

Postgraduate (PGY-1) Pharmacy Residency Program

CURBSIDE CONSULT

UNIVERSITY OF MINNESOTA

College of Pharmacy

Driven to Discover™

Updates in Pharmacotherapy

*Resident Editors: Amanda Bisel, Pharm.D., David Bunch, Pharm.D., Kyle Walburg, Pharm.D.
Faculty Editor: Jody Lounsbery, Pharm.D., BCPS*

Volume 17, Issue 3 – Third Quarter 2019

Research Updates

Primary care providers believe that comprehensive medication management improves their work-life

A summary of the PIONEER 4 trial: Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes

Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

Therapeutic Thoughts

Use of psychoactive medications in older adults

Updates in osteoporosis: the 2019 Endocrine Society Clinical Practice Guidelines

Pharmacotherapy options for treating opioid use disorder

From the Pharmacy Press

Potential role for pharmacogenomic testing in combating opioid epidemic

Doxycycline and tooth discoloration update: the tooth behind the matter

Kratom use and toxicities in the United States

Miscellaneous News

Piecing together new Board of Pharmacy legislative changes

Stronger warnings implemented for eszopiclone, zaleplon, and zolpidem

Talking prescription labels

New Drug Updates

Bremelanotide (Vyleesi™): a new treatment for hypoactive sexual desire disorder in premenopausal women

Research Updates

Primary care providers believe that comprehensive medication management improves their work-life¹

*Sarah Shockley, PharmD
Fairview Pharmacy Services*

Background: Research has previously shown that comprehensive medication management (CMM) services provided by pharmacists contributes to the Triple Aim, which is a goal that focuses on improving patients' health, enhancing patients' care experience, and decreasing health care costs. The new Quadruple Aim adds the goal of improving the work-life of health care providers. With over half of all physicians experiencing workplace burnout, it is important to identify what factors could improve provider well-being. The potential role of pharmacists and CMM on these measures has not been established; however, emerging research from Funk et al. suggests that team-based care can improve engagement and decrease provider burnout.

Purpose: To determine the perceived impact of pharmacist-delivered CMM services on physician work-life.

Study Design: PCPs (defined as physicians, physician assistants, or nurse practitioners) from four health systems in Minnesota were selected for the study. Pharmacists from each health system were contacted and asked to help identify two to eight PCPs to be interviewed. Overall, eight pharmacists identified 16 PCPs to be interviewed. Interviews were conducted with one or two interviewers until no new themes were identified showing saturation was achieved. Interviews were semi-structured and focused on the positive and negative effects of CMM on the PCP's clinical work, professional satisfaction, and burnout. The interviews included questions related to limitations and areas of improvement for CMM. PCPs also completed an activity involving placing notecards with various clinical functions on a 0 to 10 scale to describe how they felt CMM affected that function and why. Two investigators developed a codebook of the themes by independently coding two transcripts using an inductive approach and then had all transcripts coded in the software program NVivo.

Results: Six dyadic and four one-on-one interviews with PCPs were conducted by researchers between September and November 2017. PCPs described pharmacists as collaborative partners whose relationship led them to feel supported, reassured, and less burned out. PCPs described the extensive knowledge that pharmacists have and the time they saved having pharmacists help them decide on a variety of tasks including medications, treatment options, and prescription coverage. PCPs also noted that during a pharmacist's assessment, medication-related problems are uncovered that otherwise might have been missed.

Pharmacists also helped decrease the workload on PCPs by assisting with indirect care such as patient phone calls, inbox messages, and refill requests. PCPs described high satisfaction in the care they were providing because they could rely on CMM services for certain aspects of care. They also noted how CMM helps them achieve their clinic quality measures. The main barriers noted by the PCPs were being unsure if CMM services would be covered for their patients, the possibility of PCPs not having a trusting relationship with their clinical pharmacist, and patients being unaware of the benefits of CMM and being unwilling to attend the appointment. Suggestions for improvement that PCPs offered included having a full-time clinical pharmacist in clinic and having pharmacists identify more patients from the PCPs' schedules for CMM services.

Conclusions: While it was acknowledged that pharmacists providing CMM in clinics can result in a cost burden to the clinic, the themes identified in this study shed light on how one can build a value proposition for collaborative CMM services using the Quadruple Aim as a framework. PCPs expressed that they feel having clinical pharmacists providing CMM in their clinic makes them more efficient while providing better care and reducing burnout. Many of the themes identified in the study are connected to five of the seven key drivers of burnout including workload and job demands, work-life integration, social support and community at work, efficiency and resources, and meaning in work.

Key Point: Surveyed PCPs believe that having clinical pharmacists providing CMM services at their clinic positively affects their work-life and reduces burnout.

A summary of the PIONEER 4 trial: Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes²

*Analisa Buysse, PharmD
Avera Marshall Regional Medical Center*

Background: Glucagon-like peptide-1 (GLP-1) agonists have become commonplace in the treatment of type 2 diabetes. In addition to effectively lowering HbA_{1c}, agents in the GLP-1 agonist class also provide cardiovascular benefit – namely, liraglutide (Victoza®) and semaglutide (Ozempic®). However, many patients hesitate to initiate therapy with these agents because they do not desire to use injectable medications. An oral formulation of the GLP-1 agonist, semaglutide may soon change this landscape as it has yielded promising results in previous phase 2 and phase 3 trials.

Purpose: The objective of the PIONEER 4 trial was to compare the efficacy and safety of oral semaglutide with subcutaneous liraglutide and placebo in patients with

type 2 diabetes currently taking metformin with or without a sodium-glucose cotransporter-2 inhibitor.

Study Design: The PIONEER 4 trial was a randomized, multi-center, 52 week, double-blind, double-dummy, active-controlled, and placebo-controlled phase 3a study. The primary outcome was the change in HbA_{1c} from baseline to 26 weeks. A notable secondary endpoint included the change in body weight from baseline to week 26. Results were assessed using both intention-to-treat and per-protocol principles and analyzed using ANCOVA and a mixed model for continuous endpoints, respectively. Power was set at 90% to confirm the superiority of semaglutide to placebo and the non-inferiority of oral semaglutide to liraglutide using a non-inferiority margin of 0.4%. Alpha was set at 0.05.

