CURBSIDE CONSULT

Postgraduate (PGY-1) Pharmacy Residency Program

COLLEGE OF PHARMACY
UNIVERSITY OF MINNESOTA
Driven to Discover℠

Updates in Pharmacotherapy

Resident Editors: *Athena Cannon, PharmD; Madeleine Davies, PharmD; Hailey Haugen, PharmD*
Faculty Editor: *Jody Lounsbery, PharmD, BCPS*

RESEARCH UPDATES

Effect of Cytisine vs Varenicline on Smoking Cessation: A Randomized Clinical Trial[1]

Kristopher Nguyen, PharmD
New Ulm Medical Center

Background: Tobacco use remains a large modifiable risk factor that, when stopped, can impact patient health in a positive and significant way. Treatment choices include both over-the-counter and prescription medications with varenicline being an effective and popular, albeit costly, option. Cytisine is a plant-derivative that is a selective partial agonist at nicotinic acetylcholine receptors and has been used in European countries as a smoking cessation aid for decades. Cytisine has not been evaluated by the Food and Drug Administration (FDA) and is not available in the US; however, past trials have demonstrated safety and efficacy of cytisine as a treatment option.

Purpose: The objective of the study was to evaluate whether cytisine was non-inferior to varenicline as a smoking cessation medication.

Study Design: A non-inferiority, open-label randomized clinical trial was completed in Australia from November 2017 through May 2019. Eligible patients were at least 18 years of age, a current daily smoker, and willing to make a quit attempt using medications. A total of 1,452 participants were randomized to receive either varenicline 0.5 mg titrated to 1 mg twice daily for an 84-day course of treatment or cytisine 1.5 mg six times daily for a 25-day course of therapy. The primary outcome was continuous abstinence from smoking which was determined by patient self-report of not having smoked five or more cigarettes during the 6-month period preceding the 7-month follow-up and verified by a carbon monoxide breath test. Follow-up was conducted at 2, 4, 16, and 28 weeks for both groups. The primary safety outcome was the difference in the rate of adverse events between groups.

Results: For the primary endpoint, cytisine was inferior to varenicline for continuous abstinence from smoking with 6-month abstinence rates at 11.7% for cytisine group and 13.3% for the varenicline group (risk difference, -1.62% [1-sided 97.5% CI - 5.02 to ∞]; P=0.03) with -5.0% being the cut off for noninferiority. The incidence rate ratio (IRR) for self-reported adverse events occurred less frequently in the cytisine group (997) compared with the varenicline group (1,206) (IRR 0.88 [95% CI 0.81 - 0.95]; P=0.002). The most frequently reported adverse events were abnormal dreams and nausea which were less frequent in the cytisine group. Baseline characteristics, smoking history, and average cigarettes per day were balanced across both treatment groups.

Conclusions: Based on the results of this study, cytisine was inferior to varenicline as a therapeutic option for continuous abstinence rates from smoking. There were several limitations present such as the open-label design, unclear optimal dose and duration of cytisine treatment, and limited behavioral therapy offered to patients. Another limitation was that the carbon monoxide test used for the primary outcome can only

Volume 19, Issue 3 – 3rd Quarter 2021

detect smoking within 24 hours. A promising finding was the significantly lower rates of adverse events in the cytisine group.

Key Points: Cytisine has not been evaluated by the FDA and is not available as a treatment option in the US. Although this trial found cytisine to be inferior to varenicline in continuous smoking abstinence rates, cytisine still has potential as a safe and efficacious treatment option. Future blinded, randomized controlled trials need to be performed in order to further assess efficacy and safety.

Tripe vs Dual Inhaler Therapy for Treatment of Persistent Uncontrolled Asthma[2]

Sara Leistico, PharmD,
Minnesota Direct Care and Treatment

Background: Inhalers are commonly used for the treatment of persistent asthma. For patients ≥6 years of age with moderate to severe asthma, international guidelines recommend dual therapy with an inhaled corticosteroid (ICS) and a long-acting inhaled β2 agonist (LABA). There are only weak recommendations for adding a long-acting muscarinic antagonist (LAMA) to treatment in patients who continue to have uncontrolled symptoms. Other therapy escalations include oral corticosteroids, which have a higher risk of adverse effects and biologics, which have a substantially higher cost for treatment. If triple inhaler therapy controls a patient's asthma symptoms, systemic therapies like corticosteroids and biologics can be avoided.

Purpose: To compare dual inhaler therapy (ICS plus LABA) and triple therapy (ICS, LABA, and LAMA) outcomes and adverse events in adults and children with persistent uncontrolled asthma.

