Postgraduate (PGY-1) Pharmacy
Residency Program

CURBSIDE CONSULT

University of Minnesota
College of Pharmacy
Driven to Discover℠

Updates in Pharmacotherapy

***Resident Editors*: Courtney Christopher, Pharm.D., Kaity Kuske, Pharm.D., Natalie Roy, Pharm.D.**
***Faculty Editor*: Jean Moon, Pharm.D., BCACP**

Volume 15, Issue 3 – Third Quarter 2017

Research Updates

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (The CANVAS Program)[1]

Caitlin Strand, Pharm.D.
Westside Community Health Services

Background: Sodium-glucose Co-transporter2 (SGLT2) inhibitors have shown promise in reducing the risk of cardiovascular (CV) death in patients with type 2 diabetes. The EMPA-REG trial of empagliflozin (Jardiance®) was an exciting development for diabetes management, as it showed that this medication minimized CV risk. The CANVAS Program sought to prove similar efficacy for canagliflozin (Invokana®) in reducing CV and renal risk.

The CANVAS Program was comprised of two double-blind, randomized, placebo-controlled studies developed to test the non-inferiority [HR below 1.3] of canagliflozin to placebo. The first study, CANVAS, started in 2009. Data from CANVAS was "unmasked" and included in regulatory filing documents for FDA approval for canagliflozin; thus, a new trial was needed to continue studying the drug. Therefore, CANVAS-R started in 2014 to explore canagliflozin's renal effects and ongoing CV impact.

Purpose: The primary outcome was a composite of death from CV causes, nonfatal myocardial infarction, or non-fatal stroke. Secondary outcomes were death from any cause, death from CV causes, progression of albuminuria (30% increase and change in albuminuria status) and the composite of death from CV causes and hospitalization for heart failure.

Study Design: The studies included patients with type 2 diabetes who had an A1c between 7% and 10.5%. Patients were included if they were 30 years or older with a history of symptomatic atherosclerotic CV disease or if they were 50 years or older with two or more risk factors for CV disease (diabetes for at least 10 years, SBP ≥140 mm Hg on antihypertensive(s), current smoker, microalbuminuria or macroalbuminuria, or HDL < 38.7 mg/dL). Patients were excluded if they had an eGFR < 30 mL/min/1.73m2, a history of diabetic ketoacidosis, type I diabetes, pancreas or beta-cell transplant, history of one or more hypoglycemic episodes, or inadequately controlled thyroid disorder.

Results: The CANVAS trial showed significantly fewer primary outcome events among patients treated with canagliflozin compared with placebo. The composite endpoints occurred in 26.9 vs 31.5 participants, respectively, per 1000 patient years (HR 0.86 [95% CI 0.75-0.97]).

Renal outcomes also favored canagliflozin vs placebo with a progression of albuminuria in 89.4 vs 128.7 participants, respectively, per 1000 patient years (HR 0.73 [95% CI 0.67-0.79]) and a greater regression of albuminuria at 293.4 vs 187.5 participants, respectively, per 1000 patient years (HR 1.7 [95% CI 1.51-1.91]). The composite renal outcome also had a significant reduction among canagliflozin patients of 5.5 vs 9, respectively, per 1000 patient years (HR 0.6 [95% CI 0.47-0.77]).

Of note, canagliflozin patients showed an increased rate of amputations at 6.3 vs 3.4 amputations per 1000 patient years (HR 1.97 [95% CI 1.41-2.75]). 71% of amputations were at toe or metatarsal and the highest risk of amputation was among patients with a history of amputation or peripheral vascular disease (PVD). Fracture rate was also higher with canagliflozin, occurring at a rate of 15.4 vs 11.9 fractures per 1000 patient years (HR 1.26 [95% CI 1.04-1.52]).