Patients were randomized in a 2:2:1 ratio to receive oral semaglutide (initiated at a once-daily dose of 3mg, which was then titrated to 7mg after four weeks and 14mg after eight weeks), subcutaneous liraglutide (initiated at 0.6mg daily, titrated to 1.2mg after one week and 1.8mg after two weeks), or placebo. Patients were informed to take the oral study drug with up to half a glass of water in a fasted state every morning, at least 30 minutes prior to their first meal.

Results: After 26 weeks, the average change from baseline in HbA_{1c} was -1.2% for oral semaglutide, -1.1% for liraglutide, and -0.2% for placebo when analyzed using the intention-to-treat principle. Authors asserted based on these data that oral semaglutide was non-inferior to subcutaneous liraglutide [estimated treatment difference (ETD) -0.1%, 95% CI -0.3 to 0.0; P<0.0001 for non-inferiority] and superior to placebo [ETD -1.1%, 95% CI -1.2 to -0.9; P<0.0001]. When analyzed using the per-protocol principle, oral semaglutide decreased the HbA_{1c} more than both subcutaneous liraglutide [ETD -0.2%, 95% CI -0.3 to -0.1; P=0.0056] and placebo [ETD -1.2%, 95% CI -1.4 to -1.0; P<0.0001].

Notably, patients randomized to oral semaglutide lost more weight by week 26 than patients receiving liraglutide [-4.4 kg vs -3.1 kg, ETD -1.2 kg, 95% CI -1.9 to -0.6; P=0.0003] and placebo [ETD -3.8 kg, 95% CI -4.7 to -3.0; P<0.0001] when assessed using an intention-to-treat analysis.

Side effects were reported by 80% (229/285) of patients treated with semaglutide, 74% (211/284) treated with liraglutide, and 67% (95/142) receiving placebo. Authors stated that the higher incidence of adverse effects in the semaglutide group was largely due to gastrointestinal side effects, such as transient nausea and diarrhea.

Conclusions: Overall, oral semaglutide offers a promising future oral alternative for patients with type 2 diabetes who would benefit from GLP-1 agonist therapy but refuse injections. The adverse effect profile of oral semaglutide appears similar to subcutaneous GLP-1 agonists, although may cause additional gastrointestinal side effects based on the results of this study. Further studies would be necessary to prove the presence of cardiovascular benefit with oral semaglutide as has been documented with injectable GLP-1 agonists.

Key Point: An oral GLP-1 agonist option is likely on the horizon for type 2 diabetes treatment.

Canagliflozin and renal outcomes in type 2 diabetes and nephropathy₃

*Alicia Smith, PharmD
First Light Health System*

Background: Exploratory results of previous trials involving SGLT2 (sodium-glucose cotransporter 2) inhibitors, including the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME trials, have suggested that SGLT2 inhibitors may improve renal outcomes in patients with type 2 diabetes. These previous studies have shown improvement in renal outcomes in patients at low risk of developing kidney failure. Currently, data is limited surrounding renal outcomes of SGLT2 inhibitors when used in patients at high risk of developing renal failure.

Objective: To examine the effects of canagliflozin and placebo in decreasing the incidence of end stage kidney disease and death from renal or cardiovascular causes when used in patients with type 2 diabetes and albuminuric chronic kidney disease (CKD).

Study Design: This study is a randomized, double-blind, placebo controlled trial, which occurred across 690 sites in 34 countries. Exclusion criteria included the following: history of diabetic ketoacidosis or type 1 diabetes, non-diabetic renal disease, renal transplant or dialysis, uncontrolled hypertension, hyperkalemia at baseline, Class IV congestive heart failure, myocardial infarction/unstable angina/revascularization within 12 weeks of randomization, history of amputation, and pregnancy. Patients included in the trial were at least 30 years of age with type 2 diabetes and an A1C between 6.5-12%. Inclusion criteria included patients with CKD defined as an eGFR of 30-90 mL/min/1.73 m² and albuminuria (urinary albumin:creatinine ratio >300 mg/g). Patients also needed to be treated with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) for at least four weeks prior to

randomization. Patients were randomized to canagliflozin 100 mg by mouth daily or placebo. The primary outcome was a composite of end-stage kidney disease (dialysis, kidney transplant, eGFR <15 mL/min/1.73 m²), doubling of serum creatinine level from baseline, or death from renal or cardiovascular disease.

Results: Out of a total of 4401 patients included in the study, the event rate per 1000 patient-years of the primary composite outcome in the canagliflozin group was 43.2, compared to 61.2 in the placebo group (HR 0.7 [95% CI 0.59 - 0.82], P=0.00001). In the end-stage renal disease component, the event rate per 1000 patient-years in the canagliflozin group was 20.4, compared to 29.4 in the placebo group (HR 0.68 [95% CI 0.54 - 0.86], P=0.002). In the doubling of serum creatinine component, the event rate per 1000 patient-years in the canagliflozin group was 20.7, compared to 33.8 in the placebo group (HR 0.6 [95% CI 0.48 - 0.76], P<0.001). For the components of renal and cardiovascular death, there were no significant between-group differences found. Subgroup analysis revealed that the patients with the greatest benefit in the primary composite outcome were those with an eGFR 45 to <60 mL/min/1.73 m² (HR 0.52 [95% CI 0.38 - 0.72]) and those with a urinary albumin:creatinine ratio (UACR) >1000 mg/g (HR 0.67 [95% CI 0.55 - 0.81]). Diabetic ketoacidosis occurred more frequently in the canagliflozin group when compared to placebo, 2.2 versus 0.2 events per 1000 patient-years respectively (HR 10.8 [95% CI 1.39 - 83.65]). No significant differences were found between groups for the side effects of amputation, fracture, hyperkalemia, or acute kidney injury.