Study Design: Studies for this systematic review and meta-analysis were selected independently by two investigators. They selected randomized controlled trials (RCTs) comparing triple vs dual inhaler therapy in patients with moderate to severe asthma from data sources: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials , the World Health Organization International Clinical Trials Registry , Food and Drug Administration , and European Medicines Agency databases from November 2017 to December 8, 2020, without language restrictions. Two independent reviews extracted data and assessed the risk of bias. Random-effects meta-analyses were used, including patient-level exacerbation data. Studies were excluded if they were observational, preclinical, or limited to patients with chronic respiratory diseases other than asthma. All disagreements were resolved through consensus and authors were contacted in instances of unclear or missing data. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) and the Cochrane approaches were used to guide the conduct of the review which was prospectively registered. In addition, the study was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Results: Twenty RCTs enrolling 11,894 children and adults (mean age, 52 years [range, 9 – 71 years], 57.7% female) were included in the review. Compared to dual inhaler therapy, triple therapy was significantly associated with a reduction in severe exacerbation risk (9 trials [9,932 patients]; 22.7% vs 27.4%; risk ratio, 0.83 [95% CI 0.77 - 0.90]). Results for milder exacerbations were similar. Triple therapy was also significantly associated with improvement in asthma control (14 trials [11,230 patients]; standardized mean difference [SMD], −0.06 [95% CI −0.10 - −0.02]; mean difference in ACQ-7 scale, −0.04 [95% CI −0.07 - −0.01]). In addition, triple therapy was significantly associated with spirometry indices improvement as measured by trough FEV1 (18 trials [11,715 patients]; mean difference, 0.08 L [95% CI 0.07 - 0.10] I2 = 0%; high-certainty evidence). No significant differences between dual vs triple therapy were found in asthma-related quality of life (7 trials [5247 patients]; SMD, 0.05 [95% CI −0.03 - 0.13]; mean difference in AQLQ score, 0.05 [95% CI −0.03 - 0.13]; moderate-certainty evidence) or mortality (17 trials [11,595 patients]; 0.12% vs 0.12%; risk ratio, 0.96 [95% CI 0.33 - 2.75]; high-certainty evidence). Increase in dry mouth and dysphonia was significantly associated with triple inhaler therapy (10 trials [7395 patients]; 3.0% vs 1.8%; risk ratio, 1.65 [95% CI 1.14 - 2.38]; high-certainty evidence). However, treatment-related and serious adverse events were not significantly different between triple and dual therapy based on moderate-certainty evidence.

Conclusions: The results of this meta-analysis and systematic review support the use of triple inhaler therapy for children (≥6 years old) and adults with moderate to severe asthma. Among this population, triple therapy was significantly associated with fewer severe asthma exacerbations and modest improvements in asthma control compared to dual therapy. There were no significant differences in quality of life or mortality between triple and dual inhaler therapy.

Key Point: In patients ≥6 years of age with persistent moderate to severe asthma, triple inhaler therapy can be used to improve asthma control in order to avoid prescribing systemic therapies like steroids and biologics that may increase adverse events and cost.

Tirzepatide vs Semaglutide Once Weekly in Patients with Type 2 Diabetes[3]

Anna Lange, PharmD, Goodrich Pharmacy

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists are effective agents in the treatment of type 2 diabetes. GLP-1 agonists work by stimulating insulin secretion in hyperglycemic

states, suppressing glucagon secretion in hyperglycemic or euglycemic states, delaying gastric emptying, decreasing appetite, and aiding in weight loss. Additionally, they are known for their cardio-protective and renal-protective effects. Unlike semaglutide, tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. GIP is insulinotropic as well as glucagonotropic in a glucose-dependent manner and has abundant receptors in adipose tissue. Its dual activity may provide a greater effect on hemoglobin A1C and weight loss than GLP-1 receptor agonists alone.

Objective: The objective of this study was to assess the safety and efficacy of once weekly tirzepatide (GIP/GLP-1 receptor agonist) compared to once weekly semaglutide (GLP-1 agonist) in reducing hemoglobin A1C levels from baseline to 40 weeks.

Study Design: This was an open-label, parallel-group, randomized, active-controlled, phase III trial conducted at 128 sites. Patient inclusion criteria: ≥18 years old, type 2 diabetes with hemoglobin A1C of 7.0-10.5%, on at least 1,500 mg metformin/day, BMI >25, and stable weight over the last three months. A total of 1,789 patients were randomly assigned into four treatment groups to receive a once-weekly subcutaneous injection of either tirzepatide 5 mg, 10 mg or 15 mg, or semaglutide 1 mg for a 40-week treatment period, followed by a 4-week safety follow-up period. The primary outcome was the change in hemoglobin A1C from baseline to 40 weeks. The key secondary outcomes were change in weight from baseline to 40 weeks and target hemoglobin A1C of less than 7.0% and less than 5.7%.

Results: Tirzepatide was found to be superior to semaglutide in terms of change in hemoglobin A1C and weight from baseline to 40 weeks. The mean change in A1C was -2.01% with the 5 mg dose (P=0.02), -2.24% with the 10 mg dose (P<0.001), and -2.30% with the 15 mg dose of tirzepatide (P<0.001). Patients randomized to tirzepatide 15 mg lost an average of 11.2 kg, compared with 5.7 kg on maximum dose semaglutide (P<0.001). In addition to the weight loss, 82 to 86% of patients on tirzepatide reached an A1C of <7%, while 79% of patients on semaglutide reached an A1C of <7%. The most common side effects were gastrointestinal in nature. Nausea was reported in 17 to 22% of patients who received tirzepatide and in 18% who received semaglutide, diarrhea was reported in 13 to 16% and 12%, vomiting in 6 to 10% and 8%, and decreased appetite in 7 to 9% and 5%, respectively. Gastrointestinal upset increased with higher doses. Hypoglycemia occured at a rate of 1.7% in tirzepatide 15 mg compared to 0.4% in semaglutide, with two instances of severe hypoglycemia in the 5 mg and 15 mg tirzepatide groups. Both patients were able to continue the rest of the trial safely after treating the hypoglycemia.

Conclusion: Tirzepatide, a dual GIP/GLP-1 receptor agonist, exhibits A1C lowering and weight loss effects similar to semaglutide, but to a greater extent. Regarding safety, severe hypoglycemia occured at a higher rate in tirzepatide, but all patients recovered and finished the trial. Tirzepatide demonstrated superior efficacy in comparison to maximum dose semaglutide in both lowering of hemoglobin A1C and weight from baseline to 40 weeks.