Among patients taking canagliflozin, the study showed significant changes in intermediate cardiovascular markers including an A1c reduction of 0.58% [95% CI -0.56 to -0.61%], a reduction in body weight by 1.6 kg [95% CI -1.7 to -1.51 kg], reduced systolic blood pressure by 3.93 mmHg [95% CI -4.3 to -3.56], diastolic blood pressure reduction of 1.39 mmHg [95% CI 1.61 to -1.17], and an increase of both HDL by 2.05 mg/dL [95% CI 1.77-2.33] and LDL by 4.68 mg/dL [95% CI 3.64-5.73].

Conclusions: Canagliflozin reduced the frequency of the primary endpoint of composite death from CV causes, non-fatal MI, and non-fatal stroke. It also slowed the progression of albuminuria compared with placebo. However, it showed an increased risk of amputation in patients with a history of amputations or PVD.

Key Point: The CANVAS Program studies support that CV benefits are a class effect for SGLT2 inhibitors. However, the increased risk of amputation may lead clinicians to steer towards other SGLT2s.

Efficacy of Tramadol ER for Opioid Withdrawal[2]

Brittany Bailey, Pharm.D.
Avera Marshall Regional Medical Center

Background: Current first-line treatment of opioid use disorder (OUD) is medically supervised withdrawal. Medications used to manage withdrawal symptoms include clonidine and buprenorphine. Buprenorphine, has shown in past studies to be more effective than clonidine at suppressing withdrawal symptoms; however it also has the potential for abuse. Tramadol ER is an opioid agonist dosed once-daily, with less abuse potential.

Objective: Evaluate the efficacy of tramadol ER as an option to treat opioid withdrawal symptoms during supervised opioid withdrawal.

Study Design: This trial was a randomized 1:1:1, double-blind, double-dummy, placebo-controlled opioid withdrawal procedure. Patients recruited met DSM-IV criteria for opioid dependence and had a urine sample positive for opiates. Exclusion criteria included pregnancy, hypotension, physical dependence on alcohol and/or benzodiazepines requiring treatment, history of seizures, allergies to study medications, or current enrollment in opioid agonist treatment. Subjects were followed through three study phases. In phase one (stabilization phase), all subjects were given morphine 30 mg subcutaneous four times daily for seven to ten days followed by a naloxone challenge to determine level of physical dependence. Level of physical dependence was scored using the Clinical Opiate Withdrawal Scale (COWS) scores, completed by professional staff, and the Subjective Opiate Withdrawal Scale (SOWS) completed by participants. Subjects were stratified by sex, race, CYP2D6 (extensive, intermediate, and ultra-extensive poor metabolizer genotypes) and peak COWS score. In phase two (taper phase), stratified patients were randomized to receive starting doses of clonidine 0.4 mg/day, tramadol ER 300 mg/day, or buprenorphine/naloxone 4/1 mg/day. After day two of the taper phase, doses of each medication were reduced until day seven. Phase three was the post-taper period, occurring from day eight through day fourteen, during which all subjects received placebo. At least one dose of study drug was received by 103 subjects which was not enough to meet 80% power. Chi-square test was used for dichotomous variables and one-way ANOVA was used for continuous data results between the three groups. The primary endpoint was a comparison of opioid withdrawal symptoms (COWS and SOWS scores) during taper versus post-taper, using the modified intention to treat population (at least one dose of study drug). The secondary endpoint of retention was measured as enrollment on the final day of taper. Adverse effects and withdrawal symptoms were not differentiated.

Results: No statistically significant differences between treatment groups was found. Of the total participants, 85.4% were men and 41.7% were white. Regarding the primary outcome, initial mean peak COWS score was 8-9 on day one of taper for all three treatment arms. The time-course analyses of taper and post-taper showed significant reduction in COWS mean peak rating per day with taper mean of 5.19 and post-taper mean of 3.97 (F_{2170}=3.6; P=0.03). The area under the curve (AUC) of the COWS total scores, showed statistically significant reductions ($F_{2,159}$ = 14.6, p<0.001) in mean score from taper to post-taper periods for clonidine (taper: 6; post-