Conclusions: Canagliflozin was found to have a lower risk of the primary composite outcome (end-stage kidney disease [dialysis, kidney transplant, eGFR <15 mL/min/1.73 m²], doubling of serum creatinine level from baseline, or death from renal or cardiovascular disease) compared to placebo in patients with type 2 diabetes and CKD. Patients with the greatest potential benefit include those with an eGFR 45 - 60 mL/min/1.73 m² and those with a UACR >1000 mg/g. A limitation of the study is that it was stopped at a planned interim analysis which may contribute to overestimating the effects found. Future research could explore if other SGLT2 inhibitors provide similar benefits as canagliflozin in patients with type 2 diabetes and CKD.

Key Point: Canagliflozin may be an effective treatment option for patients with type 2 diabetes and CKD to provide renal and cardiovascular protection independent of blood glucose levels.

Therapeutic Thoughts

Use of psychoactive medications in older adults⁴⁻⁸

Emily Hulke, PharmD
Goodrich Pharmacy

Background: Falls are the leading cause of injuries among adults aged 65 and older, with three million older adult patients per year treated in emergency departments for fall injuries. The Centers for Disease Control (CDC) reported that in 2015, the total medical costs for falls was over \$50 billion with Medicare and Medicaid covering 75% of these costs. Both intrinsic risk factors such as age and poor vision, and extrinsic factors including footwear and medication use can contribute to falls. Psychoactive medications, those that act primarily on the central nervous system, can cause side effects that increase the risk of falls by causing confusion, drowsiness, vision disturbances, and orthostatic hypotension. Examples of psychoactive medications include benzodiazepines, antipsychotics, anticonvulsants, opioids, and certain antidepressants.

A study published by Landi et al. found that users of any psychoactive drugs had an increased risk of falls by approximately 47% [OR 1.47 95% CI 1.24-1.74] in community dwelling older adults. Additionally, Campbell et al. found that pharmacist-led discontinuation of psychoactive medications in older adults could reduce falls by 66%. Understanding the prevalence of psychoactive medication use and changes in use over time allows health professionals and policy makers to prioritize and evaluate the impact of reducing psychoactive medication use on older adult falls.

Evidence: A recent study was conducted to estimate the prevalence of psychoactive medication use in older adults in 2013 and compare it to previous estimates from 1996. The data source for this study by Haddad et al. was Cost and Use Data files from 2013 which combine Medicare claims data and survey data from the Medicare Current Beneficiary Survey. Participants were included if they were age 65 years or older, community-dwelling, and had a complete year of prescription use data. A total of 6,969 patients were looked at which represented 33,268,104 community-dwelling Medicare beneficiaries. A majority of the beneficiaries were 65-74 years of age (51.5%) and white (85.3%). There were seven classes of medications defined as psychoactive in the study: opioids, benzodiazepines, non-benzodiazepine sedative hypnotics, antipsychotics, anticonvulsants, tricyclic antidepressants (TCAs), and selective-serotonin reuptake inhibitors (SSRIs). Using data from the 2013 report, they found that 53.3% of community dwelling older adults age 65 and older used at least one

psychoactive medication class known to increase fall risk, a significant increase from the 15% reported by Moxey et al. in 1996. Of those, 29.6% used medications from one psychoactive medication class, 14.5% used two classes, and 9.2% used three or more classes during the calendar year. The most frequently used classes were opioids (34.9%), benzodiazepines (15.4%), SSRIs (14.3%), and anticonvulsants (13.3%). The prevalence of use in 2013 was considerably higher compared to the 1996 data for all of these classes with the exception of TCAs.

Discussion and Clinical Impact: The use of psychoactive medication use rose substantially in older adults between 1996 and 2013. Although the data used for this study is slightly outdated, it still shows that the use of psychoactive medications by older adults deserves greater attention.

With the use of psychoactive medications in older adults on the rise, health care providers should be sure to assess for medication that could be increasing fall risk during all patient encounters, especially in older patients. Pharmacists should continue to provide comprehensive medication management and serve as resources for providers by providing recommendations on how to reduce or discontinue high-risk medication use in older adults. The CDC's Stopping Elderly Accidents and Injuries initiative recommends stopping high-risk psychoactive medications when possible and switching to a safer alternative. When this is not appropriate, the dose should be reduced to the lowest effective dose. Resources including the Screening Tool of Older Person's Prescriptions (STOPP), AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, www.deprescribing.org, and anticholinergic burden indices can assist pharmacists in identifying potentially inappropriate medications that could be contributing to falls, including psychoactive medications, in older adults.

Updates in osteoporosis: the 2019 Endocrine Society Clinical Practice Guidelines⁹⁻¹⁰

Meg Tapp, PharmD
Essentia Health

Background: Osteoporosis is a debilitating disease, and 50% of postmenopausal women will experience at least one osteoporotic fracture in their lifetime. Fortunately, there is an array of safe and effective treatments available to improve bone density in women with osteoporosis. These medications are often underused; in recent years bisphosphonate use in the United States has decreased. The Endocrine Society recognized the

need for updated guidance, and published recommendations based on a meta-analysis of 106 randomized controlled trials involving 193,987 women. These guidelines have several distinctions from previously published American College of Physicians (ACP) and National Osteoporosis Foundation (NOF) guidelines.

Evidence: In the United States, pharmacological therapy for osteoporosis is indicated for postmenopausal women with history of hip or vertebral fracture; T-score of -2.5 or less at the femoral neck, hip, or lumbar spine; or T-score of -1 to -1.25 plus FRAX score of $\geq 20\%$ for major fractures or $\geq 3\%$ for hip fractures. The Endocrine Society recommends treatment for all women meeting these criteria, regardless of age and especially if they have had a fracture in the past two years. Contrary to ACP guidelines, the Endocrine Society recommends bone mineral density (BMD) monitoring every one to three years during treatment.