Key Point: Tirzepatide is a promising new therapy for use in type 2 diabetes and showed significant A1C and weight loss benefits. Further studies comparing it to other GLP-1 receptor agonists are needed.

THERAPEUTIC THOUGHT

Flozins, The New Statins for Heart Failure?[4-7]

Sonal Divecha, PharmD,
Community-University Health Care Center

Background: Ambulatory care providers are vital in screening and initiating appropriate therapy in patients who are at an increased risk of heart failure which is commonly seen in patients with diabetes. Evidence-based medicine guides initiation of medications for diabetes that are known to reduce progression of cardiovascular and renal disease. As such, sodium-glucose co-transporter-2 inhibitors (SGLT2i) have proven their place in therapy by reducing hemoglobin A1C and blood pressure, claiming their superiority if heart failure or chronic kidney disease is present in addition to diabetes. Heart failure, a progressive disease, accounts for the increased morbidity and mortality surrounding such patients and as with other chronic conditions, the novel use of current therapeutics extending beyond their primary indication is an emerging science. The American Diabetes Association (ADA) guidelines denote SGLT2i to hold a significant role in the prevention and treatment of heart failure in patients with diabetes. Pharmacists in particular can play a vital role in implementing evidence-based medicine to individualize and optimize medication use.

Evidence: Numerous trials evaluating the safety, efficacy, and place in therapy of each of the SGLT2i were conducted. The EMPA-REG and EMPA-REG OUTCOME trials demonstrated that empagliflozin treatment resulted in a significant reduction in hospitalization for heart failure or cardiovascular death in patients with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD). Similarly, the CANVAS trial showed that the use of canagliflozin in patients with heart failure was associated with a

reduced risk of hospitalization for heart failure or cardiovascular death. This trial revealed a greater benefit in patients with established heart failure in comparison to those without. Thus, paving the way to prove canagliflozin's efficacy and place in therapy in preventing hospitalization for heart failure. The DECLARE-TIMI 58 and DAPA-HF trials evaluated the use of dapagliflozin in patients with non-type 2 diabetes, with or without ASCVD. These studies also revealed a significant reduction in hospitalization for heart failure or cardiovascular death supporting the Food and Drug Administration approval of dapagliflozin for heart failure. The development of more focused trials to seek a link between cardiovascular outcomes with the use of SGLT2i have provided sufficient evidence to support their role in risk reduction. As these effects are independent of blood glucose lowering, the underlying mechanism of cardiovascular risk reduction is yet to be identified but proves promising.

Discussion & Clinical Impact: Per an article from Chim et al. one possible mechanism of action of SGLT2i that could shed light on its use in ASCVD reduction is via the promotion of diuresis, resulting in reduced plasma volume, blood pressure, preload, afterload, cardiac stiffness, and remodeling. The key trials described above have provided the foundation for extending the indication of SGLT2i for this use. This new possible indication of ASCVD reduction for SGLT2i closely correlates with the historic use of HMG-CoA reductase inhibitors, more commonly referred to as statins, in the primary prevention of ASCVD. In this case, guideline driven therapy was based on risk-enhancing factors, and used related laboratory markers to direct its implementation. As with statins, more data is needed to individualize a risk-based systematic process to guide the use of SGLT2i to provide an array of safe and effective cardio-renal therapies. Similar to other novel therapeutic agents, the current market for SGLT2i is limited by brand patents preventing their widespread application. Despite large, multicenter population trials, there is limited evidence on the applicability of SGLT2i in patients without type 2 diabetes,with or without risk factors for heart failure. Yet, current data provides promising results to a potential indication of cardiovascular risk reduction based on the science and pleiotropic effects of the drug.

Best Practice for Use of Short-Course Antibiotics in Common Infections[8-13]

Lauren Ostlund, PharmD,
Broadway Family Medicine

Background: Healthcare providers are asked to navigate the fine balance between efficacy and safety when determining medication regimens for patients. When it comes to the use of antibiotics, this ambivalence is accentuated due to the potential risks that come with both under- and over-treatment. As antibiotic resistance continues to be a concern in patient care, the importance of appropriate antibiotic use in common infections remains at the forefront of prescribers' minds; treatment courses need to be long enough to clear the infection, but short enough to mitigate antibiotic resistance and unnecessary patient exposure to adverse effects. There is also a thought that shorter courses may lead to increased adherence to antibiotic regimens due to the potential for decreased monetary cost and regimen complexity, which may then help support reduction in antibiotic resistance.

Evidence & Discussion: A mitigation factor for decreasing antibiotic resistance includes shorter durations of antibiotic courses when cure outcomes lack a statistically significant difference when compared to longer durations of antibiotic treatment. A recently published article from the American College of Physicians (ACP) discusses best practice advice for short-course antibiotic treatments of the following common bacterial infections: acute bronchitis in chronic obstructive pulmonary disease (COPD) exacerbation, community-acquired pneumonia (CAP), urinary tract infections (UTIs), and cellulitis. Antibiotic selection should still include assessment of most commonly reported bacterial pathogens and resistance patterns to increase effectiveness of chosen treatment.

Avoiding antibiotic treatment in patients with bronchitis has been encouraged to prevent unnecessary exposure to antibiotics and their subsequent adverse effects when the cause is likely non-bacterial. However, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for treatment of COPD exacerbations recommends five to seven days of antibiotic treatment if the patient has evidence to support presence of bacterial infection (i.e. increased sputum purulence and increased dyspnea and/or increased sputum volume). Analysis of additional studies now supports treatment in COPD exacerbations with evidence of bacterial infection to be limited to five days.

