing its effects.

The efficacy and safety of bezlotoxumab was evaluated in two randomized, double-blind, placebo-controlled, multicenter, phase 3 trials (MODIFY I and II).[1,6-10] Enrolled patients received standard of care (SoC) antibacterial treatment, with randomization stratified according to therapy received (vancomycin/fidaxomicin/metronidazole) and treatment setting (inpatient/outpatient). Patients had a confirmed diagnosis of CDI defined as diarrhea (3+ loose bowel movements ≤24 hours) and a *C. difficile* toxin positive stool test.[1,6-10] Patients were randomly assigned to receive 10-14 days of SoC and a single 10 mg/kg bezlotoxumab infusion (n=810) or placebo (n=803).[1,6-10] The primary efficacy endpoint was *C. difficile* infection recurrence and the secondary efficacy endpoint was sustained clinical response, or global cure rate. Both MODIFY I and II showed that a single dose of bezlotoxumab was superior to placebo for preventing recurrent CDI (p=0.0003), with a 10% average reduction in recurrence rates.[3] In trial 1, 60.1% of bezlotoxumab patients and 55.2% of placebo patients met criteria for having a sustained clinical response.[1,6-10] In trial 2, 66.8% of bezlotoxumab patients and 52.1% of placebo patients met criteria for having a sustained clinical response.[1,6-10] Increased infusion reactions (10%), nausea (7%), pyrexia (5%) and headache (4%) were the only notable differences in adverse effects between bezlotoxumab and placebo.[1,6-10]

The limited literature available has shown that bezlotoxumab may be a safe and tolerable way to prevent the recurrence of CDI, although additional published clinical data is needed prior to identifying its appropriate place in therapy. Before verifying and dispensing this medication, pharmacists should be aware of a few key points. Fortunately, there are no current black box warnings or contraindications for the use of bezlotoxumab, but in Phase 3 clinical trials some patients with pre-existing congestive heart failure (CHF) were found to have worsening CHF. Due to this there is a warning included in the package insert that states bezlotoxumab should only be used in patients with known CHF if the benefit is thought to outweigh the risk. The side effect profile of bezlotoxumab is mild with the three most common adverse events being nausea, pyrexia, and headache. No metabolic drug-drug interactions are expected because the drug is eliminated via catabolism. The approved dosing of bezlotoxumab is a single dose of 10 mg/kg infused intravenously over 60 minutes with a 0.2 to 5-micron filter. Before use, bezlotoxumab must be diluted to a final concentration between 1 mg/mL and 10 mg/mL. Lastly, bezlotoxumab must be stored in the refrigerator until diluted. The prepared solution must be administered within 16 hours if kept at room temperature or within 24 hours if kept refrigerated.[1] The cost of bezlotoxumab is not yet available from the manufacturer.

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