Similar to ACP and NOF guidelines, the Endocrine Society recommends bisphosphonates or denosumab as first-line treatment for osteoporosis. While ACP has the same drug holiday recommendations for both drug classes, these new guidelines suggest reassessing bisphosphonate use after five years (three years for zoledronic acid) and denosumab use after 5-10 years. Patients who remain at high risk for fractures should continue therapy. If a drug holiday is pursued, BMD should be monitored every two to four years post-bisphosphonate and every one to three years post-denosumab. If denosumab is stopped, a bisphosphonate should be used to prevent rapid bone loss. For either drug class, therapy should be resumed if there is loss in BMD or a fracture occurs.

Teriparatide and abaloparatide have their place in all guidelines for women with severe or multiple fractures; they may be used for up to two years and followed by anti-resorptive therapy. Older guidelines have moved away from the use of raloxifene, hormone replacement therapy, and calcitonin, but the Endocrine Society does recommend these medications as second-line therapy for women with specific indications. Raloxifene may be used in patients with low risk for deep vein thrombosis (DVT) and high risk for breast cancer. Hormone replacement therapy should only be used for patients with low risk of DVT, stroke, or myocardial infarction with no history of breast cancer and who are <60 years of age or <10 years post-menopause. Calcitonin is reserved as a last-line therapy.

The Endocrine Society guidelines are unique in that they are the first osteoporosis guidelines to include women's preferences regarding treatment options. Results from a meta-analysis of 15,348 postmenopausal (Barrionuevo

et al.) concluded women consider efficacy and adverse effects top priority, followed by convenience; overall the oral route was preferred unless injections were less frequent. Surprisingly, cost and duration of treatment were the least important considerations.

Discussion and Clinical Impact: While many recommendations in the Endocrine Society guidelines are similar to ACP and NOF guidelines, there are several key differences. ACP removed BMD monitoring from their recommendations; the Endocrine Society re-introduces monitoring every one to three years. Bisphosphonates and denosumab are still preferred first-line agents; however, recommendations for duration of treatment and initiation of drug holidays differ. The Endocrine Society Clinical Practice guidelines also resurrect specific recommendations for hormone replacement therapy, raloxifene, and calcitonin. This provides for an expanded range of options for many women who cannot tolerate first-line medications.

The Endocrine Society guidelines provide insight into the most important factors affecting therapy choice for osteoporotic women - namely efficacy, safety, and convenience. Such information can be used to guide patients through discussions regarding their treatment options, and should be kept in mind when making therapeutic recommendations.

Pharmacotherapy options for treating opioid use disorder¹¹⁻¹⁷

Sara Maki, PharmD
Minnesota Community Care

Background: Misuse of prescription pain medications, illicit use of fentanyl or illicit drugs such as heroin contribute to the rising rate of opioid-related overdose deaths. In 2017, the Center for Disease Control and Prevention reported that approximately 130 people died every day from an overdose. This number is only rising. As discussed in a therapy update published recently in the American Journal of Health-System Pharmacists, treatment for opioid use disorder (OUD), including methadone and buprenorphine, has been shown to "reduce opioid cravings, increase treatment retention, reduce illicit opioid use, and increase overall survival." Yet, medication-assisted treatment remains underprescribed and inaccessible to many patients. Barriers from the provider perspective may include prescribing restrictions and unfamiliarity with the current treatment options.

Buprenorphine, methadone, and naltrexone are all considered first-line agents for the treatment of OUD by the American Society of Addiction Medicine National Practice Guideline and are FDA-approved for this

indication. The choice of treatment should be a shared decision between patients and clinicians, with careful assessment of preferred treatment setting, physical dependence potential, past experiences with treatment, and evidence supporting efficacy and safety of the therapeutic options.

Evidence: Buprenorphine is a partial opioid agonist that is available in multiple dosage forms, including sublingual tablets or strips, implant, and injection. Buprenorphine has the advantage of being more accessible than methadone, as it can be prescribed in an office-based setting by a DATA-waivered provider and filled in any community pharmacy. It also has fewer drug interactions and can be co-formulated with naloxone to prevent misuse. Fiellen et al. studied the efficacy of buprenorphine as maintenance therapy versus short-term taper in a primary-care based setting. Patients who were tapered off buprenorphine were more likely to use opioids (per self-report and urine toxicology screens). Patients in the taper group also had fewer consecutive weeks of opioid abstinence compared with those who were maintained on buprenorphine (mean abstinence in weeks, 2.70 [95% CI, 1.72-3.75] vs. 5.20 [95% CI, 4.16-6.20]). Patients who had their buprenorphine tapered were less likely to complete the 14-week trial (6 of 57 [11%] vs 37 of 56 [66%]; $P < 0.001$).

Methadone, a full opioid agonist, can also be used to treat OUD. It may be a preferred treatment for patients who benefit from supervision of daily dosing and associated wraparound services because it is only available through certified Opioid Treatment Program facilities. However, risks include more respiratory depression and sedation than buprenorphine, along with a risk for QT prolongation. Dosing is complicated by a long half life, variable absorption, and high dose requirements to achieve full opioid receptor blockade.

Mattick and colleagues demonstrated in a systematic review that methadone use was significantly more effective than placebo in preventing heroin use (RR in 6 RCTs, 0.66; 95%CI, 0.56-0.87), but did not result in lower mortality (RR in 4 RCTs, 0.48; 95% CI, 0.1-2.39). A later systematic review by the same authors concluded that methadone was superior to buprenorphine in retaining patients in treatment (RR in 5 double-blind trials, 0.83; 95% CI, 0.72-0.95).

Naltrexone, a competitive antagonist of opioid receptors, is approved for treatment of OUD, but may not be preferred due to poor adherence outcomes. However, the oral formulation is the least expensive of all treatment options and may be appropriate for highly motivated patients who are able to take the medication daily. Initiation of the monthly depot injection can be challenging, as patients must be opioid free for 7-10 days to prevent precipitation of withdrawal. Minozzi and colleagues performed a systematic review to evaluate oral naltrexone for OUD, in which they found that naltrexone was not superior to other therapeutic options, but data was not statistically significant for the measures of retention in treatment, abstinence from illicit drug use, or adverse effects.