Support for limiting the duration of antibiotics to five days in the treatment of CAP, as long as the patient is clinically stable (i.e. resolved vital sign abnormalities and normal mentation and ability to eat) is also supported by ACP. Supporting evidence was evaluated from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society guideline for CAP.

Shorter courses of antibiotics in women with uncomplicated bacterial cystitis are further classified based on choice of treatment: five days of treatment with nitrofurantoin, three days of treatment with trimethoprim-sulfamethoxazole, or a one-dose treatment with fosfomycin. In men or women with uncomplicated pyelonephritis, five to seven days of treatment with a fluoroquinolone or 14 days of treatment with trimethoprim-sulfamethoxazole should be used depending on antibiotic susceptibility testing results. This evidence is supported by the guidelines through IDSA and the European Society for Microbiology and Infectious Diseases. These recommendations do not cover complicated UTIs or UTIs in the presence of pregnancy.

In the case of nonpurulent cellulitis, five to six days of antibiotic treatment is typically adequate, especially if close follow up is achievable and if the patient is able to monitor the infection site at home. This recommendation was supported by ACP after review of IDSA, the National Institute for Health and Care Excellence, and a new randomized control trial.

Clinical Impact: Healthcare providers should recognize the potential detrimental impact of antibiotic resistance and of preventable side effects from longer duration antibiotic treatment. Evidence supporting shorter courses of antibiotic therapies in common infections has the potential to combat this growing concern. Furthermore, continuous research in the lowest effective doses and shortest effective courses of therapy may continue to help decrease overuse of antibiotic regimens for common bacterial infections.

The Use of Muscle Relaxants in the Treatment of Non-Specific Low Back Pain[14-18]

Reid Larson, PharmD,
Welia Health

Background: How many people do you know with low back pain? Too many to count? If that is the case it is no surprise low back pain has been the leading cause of disability worldwide for the past 30 years according to the Global Burden of Disease study in 2017. First-line therapies include a range of non-pharmacological approaches, often accompanied with the use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, muscle relaxants (MRs), and corticosteroids. Prescription MRs are the third most commonly prescribed class of medications for the treatment of low back pain and can be classified as non-benzodiazepine antispasmodics (carisoprodol, cyclobenzaprine, methocarbamol, tizanidine, etc.), antispastics (baclofen, dantrolene), and benzodiazepines (diazepam, clonazepam, etc.). Due to variable results in clinical trials, conflicting recommendations for the use of these medications exist between international clinical practice guidelines. For example, the American College of Physicians (ACP) guideline recommends non-benzodiazepine antispasmodics as the drug of choice for acute low back pain, the National Institute for Health and Care Excellence guideline does not make a recommendation on the use of MRs, and the Belgian Health Care Knowledge Centre discourages use of MRs entirely. A recent review by Cashin et al. summarized the available evidence on safety and efficacy of MRs to help guide healthcare providers in the treatment of low back pain with evidence-based pharmacotherapy.

Evidence: In an effort to quell this controversy, Cashin et al. recently published a systematic review consisting of 49 randomised controlled trials that evaluated the efficacy and safety of MRs versus placebo, usual care, or no treatment in adults (≥18 years) for the treatment of non-specific low back pain. The trials included were assessed for the risk of bias and certainty of the evidence, and data was extracted to produce outcomes of pain intensity, disability, acceptability, and safety. Of the 41 clinical trials, 31 were selected to be further analyzed via a meta-analysis. A total of 6,505 participants comprised the sample population included in the meta-analysis.

Acute, sub-acute, and chronic pain were defined as non-specific low back pain lasting 0 to 2 weeks, 2 to 6 weeks, and ≥12 weeks, respectively. The authors found, in the case of acute low back pain, that non-benzodiazepine antispasmodics were associated with a reduction in pain intensity compared with control (mean difference −7.7 [95% CI −12.1 - −3.3]). However, they did not find a reduction in disability (mean difference −3.3 [95% CI −7.3 - 0.7]) and the evidence suggested an increase in the risk of an adverse event (RR 1.6 [95% CI 1.2 - 2.0]). Interestingly, benzodiazepines were found to have a statistically significant reduction in disability in patients with sub-acute pain (mean difference −6.9 [95% CI −12.1 - −1.7]), but showed no reduction in disability in patients with chronic low back pain. Antispastic drugs were also associated with an increase in the risk of an adverse event versus control (mean difference 2.0 [CI 95% 1.1 - 3.8]) which were more likely to cause discontinuation of treatment (mean difference 34.6 [95% CI 2.1 - 568.0]).

Discussion & Clinical Impact: In the treatment of low back pain, this study has aided in summarizing the variable efficacy and safety data previously reported. Overall, non-benzodiazepine antispasmodic drugs appear to be more effective compared to benzodiazepines or antispasmodics in reducing acute low back pain. However, there are a number of limitations that may push clinicians to avoid their use in this setting. First, the mean differences reported were based on a 0 - 100 point scale, meaning even those effects that were statistically significant were relatively insignificant (i.e. less than 8 points on a 0 - 100 point scale) and may not be clinically meaningful. Second, the meta-analysis included three studies that evaluated the use of thiocolchicoside, a non-benzodiazepine antispasmodic not approved by the Food & Drug Administration due to the possibility of severe adverse effects. The addition of these studies may have skewed the overall results of the meta-analysis towards showing benefit of MRs. Furthermore, the risks associated with MRs may outweigh their benefits, especially in older adult populations. These risks include side effects of drowsiness, dizziness, agitation, irritability, headache, increased fall risk, and possible dependence or misuse.

Non-specific low back pain typically improves over time regardless of treatment modality. Therefore, per the ACP clinical guidelines on low back pain, first-line treatments should focus on non-pharmacological options such as physical therapy, superficial heat, massage, or acupuncture. If pharmacologic treatment is warranted beyond NSAIDs or acetaminophen, MRs may be an

option in the acute setting only. Deprescribing practices should be considered in those initiated on MR therapy for chronic low back pain. Cashin et al. wrote the following conclusion to help guide clinical practice: "Although non-benzodiazepine antispasmodics might reduce pain intensity at two weeks or less for acute low back pain, the effect is unlikely to be considered clinically important."

FROM THE PHARMACY PRESS

Impact of Pharmacist and Physician Collaborations in Primary Care on Reducing readmission to Hospital: A Systematic Review and Meta-analysis[19]

Sandra Leo, PharmD,
Mille Lacs Health System

Background: Medication changes that occur during hospital admission for those with multiple chronic conditions often lead to medication discrepancies that contribute to hospital readmission rates. Patients with discrepancies are twice as likely to be readmitted to the hospital within 30 days of discharge than those without discrepancies. Previous meta-analyses have shown that hospital-based pharmacist medication reconciliation at discharge is effective for reducing hospital readmission. However, data is limited regarding the effect of pharmacist-led interventions in the primary care setting following hospital discharge.
Objective: This meta-analysis aimed to study whether pharmacist-led interventions and primary care provider (PCP) communication following hospital discharge reduces hospital readmission, as well as to describe and explore differences in the type of these interventions.

Study Design: Investigators performed a search of PubMed, EMBASE, The Cochrane Central Register of Controlled Trials, CINAHL and Web of Science to identify studies that described pharmacist-led interventions in patients transitioning from the hospital to community care. Trials were included if the participants were adult patients recently hospitalized, the pharmacist was the main contributor to an intervention in post-discharge care, at least part of the intervention occurred after discharge, and some communication occurred between the pharmacist and the patient's PCP. All studies included an all-cause hospital readmission at any time during the study period, which was the primary endpoint. Secondary endpoints included the proportion of patients who had at least one readmission at 30 days, 90 days, or 6 months after discharge and incidence of all readmissions over the stated study period.

Results: The search yielded 37 studies which included sufficient data for inclusion to either primary and/or secondary outcomes. Pharmacist intervention demonstrated a reduction in the proportion of patients with at least one hospital readmission compared to controls during the study period (RR 0.87 [95% CI 0.79 – 0.97], P=0.01). Pharmacist intervention also demonstrated a reduction in the proportion of patients with hospital readmission was shown at 90 days (RR 0.90 [95% CI 0.78 – 1.05]) or 6 months (RR 0.94 [95% CI 0.83 – 1.07]). Subgroup analyses showed pharmacist intervention reduced the proportion of patients with a hospital readmission when the intervention included a comprehensive medication review (RR 0.86 [95% CI 0.77-0.96]) and when the PCP communication was direct via telephone or face-to-face (RR 0.66 [95% CI 0.47 - 0.93], but not when the intervention was of a single component such as adherence alone (RR 0.96 [95% CI 0.68 - 1.36]) or when the PCP communication was indirect via fax or email (RR 0.89 [95% CI 0.75 - 1.05]).

Conclusions: This study shows that pharmacist intervention and communication with the PCP following discharge results in a 13% reduction in hospital readmissions, although the significantly reduced risk seems to be confined to the initial 30 days following hospital discharge. Benefits of pharmacist intervention are most effective when communication occurs via direct means, as well as when the intervention provides more comprehensive medication assessment. One limitation of this study was that the results were only statistically significant when stratified by type of studies; the included non-randomized control trials (RCT) showed a risk reduction in favor of pharmacist intervention while the RCTs did not. Another limitation was the moderate level of heterogeneity with regards to the primary outcome of hospital readmission at any time, as well as significant heterogeneity to a substantial degree in regards to the secondary outcome of total readmission incidence.

Key Point: Pharmacist interventions that involve communication with PCP following patients' hospital discharge may help to reduce readmission rates at 30 days. Direct communication and comprehensive interventions are likely the most effective methodology for reducing readmission risk.

Implementation of Pharmacy-Led Services to Identify and Treat Osteoporotic Fractures[20]

Erica Hanson, PharmD,
Cash Wise Clinic Pharmacy

Background: Osteoporosis is defined as a bone mineral density T-score of -2.5 or less, which can lead to an increased risk of fractures. Osteoporosis-related hip fractures can increase mortality by 36% within one year after the fracture occurs, and fractures increase healthcare costs and can lead to patients

requiring hospitalization. Bone mineral density tests, often done with a dual-energy X-ray absorptiometry (DXA) scan, are recommended every two years for men 70 years old and older by the National Osteoporosis Foundation. However, many patients are not screened until after suffering a fracture. Patients in rural settings may have an added disadvantage obtaining DXA scans, as less services may be available and distance to see a physician may be an issue.

Purpose: This study aimed to develop and implement a service that is pharmacist and pharmacy student-led to increase DXA screening rates and treat those at high risk of fractures. It focused on education, initial assessment and plan, and coordination of follow-up care for rural veterans.