Discussion and Clinical Impact: Koehl and colleagues determined that there is not sufficient evidence to make a definitive recommendation on whether buprenorphine or methadone is a more effective treatment to reduce opioid use, decrease mortality from overdose, increase daily functioning, or maintain patients in treatment. The important next step in treating OUD is expanding services to reach more patients. Choice of treatment must be a shared decision between patients and their care team, with careful consideration of previous treatment, future priorities, treatment setting, availability of medication, and potential for continuing care.

From the Pharmacy Press

Potential role for pharmacogenomic testing in combating opioid epidemic¹⁸⁻²⁰

*Anna K Hanson, PharmD
Essentia Health*

Background: The Centers for Disease Control and Prevention estimates that 130 Americans die each day from an opioid overdose, with a six-fold increase in deaths from 1999 to 2017. In addition to lives lost, the cost of medical management of patients with opioid abuse and addiction is estimated at \$29.4 billion each year. Considering the magnitude and continued escalation of the opioid epidemic, it is likely a multi-faceted approach is necessary to address it. Marcalus

and Bristow-Marcalus suggest that pharmacogenomic testing is one such avenue to fight the opioid epidemic.

Evidence: The well-documented metabolic pathway of codeine and morphine offers some insight into the pharmacogenomic variations of patients' response to opioid therapy for pain. Metabolized by the enzyme cytochrome P450 2D6 (CYP2D6), codeine is altered to its highly active metabolite, morphine. According to Marcalus and Bristow-Marcalus, patients who are ultrarapid or poor metabolizers of codeine are at increased risk of abuse due to the unexpectedly high or low conversion of codeine, respectively. Patients with these phenotypes represent a significant portion of the

U.S. population, with 6% being ultrarapid and 12% being poor metabolizers of CYP2D6. Guidelines by the Clinical Pharmacogenomics Implementation Consortium (CPIC) describe codeine prescribing recommendations based on metabolism status which could provide guidance for prescribers after pharmacogenomic testing has been performed. According to Crews et al, other opioids such as tramadol, hydrocodone, and oxycodone also undergo metabolism by CYP2D6 and are potentially affected by genetic variants.

Discussion: Marcalus and Bristow-Marcalus suggest the optimal time to assess pharmacogenomics can occur at two points of care: during preoperative screening and at time of referral to a pain specialist. Knowledge of patients' genetics at these crossroads can help guide treatment to find appropriate therapeutic doses of opioids or direct treatment toward nonopioid pain management. In addition, use of genetic testing may facilitate an open discussion concerning the appropriateness of opioid therapy for a given patient and increase patient satisfaction by providing individualized care. As with any new clinical advancement, the implementation of pharmacogenomics is not without obstacles. The use of pharmacogenomics will require education as to the interpretation and application of the new data and present other hurdles involving cost and navigation of third-party reimbursement. The global nature of comprehensive medication management (CMM) provides an excellent avenue for the incorporation of pharmacogenomics to critically evaluate gene-drug interactions and previous opioid history. This integration of pharmacogenomic testing also creates the opportunity for complete medication reviews and a gateway for expansion of broader CMM services.

Conclusion: The implementation of pharmacogenomics in opioid prescribing may be one tool in a multi-faceted approach to combat the opioid epidemic. While not without barriers, the application of pharmacogenomics in this manner may provide a more individualized approach to optimal opioid prescribing, reduce morbidity and mortality related to opioid abuse, and, as discussed by Marcalus and Bristow-Marcalus, could provide annual cost savings up to \$14,000 per patient. CMM pharmacists are uniquely positioned to provide pharmacogenomic consulting services that will have an impact on patients at risk of opioid addiction and abuse.

Doxycycline and tooth discoloration update: the tooth behind the matter²¹⁻²⁵

*Kelly Beneke, PharmD
New Ulm Medical Center*

Background: Tetracycline use and associated tooth discoloration in children was first reported in 1959. Doxycycline, brought to the market in 1967, was found to bind less readily to calcium than other medications in the class. Although there is limited evidence showing permanent tooth discoloration with doxycycline in young children, the use has been avoided in children younger than eight years old. According to the package insert, the only FDA pediatric indication for doxycycline is post-exposure inhalational anthrax. A recent article by Stultz and Eiland reviews six studies and discusses the evidence of safety of doxycycline in children younger than eight years old and the new recommendations regarding its use moving forward.

Evidence: From 1969 to 2017, six studies with approximately 338 patients were reviewed. Although methods between the studies varied for examining and evaluating the tooth discoloration, it primarily consisted of photography, direct examination, instruments, or scales. The children included in the studies were between four days and eight years old. Doxycycline doses ranged from 1 mg/kg/d to 10 mg/kg/d. Most of the medication regimens lasted less than 21 days with one 28 day course. Altogether, there were six potential tooth discoloration cases reported with three cases likely related to doxycycline. Of note, four out of the six patients were younger than two years old. These patients did not have matching controls nor were the adult teeth examined.

Discussion: From the current research regarding doxycycline use in pediatric patients younger than eight years old, The American Academy of Pediatrics states in the Red Book, "doxycycline can be administered for short durations (i.e, 21 days or less) without regard to the patient's age." It should be noted that the tooth discoloration and weakened enamel warning still exists for other tetracyclines.

Clinical Impact: The use of doxycycline can now be considered in pediatric patients with skin and soft tissue infections, atypical community-acquired pneumonia, and methicillin-susceptible *Staphylococcus aureus*. The new recommendation of doxycycline use in pediatrics younger than eight years old affords providers another oral, inexpensive treatment option for children without the risk of tooth discoloration and enamel weakening.

Kratom use and toxicities in the United States²⁶⁻³¹

Tyler Stevens, PharmD
CentraCare Health- St. Cloud

Background: Kratom is an herbal supplement made from the leaves of *Mitragyna speciosa*. Native to Southeast Asia, the leaves of this plant have been a part of traditional medicine for centuries in areas of Southeast Asia for its stimulatory and analgesic effects. Use of kratom in the United States has gained popularity since 2010, with claims that it is a safe option for the treatment of pain, mood disorders, opioid use disorder (OUD) and opioid withdrawal. While marketed as a safe alternative for OUD, the active component of kratom, mitragynine, has agonist activity at the mu opioid receptor which has potential for dependence and addiction. Other components of kratom include hydroxymitragynine and synthetic 7-hydroxymitragynine, believed to produce more potent opioid effects than mitragynine. Multiple other alkaloids with unknown potency or clinical effects can also be found in kratom. Due to increasing reports of kratom associated toxicities and deaths, the FDA has released statements warning the public on the risks associated with its use. Starting in 2012, kratom has been identified on import alerts for unapproved drugs by the FDA. Since then, they have recalled or seized large quantities of kratom on numerous occasions. The Department of Health and Human Services has recommended the DEA classify kratom as a Schedule I substance.

Purpose: To examine the prevalence of adverse effects and deaths due to kratom use.

Study design: This review article examined data from the U.S. National Poison Data System (NPDS) on voluntarily reported exposures to kratom from January 1, 2011 to July 31, 2018 and kratom-associated fatalities

identified by a county medical examiner's office in the state of New York.

Results: Of 2,312 kratom exposures reported, 935 were single kratom exposures. There was also a sharp increase in reported exposures in 2016. Route of exposure was predominantly oral (86.2%) and reason for exposure was most often intentional abuse or misuse (61.6%). The most common adverse effects reported were agitation (18.6%), tachycardia (16.9%), and drowsiness (13.6%). Serious adverse effects reported were seizure (6.1%), withdrawal (6.1%), hallucinations (4.8%), respiratory depression (2.8%), coma (2.3%), and cardiac or respiratory arrest (0.6%). Four cases of neonatal abstinence syndrome and two deaths were also reported to the NPDS. According to the New York medical examiner's office, kratom was listed as a cause or contributing factor of death in four cases, two of which, kratom was identified as the sole contributor.

Conclusion: The results presented demonstrate potential adverse effects associated with kratom, raising concerns about the risk for serious toxicity and death from kratom use. Reports of neonatal abstinence syndrome suggests kratom can produce dependence similar to opioids. The data collected by NPDS was given voluntarily, therefore the prevalence of kratom toxicity is likely greater than depicted in this report. Based on the data presented and because there have been 44 kratom-related deaths reported by the FDA, the authors pose kratom's availability as an herbal supplement should be reconsidered.

Key Point: Kratom is an herbal supplement, typically used to treat pain, OUD, and mood disorders, and is associated with serious adverse effects and death. This supplement's availability will likely be reconsidered in the near future.

Miscellaneous News

Piecing together new Board of Pharmacy legislative changes³²

Monika Tawfik, PharmD
Hennepin Healthcare

The Minnesota Board of Pharmacy recently enacted several changes effective July 1st, 2019. These changes affect both community pharmacies and primary care practitioners. Pharmacists must be ready to answer questions received by both patients and practitioners regarding these changes.

Controlled Substance Prescriptions: According to the new rules, no prescription for an opiate or narcotic pain

reliever listed in Schedule II-IV can be dispensed more than 30 days after the date on which the prescription was issued. Additionally, opiate prescriptions for acute pain can only be issued for a seven-day supply for an adult, a five-day supply for a minor under 18 years of age, and four days for acute dental pain. These limits do not apply to pain related to cancer care, palliative care, hospice, or other end-of-life care. However, pharmacists must continue to act with professional judgment if a prescription is written for acute pain and exceeds these quantity limits, but has been deemed appropriate.

Prescriptions for Schedule III-V medications can still have up to five refills within six months; however, each

refill must be dispensed no more than 30 days after the last fill was dispensed. Although prescribers can no longer issue multiple opiate prescriptions at a time, prescriptions for stimulant medications are not affected by this rule.

Emergency Refills: Although many pharmacies have had their own rules regarding emergency prescription refills, the new rules specify certain requirements that must be met and various restrictions. The requirements include: patient compliance (determined by the pharmacist's professional judgement); pharmacy must have a record of the prescription drug order; the pharmacist must try to contact the prescriber to obtain authorization of a refill; the drug is necessary to sustain life or continue therapy for a chronic condition; failure to dispense the medication would result in harm to the patient; and the drug is not a controlled substance, except for controlled substances used to treat seizure disorders, in which a 72-hour supply can be dispensed. If these requirements are met, the pharmacist can dispense up to a 30-day supply of the medication, but must notify the practitioner no later than 72 hours. The pharmacist cannot dispense or sell the same drug to the same patient as an emergency refill more than once per year.

Therapeutic Substitution: There are no changes to this practice as pharmacists have been engaging in therapeutic substitution for several years. However, the new rules provide clarity and guidance. Therapeutic substitutions are allowed if the pharmacist has a written protocol with each prescriber that outlines the class of medication and is designed for the same indication. The pharmacist must communicate the change to both the patient and the practitioner. When communicating to the practitioner, the pharmacist is required to include the name and manufacturer of the substituted drug and the reason for substitution.

Pharmacist Administration of Medications:

Pharmacists can now administer drugs by intramuscular (IM) and subcutaneous (SQ) routes when used for treatment of alcohol or opioid dependence or mental illness. A collaborative practice agreement or protocol is required for drugs administered by IM or SQ routes when used for the treatment of mental illness. However, it is acceptable for a prescription to indicate the pharmacist to administer the medication. The prescriber should be notified after the administration is complete. In other cases (first dosages and medical emergencies, vaccines, and for the treatment of alcohol or opioid dependence), a protocol or collaborative practice agreement need not be in place, but the administration should follow a prescription or drug order from a

practitioner. The board will exercise discretion to protect a pharmacist who acts in good faith to administer a medication needed to treat an emergency.

Although the new rules reflect overall clarity to various pharmacy practices, the rules repeatedly affirm that pharmacists must rely on professional judgment. Thus, despite the rules, pharmacists are likely to encounter situations that may not perfectly fit the mold, and will still have to use clinical knowledge and judgment to make the best decision for the patient.