Study Design: A list of patients 70 years old and older, living in a rural or highly rural setting, and having received primary care from one Patient-Aligned Care Team at the Madison VA West Clinic was generated in January 2018. Patients were excluded if they had a prior DXA scan in the last two years, had changed providers, were residing in a hospice facility, or had died since the list was generated. Eligible patients were contacted via telephone from November 2018 to February 2020 and offered a DXA screening. The pharmacy was given results after a densitometrist reviewed completed scans. If the patient was diagnosed with osteoporosis or osteopenia, levels for serum creatinine, vitamin D, and serum calcium were also obtained. Patients diagnosed with osteoporosis and osteopenia then completed a fracture risk assessment tool (FRAX) to estimate the probability of a fracture over the next ten years to determine eligibility for medications. A flow chart was created to assist the decision-making of appropriate pharmacologic therapy with an oral bisphosphonate, vitamin D, and/or calcium. Patients with contraindications to oral bisphosphonates were referred to the specialty osteoporosis clinic.

Results: A total of 196 patients were eligible to be contacted for a DXA scan. Of those, 154 patients participated in the telephone encounter, and 115 patients completed the scan. Of the patients who completed a DXA scan, 57 (50%) were diagnosed with osteoporosis or osteopenia, and 33 (58%) were eligible for antiresorptive therapy based on their FRAX score. Of these 33 veterans, 12 (36%) were started on alendronate.

Conclusion: This study concluded that pharmacist-led osteoporosis services can help increase bone mineral density screening rates and increase the number of patients receiving pharmacologic therapy. The percentage of patients in this study who received a DXA scan increased three-fold compared to the pre-implementation DXA screening rate. Half of those screened in the study had a diagnosis of osteoporosis or osteopenia, and about a third of those patients were started on alendronate. Although a long-term endpoint of a bone fracture was not studied, initiating an osteoporosis program for rural veterans helped screen and treat patients who may not have had access to healthcare.

Key Point: Pharmacists involved with screening and initiating drug therapy for patients with osteoporosis have the potential to reduce fracture risk in older adult male patients.

Community Pharmacists' Perceptions of Participation in a Sustainable Value-based Care Model for Comprehensive Medication Management[21]

Alyssa Falleni, PharmD,
Hennepin Healthcare

Background: Comprehensive medication management (CMM) is a service delivered to patients with the goal to identify, resolve, and prevent medication therapy problems to optimize medication use. CMM, through pharmacist intervention, is a well-documented strategy to reduce the burden of suboptimal medication use in the US, improve clinical outcomes, and reduce overall costs to the healthcare system. Despite evidence showcasing the benefits of CMM, the consistent adoption of this practice in the community has been sporadic. Common barriers to CMM implementation are the lack of compensation for clinical services, time restraints, workflow interruption, and lack of knowledge in billing/documentation. However, even when a barrier such as compensation is addressed, pharmacist engagement has been limited. For example, despite Minnesota Medicaid adopting a payment model for CMM services, only 3.5% of 37,000 eligible Medicaid beneficiaries completed a CMM visit in 2011. Of 110 pharmacy organizations who submitted data, less than 5% were submitted by community pharmacists. Even when strong evidence exists for pharmacy interventions, real-world implementation takes time and consideration due to competing demands and barriers. In 2015, HealthPartners expanded their value-based care model for CMM services to include Partners in Excellence (PIE), a performance-based component. The aim was to incentivize participating pharmacies with bonus payments to conduct CMM visits in order to achieve engagement and quality metrics. Each quarter, HealthPartners provides lists of patients at risk for medication-related problems, based on collected claims data and medical history, to participating pharmacies. Three performance benchmarks are set for quality: blood pressure goal <140/90 mmHg, tobacco-free status, and hemoglobin A1c <8%. The engagement metric is defined as CMM services offered to at least 40% of eligible patients in a given year. Bonus payments would be granted based on achievement of these metrics.

Purpose: Participation by community pharmacists has been limited in the PIE program since its conception, prompting this study to examine three early intervention implementation outcomes: acceptability, appropriateness, and feasibility. For context, *acceptability* is the different stakeholders' perceptions that a new service model is agreeable, *appropriateness* is the

perceived fit or compatibility of a service for a specific practice setting, and *feasibility* is the extent to which a new service can be successfully used or carried out.

Study Design: This particular study was carried out through semi-structured, one-on-one qualitative interviews with a group of 10 pharmacists and four CMM pharmacy managers from participating sites.

Results: For acceptability, participants were in agreement that the clinical metrics were aligned with the conditions commonly affecting their patients. However, they felt there were other conditions that should be addressed and the narrowed metrics may prevent that exploration. Barriers were smoking cessation patient engagement, billing through the HealthPartners' online portal, and delivering longitudinal CMM to patients who change insurers. When discussing appropriateness, participants felt that the PIE program aligned with their belief that community pharmacists play a role in patient care. However, many participants expressed concerns about the cost of the necessary software and the amount of time needed for patient visits, documentation, and billing. For the feasibility of collecting pertinent clinical information to conduct CMM, participants varied in their opinions, with some stating it was provided through their pharmacy and others expressing challenges with reaching out to a patient's clinic.

Conclusions: CMM is an important tool for community pharmacists to address medication therapy problems. Community pharmacists and managers have positive perceptions of the use of a value-based care model but many identified implementation barriers to adopting a sustainable model in practice. The many barriers that exist for community pharmacies include patient and provider buy-in, time availability, the process to collect clinical information, documentation/billing, and delivering longitudinal CMM to patients who change insurers.

Key Point: The insight from this study could assist in developing a process to implement CMM more consistently in the community setting. Additionally, this study highlighted the role payers have in overcoming certain barriers, like providing pharmacies with clinical information, educating patients on the service, and offering flexible payment models. Moving forward, it is important that community pharmacy leaders ensure pharmacists have dedicated time, documentation resources, and technician support to provide CMM.

MISCELLANEOUS NEWS

Zantac™ is Back: Same Brand, A Familiar but Different Ingredient[22-24]

Bobby LeDuff, PharmD,
Essentia Health

All products of ranitidine were recalled by the Food and Drug Administration (FDA) in April 2020 due to alarming amounts of N-Nitrosodimethylamine (NDMA) found in prescription and over the counter formulations. According to the FDA, NDMA is commonly ingested at low levels through water and certain foods; moreover, ingestion of NDMA at low levels is considered to be safe. According to Lim et al., NDMA is classified as a probable human carcinogen when people are exposed to sustained higher levels. Initial laboratory testing of ranitidine found low levels of NDMA, but clinicians found that these levels increased over time beyond the acceptable daily intake limit, even under normal storage conditions. With these discoveries, all ranitidine products are likely to remain off the market for the foreseeable future.

After more than a year of being off the market, Zantac™ is coming back to the market but with a new active ingredient, famotidine. Zantac™ will now be marketed as Zantac 360°™ Original Strength, which will be famotidine 10 mg, and Zantac 360°™ Maximum Strength, which will be famotidine 20 mg. It is important to note that the "360" in the rebranding has nothing to do with the quantity, dosing, or strength of the product and may lead to patient and prescriber confusion. Some ways to prevent confusion are to use both brand and generic name when referring to the product and review patient charts and medication lists for duplicate therapy. The rerelease of Zantac 360°™ will be an interesting experience for pharmacists to say the least.

Unsafe Drugs Now Safe? FDA's Request to Change Statin Warning in Pregnancy[25-26]

Ryan Albrecht, PharmD,
Coborn's CSC

Statins, HMG-CoA reductase inhibitors, have revolutionized the way we treat hyperlipidemia. However, since the first statin, lovastatin, hit the market in 1987 there has been a warning attached to the class to avoid use in pregnancy. That warning was given by the US Food and Drug Administration (FDA) based on animal studies linking statin use to birth defects and the belief that short-term use of statins in pregnancy would not provide substantial benefit of preventing cardiovascular disease in mothers. Manufacturers have since included this warning as a contraindication for all statins. Now, 34 years later, the FDA is changing its stance and recommending the removal of this contraindication for all statins. The reason behind this new

recommendation, according to the FDA's Drug Safety Communication from July 20, 2021, is the overwhelming amount of evidence showing a benefit of statin use in preventing cardiovascular events. In addition, they cite a lack of data from published studies showing a link between statin use and birth defects. The FDA believes that removal of the contraindication will allow for an individualized approach to statin therapy in pregnant patients. It is still recommended that most patients be taken off statins during pregnancy, but those at very high-risk for stroke or heart attack may benefit from continuation of therapy. With this change, the FDA urges that side effects be reported using the MedWatch program. Due to the small number of very high-risk pregnant patients that this change targets, it is unlikely that this recommendation by the FDA will widely change statin prescribing. However, it is reassuring that data driven changes are being made to ensure individualized patient therapy.

New Approval for SHINGRIX Vaccine[27-28]

Hanna Friedrich, PharmD,
Cub Pharmacy

On July 26, 2021 the Food and Drug Administration (FDA) announced a new and exciting approval for the SHINGRIX vaccine. The new approval is for adults 18 years and older with qualifying immunocompromised conditions. GlaxoSmithKline's SHINGRIX vaccine was approved in 2017 as a two dose series for adults 50 years of age and older for the prevention of Herpes Zoster, also known as shingles. Of note, the vaccine is not indicated for the prevention of primary varicella infection, or chickenpox. SHINGRIX is an inactive adjuvant, recombinant vaccine which is safe to co-administer with other vaccines, irrespective of the timing of any live vaccines previously administered. According to the Centers for Disease Control and Prevention (CDC), SHINGRIX is 97% effective in preventing shingles in adults 50-69 years old who receive both doses. The current approval is for two separate doses to be administered intramuscularly two to six months apart. The FDA has now approved the administration of the second dose in immunosuppressed patients in as little as one month after the first dose. This will allow immunocompromised patients to reach immunity faster. This expanded indication will have a positive impact on the pharmacy profession, as well as improve patient outcomes. Access to the vaccine for high-risk patients will help prevent complications and worsening of their chronic conditions. Pharmacists are the most accessible health care provider. With this unique position, pharmacists will have an opportunity to help many patients improve their overall health. At the time of this publication, the Advisory Committee on Immunization Practices (ACIP) had not published updated recommendations. It is imperative to wait for ACIP to define qualifying immunodeficiency immunosuppressed disease states, and immunosuppressive drug therapy before implementation of this new indication. For further information and updates on qualifying conditions, check the ACIP meeting agendas found at: https://www.cdc.gov/vaccines/acip/meetings/agenda-archive.html.

For meeting minutes use the following link for more information: https://www.cdc.gov/vaccines/acip/meetings/minutes-archive.html

REFERENCES

1. Courtney R, McRobbie H, Tutka P. Effect of cytisine vs varenicline on smoking cessation: a randomized clinical trial. *JAMA*. 2021;326(1):56-64. doi:10.1001/jama.2021.7621
2. Kim LH, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs Dual Inhaler therapy and ASTHMA outcomes in moderate to severe asthma. *JAMA*. 2021;325(24):2466. doi:10.1001/jama.2021.7872
3. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med.* 2021;385:503-515. doi: 10.1056/NEJMoa2107519
4. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZ. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *American Heart Association Circulation*. 2017;136:1643–1658. DOI: 10.1161/CIRCULATIONAHA.117.030012
5. Chim C, Newaz S. SGLT2 inhibitors and heart failure outcomes. *U.S. Pharmacist*. 2020;45(2):18-22. https://www.uspharmacist.com/article/sglt2-inhibitors-and-heart-failure-outcomes. Accessed August 7, 2021.
6. Freaney P, Lloyd-Jones D, Khan, S. Could flozins be the statins for risk-based primary prevention of heart failure? *JAMA Cardiol.* 2021;6(7):741-742. doi:10.1001/jamacardio.2021.1133
7. Shim CY, Seo J, Choi, et al. Randomized, controlled trial to evaluate the effect of dapagliflozin on left ventricular diastolic function in patients with type 2 diabetes mellitus. *Circulation*. 2021;143(5):510-512. doi:10.1161/CIRCULATIONAHA.120.051992.