Stronger warnings implemented for eszopiclone, zaleplon, and zolpidem³³

Brenda Shih, PharmD

Community University Health Care Center (CUHCC)

The FDA announced in April 2019 that eszopiclone, zaleplon, and zolpidem ("Z-drugs") require a new boxed warning for the occurrence of rare but serious injuries and deaths from complex sleeping behaviors after taking the drugs. Complex sleep behaviors include activities that patients engage in while they are not fully awake, such as sleepwalking and driving. In addition, a new contraindication was added, stating that patients with a history of complex sleep behaviors after taking eszopiclone, zaleplon, or zolpidem are now contraindicated from taking these drugs.

The association between the "Z-drugs" and complex sleep behaviors has previously been included in prescribing information. However, after evaluation of 66 case reports submitted in the FDA Adverse Event Reporting System, the FDA added the boxed warning and contraindication to make the warning more prominent. Of the 66 cases, 46 involved non-fatal serious injuries, such as accidental overdoses, falls, burns, near-drowning, exposure to extreme temperatures, and self-injuries. The other 20 reports involved fatal injuries from carbon monoxide poisoning, drowning, hypothermia, motor vehicle accidents, and apparent suicide.

What does this update mean to practitioners? To ensure the safety of patients, practitioners should not prescribe "Z-drugs" to patients who have a history of complex sleep behaviors after taking these drugs. Patients should be educated that rare but serious injuries are associated with "Z-drugs" and if complex sleep behaviors occur they should discontinue the drug. The patient medication guide must also be dispensed upon first fill and refills.

Talking prescription labels³⁴

*Sara Massey, PharmD
MOBE*

Over 3.4 million Americans over the age of 40 are considered legally blind or visually impaired. One company is attempting to improve patient safety within this population by expanding a unique pharmacy service.

Walmart and Sam's Club pharmacies recently announced a service expansion of a labeling system, which will be offered nation-wide to patients. The labeling system is most beneficial for patients who are blind or visually impaired as the system allows for prescription labels to be read aloud to patients at home. This is done by placing a radio-frequency identification label to the bottom of the prescription bottle, which when combined with the En-Vision America's ScripTalk Station, allows important information to be read aloud to the patient. The system reads aloud the patient's name, prescription number, drug name, dosage, instructions for use, warnings, educational leaflet information, and pharmacy information. The ScripTalk Station and enhanced prescription labels are provided to patients free of charge. This service can be requested by a patient and the patient's Walmart or Sam's Club

pharmacy will be equipped to dispense the ScripTalk labels and station typically within 7-10 days.

To date, Walmart and Sam's Club are the first companies to expand these services nation-wide in the community setting. Most pharmacies are currently encouraging the use of auditory aid phone apps or making visual alterations to prescription labels including the addition of braille, large print, or color coding bottles based on the time of day medication is to be taken. The Walmart company has been working on the implementation of ScripTalk since 2012. During this time approximately 1,200 Walmart and Sam's Club pharmacies have been equipped with the audible prescription label services. Moving forward, the company plans to expand this number by 25 stores each month within the coming years.

All patients, especially those who have disabilities, need health professionals to actively advocate for them. Pharmacists can advocate for blind and visually impaired patients by encouraging and using the ScripTalk services while caring for these patients.

New Drug Updates

Bremelanotide (Vyleesi™): a new treatment for hypoactive sexual desire disorder in premenopausal women³⁵⁻³⁸

*Jamie Erickson, PharmD
Cashwise Clinic Pharmacy/Carris Health*

In June 2019, the FDA approved bremelanotide (Vyleesi™), a subcutaneous autoinjector for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Generalized HSDD is characterized by a low sexual desire that is present regardless of one's sexual activity, situation, or partner and causes marked distress or interpersonal difficulty. This treatment should not be used for HSDD caused by a co-existing medical or psychiatric condition, relationship complications, or as a result of medication or other drug substance. Bremelanotide is not indicated for the treatment of HSDD in postmenopausal women, men, or to enhance sexual performance.

The mechanism by which bremelanotide improves HSDD in women is unknown; however, it is a nonselective melanocortin receptor (MCR) agonist. Bremelanotide is administered as a 1.75 mg

subcutaneous injection in the abdomen or thigh at least 45 minutes prior to anticipated sexual activity. It should not be used more than once in 24 hours or more than eight doses per month. The efficacy of bremelanotide was studied in two identical, Phase 3, 24-week, randomized, double-blind, placebo-controlled trials. Approximately 25% of patients treated with bremelanotide and 17% of patients treated with placebo had an improvement in sexual desire score of 1.2 or more using the Female Sexual Function Index (FSFI). In addition, approximately 35% of patients treated with bremelanotide and 31% of patients treated with placebo had an improvement in the level of distress associated with low sexual desire score of 1 or more using the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13).

The most notable adverse effects seen with bremelanotide treatment are nausea (most commonly with first injection), flushing, injection site reactions, headache, and transient increases in blood pressure and reductions in heart rate. Bremelanotide is contraindicated for use in patients with cardiovascular disease or uncontrolled hypertension and it is not

recommended for use in patients at high risk for cardiovascular disease. Potentially irreversible focal hyperpigmentation of the face, gingiva, and breasts is a rare side effect that is more common in patients with dark skin. Bremelanotide can be used as needed, which

may be an advantage over flibanserin (Addyi®), which is a daily oral treatment for HSDD in premenopausal women. Bremelanotide is not yet available in pharmacies but the average wholesale price is \$1078.80 per box containing four single-dose autoinjectors.