(continued)

8. Lee RA, Centor RM, Humphrey LL, Jokela JA, Andrews R, Qaseem A. Appropriate use of short-course antibiotics in common infections: best practice advice from the American College of Physicians. *Ann Intern Med*. 2021;174:822-827. doi: 10.7326/M20-7355. 6 April 2021.
9. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). Global initiative for chronic obstructive lung disease.
10. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. *Am J Respir Crit Care Med*. Vol 200, Iss 7, pp e45–e67, Oct 1, 2019. doi: 10.1164/rccm.201908-1581ST
11. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by Infectious Disease Society of America and the European Society for Microbiology and Infectious Diseases. *ClinInfect Dis*. 2011;52(5):e103–e120. doi: 10.1093/cid/ciq257
12. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infectious: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):147–59. doi: 10.1093/cid/ciu444.
13. Leimbach N. Shorter Courses of antibiotics may sometimes be better in the long run. *Pharmacy Times*. Nov 18, 2016. https://www.pharmacytimes.com/view/shorter-courses-of-antibiotics-may-sometimes-be-better-in-the-long-run. Published November 18, 2016. Accessed August 27, 2021.
14. James SL, Abate D, Abate KH, et al. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392:1789-858. doi:10.1016/S0140- 6736(18)32279-7.
15. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2017;166(7):514-530. doi:10.7326/M16-2367
16. National Guideline Centre (UK). *Low Back Pain and Sciatica in Over 16s: Assessment and Management*. London: National Institute for Health and Care Excellence (UK); November 2016.
17. Van Wambeke P, Desomer A, Ailliet L, et al. Low back pain and radicular pain: assessment and management. KCE Report 287. Belgian Health Care Knowledge Centre, 2017.
18. Cashin AG, Folly T, Bagg MK, et al. Efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain: systematic review and meta-analysis. *BMJ*. 2021;n1446. doi:10.1136/bmj.n1446
19. Foot H, Scott I, Sturman N, et al. Impact of pharmacist and physician collaborations in primary care on reducing readmission to hospital: A systematic review and meta-analysis . *Res Social Adm Pharm*. 2021:doi: 10.1016/j.sapharm.2021.07.015.
20. Wopat M, Breslow R, Chesney K, et al. Implementation of a pharmacist and pharmacy student-led primary care service to identify and treat rural veterans at risk for osteoporotic fracture]. *J Am Pharm Assoc.* 2021; doi:10.1016/j.japh.2021.07.011.
21. Pestka DL, Stoa MK, Sorensen TD, Blanchard CM. Community pharmacists' perceptions of acceptability, appropriateness, and feasibility of a value-based care model for comprehensive medication management. *J Manag Care Spec Pharm*. 2021;27(7):865-872. doi:10.18553/jmcp.2021.27.7.865
22. FDA requests removal of all ranitidine products (zantac) from the market. U.S. Food and Drug Administration.https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market. Published April 1, 2020. Accessed August 9, 2021.
23. Lim HH, Oh YS, Shin HS. Determination of N-nitrosodimethylamine and N-nitrosomethylethylamine in drug substances and products of sartans, metformin and ranitidine by precipitation and solid phase extraction and gas chromatography–tandem mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis. 2020;189:113460. doi:10.1016/J.JPBA.2020.113460 Published July 4, 2020. Accessed August 9, 2021.
24. Watch for unexpected ingredients in new zantac products. Pharmacist's Letter. https://pharmacist.therapeuticresearch.com/Content/Articles/PL/2021/Jul/Watch-for-Unexpected-Ingredients-in-New-Zantac-Products. Published July 2021. Accessed August 9, 2021.

(continued)

25. U.S. Food & Drug Administration. FDA Drug Safety Communication. FDA.gov. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-strongest-warning-against-using-cholesterol-lowering-statins-during-pregnancy. Published July 20, 2021. Accessed July 23, 2021.
26. U.S. Food & Drug Administration. MedWatch Online Voluntary Reporting Form. FDA.gov. https://www.accessdata.fda.gov/scripts/medwatch/. Accessed July 23, 2021.
27. GlaxoSmithKline plc. *Shingrix approved in the US for prevention of shingles in immunocompromised adults.* Available at: https://www.gsk.com/en-gb/media/press-releases/shingrix-approved-in-the-us-for-prevention-of-shingles-in-immunocompromised-adults/. Published 26 July 2021. Accessed 4 August 2021.
28. Centers for Disease Control and Prevention. *Shingrix Shingles Vaccination: What Everyone Should Know.* Available at: https://www.cdc.gov/vaccines/vpd/shingles/public/shingrix/index.html. Published January 25, 2018. Accessed August 24, 2021.

COLLEGE OF PHARMACY

UNIVERSITY OF MINNESOTA

POSTGRADUATE PHARMACY RESIDENCY PROGRAM