References

1. Funk KA, Pestka DL, Roth McClurg MT, Carroll JK, Sorensen TD. Primary Care Providers Believe That Comprehensive Medication Management Improves Their Work-Life. *J Am Board Fam Med*. 2019 Jul-Aug;32(4):462-73.
2. Pratley R, Amod A, Tetens-Hoff S, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomized, double-blind, phase 3a trial. *Lancet*. 2019;394:39-50.
3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
4. Centers for Disease Control and Prevention. Important Facts About Falls. <https://www.cdc.gov/homeandrecreationalafety/falls/adultfalls.html>. Accessed August 11, 2019.
5. Landi F, Onder G, Cesari M, Barillaro C, Russo A, Bernabei R; Silver Network Home Care Study Group. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. *J Gerontol A Biol Sci Med Sci*. 2005;60(5):622-626.
6. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized controlled trial. *J Am Geriatr Soc*. 1999;47(7):850e853.
7. Haddad YK, Luo F, Karani MV, Marcum ZA, Lee R. Psychoactive medication use among community-dwelling Americans. *J. Am. Pharm. Assoc*. 2019; 1-5.
8. Moxey ED, O'Connor JP, Novielli KD, Teutsch S, Nash DD. Prescription drug use in the elderly: a descriptive analysis. *Health Care Financ Rev*. 2003;24(4):127e141.
9. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019; 104(5):1595-1622.
10. Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, et al. Women's values and preferences regarding osteoporosis treatment: a systematic review. *J Clin Endocrinol Metab*. 2019; 104(5):1631-1636.
11. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Opioid overdose: understanding the epidemic. <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Published December 19, 2018. Accessed August 12, 2019.
12. Koehl JL, Zimmerman DE, Bridgeman PJ. Medications for management of opioid use disorder. *Am J of Health-System Pharm*. 2019;76(15):1097-1103.
13. American Society of Addiction Medicine. National practice guideline for the use of medications in the treatment of addiction involving opioid use. 2015. <https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24>. Published June 1, 2015. Accessed July 23, 2019.
14. Fiellen DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence. *JAMA Intern Med*. 2014;174(12):1947-1954.
15. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;3.
16. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or

- methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014;2.
17. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011;2.
 18. Marcalus SJ, Bristow-Marcalus S. Combating opioid addiction and abuse - 2 ways to effectively intervene in the cycle of addiction through pharmacogenomics. *JAPhA.* 2019;59(4):469-473. doi:10.1016/j.japh.2019.04.016.
 19. Centers for Disease Control and Prevention. Opioid overdose: Understanding the epidemic. <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Updated December 19, 2018. Accessed August 11, 2019.
 20. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of *cytochrome P450 2D6 (CYP2D6)* genotype. *Clin Pharmacol Ther.* 2012;91(2):321-326. doi:10.1038/clpt.2011.287.
 21. Stultz JS, Eiland LS. Doxycycline and tooth discoloration in children: changing of recommendations based on evidence of safety. *Ann Pharmacother.* 2019; doi: 10.1177/1060028019863796.
 22. Poyhonen H, Nurmi M, Peltola V, et al. Dental staining after doxycycline use in children. *J Antimicrob Chemother.* 2017;72:2887-2890.
 23. Lochary ME, Lockhard PB, Williams WT Jr. Doxycycline and staining of permanent teeth. *Pediatric Infect Dis J.* 1998; 17(5):429-31.
 24. Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected rocky mountain spotted fever. *J Pediatric.* 2015;166:1246-51.
 25. Antimicrobial agents and related therapy: tetracyclines. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, ed. *Red Book: Report of the Committee of Infectious Disease.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:905-6.
 26. Eggleston W, Stoppacher R, Suen K, Marraffa JM, Nelson LS. Kratom use and toxicities in the United States. *Pharmacotherapy.* 2019; 39(7): 775-777.
 27. Anwar M, Law R, Schier J. Notes from the field: kratom (*Mitragyna speciosa*) exposure reported to poison centers - United States, 2010-2015. *MMWR Morb Wkly Rep.* 2016; 65(29):748-9.
 28. Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom [FDA Statement]. U.S. Food & Drug Administration. Nov 2017.
 29. Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse [FDA Statement]. U.S. Food & Drug Administration. Feb 2018.
 30. FDA and Kratom [Public Health Focus]. U.S. Food & Drug Administration. April 2019.
 31. FDA oversees destruction and recall of kratom products; and reiterates its concerns on risks associated with this opioid [FDA News Release]. U.S. Food & Drug Administration. Feb 2018.
 32. 2019 Legislation Affecting MN Board of Pharmacy Licensees and Registrants. Minnesota Board of Pharmacy. https://mn.gov/boards/assets/2019MinnesotaLegislationAffectingBoardofPharmacyLicenseesandRegistrants06142019_tcm21-388725.pdf. Updated June 14, 2019. Accessed July 22, 2019.
 33. FDA requires stronger warnings about rare but serious incidents related to certain prescription insomnia medicines [News Release]. U.S. Food and Drug Administration. 2019. <https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warnings-about-rare-serious-incidents-related-certain-prescription-insomnia>
 34. Antrim A. *Talking Prescription Labels Offered Nationally in Certain Pharmacies.* Cranbury, NJ: Pharmacy Today; 2019.
 35. Vyleesi™ (bremelanotide) [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210557s000lbl.pdf. Accessed August 12, 2019.
 36. U.S. Food & Drug Administration. FDA approves new treatment for hypoactive sexual desire disorder in premenopausal women. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-hypoactive-sexual-desire-disorder-premenopausal-women>. Published June 21, 2019. Accessed August 12, 2019.

37. Shifren, JL. Overview of sexual dysfunction in women: Management. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc; 2019. https://www.uptodate.com/contents/overview-of-sexual-dysfunction-in-women-management?search=hsdd&source=search_result&selectedTitle=1~20&usage_type=default&display_rank=1. Accessed August 12, 2019.
38. Active Ingredient: Bremelanotide. RED BOOK Online. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Truven Health Analytics; 2019. https://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/CS/231945/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/80D546/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.ShowProductSearchResults?SearchTerm=VYLEESI&searchType=redbookProductName&searchTermId=49422&searchContent=REDBOOK&searchFilterAD=filterADActive&searchFilterRepackager=filterExcludeRepackager&searchPattern=%5Evyleesi Accessed August 12, 2019.