taper: 3.4) and tramadol ER (taper: 4.6; post-taper: 3.2), but not buprenorphine (taper: 4.6; post-taper: 5.6). The AUC of the mean Subjective Opiate Withdrawal Scale (SOWS) total scores also resulted in significant reductions ($F_{2,159}$ = 17.7, p<0.001) in withdrawal severity between taper and post-taper periods for clonidine (taper: 13.1; post-taper: 3.2; p<0.001) and tramadol ER (taper: 7.4; post-taper: 2.8; P=0.03), but not buprenorphine (taper: 6.4; post-taper: 7.4). Regarding the secondary endpoint of retention to the last taper day, tramadol ER (26 [72.2%]) showed no statistical difference compared to buprenorphine (28 [90.3%]) or clonidine (22 [66.1%]) (X_2=8.5, P=0.1]). Most common adverse effects, seen in all treatment arms, included abdominal pain, agitation, anxiety, chills, headache, insomnia, muscle aches, restlessness, rhinorrhea, and tremor. The percent range of patient experiencing an adverse effect was approximately 0-50% for each treatment arm.

Conclusions: Results of this trial show potential of tramadol ER as an effective treatment option for opioid withdrawal symptoms with statistically significant reduction in COWS and SOWS scores. While buprenorphine showed lower taper COWS and SOWS scores, both tramadol ER and clonidine had lower post-taper scores compared to buprenorphine. Tramadol ER shows similar risk of adverse effects compared with clonidine and buprenorphine. Future research should be completed to include a larger sample size to meet 80% power and a study design focused on inferiority or superiority of tramadol ER compared to buprenorphine and clonidine for treatment of withdrawal symptoms.

Key Point: In treatment of OUD with medically supervised withdrawal, tramadol ER may be an effective option to reduce withdrawal symptoms when comparing taper and post-taper opiate withdrawal scale scores.

Insulin Degludec vs Insulin Glargine U100: Hypoglycemic Outcomes in At-Risk Type 2 Diabetics[3]

Kirstin Gramith, Pharm.D.
Essentia Health

Background: Glycemic control is necessary to reduce complications in type 2 diabetic patients. Despite insulin being the most effective blood glucose lowering therapy, patients are often reluctant to start insulin therapy. Concern of hypoglycemia can negatively influence patient perception of insulin therapy and hypoglycemia itself can limit achieving adequate glycemic control. Previous trials conducted for the approval of insulin degludec (IDeg) showed lower rates of overall and nocturnal hypoglycemia compared with insulin glargine U100 (IGlar). The SWITCH 2 Randomized Clinical Trial was designed to further accept or reject these findings.
Objective: To determine if IDeg is associated with less hypoglycemia compared with IGlar in adults with type 2 diabetes mellitus (T2DM) and at least one risk factor for hypoglycemia.

Study Design: This was a randomized, double-blind, multicenter, treat-to-target crossover study. There were two 32 week treatment periods, which consisted of a 16 week titration period and a 16 week maintenance period. Participants were randomly assigned in an 1:1 ratio to receive IDeg followed by crossover to IGlar (IDeg-first arm) or vice versa (IGlar-first arm). Insulin was titrated in multiples of two units once weekly to a fasting blood glucose target of 71 to 90 mg/dL.
Patients were eligible for this study if the following criteria were met: age ≥ 18 years, diagnosed with T2DM, hemoglobin A1c (HbA1c) ≤ 9.5%, treatment with any basal insulin with or without oral antidiabetic medications and presence of at least one risk factor for developing hypoglycemia. Patients were ineligible for this trial if treated with bolus or premixed insulin or a sulfonylurea prior to trial start.

Rate of overall symptomatic hypoglycemic episodes (either severe and requiring third party assistance or blood glucose confirmed [< 56 mg/dL], with symptoms of hypoglycemia) during the maintenance period was the primary endpoint. Rates of nocturnal symptomatic hypoglycemic episodes occurring between 12:01 AM and 5:59 AM and percentage of patients who experienced severe hypoglycemic episodes in the maintenance period were secondary endpoints. Change in HbA1c after each treatment period was an efficacy endpoint.

Endpoints were assessed using an intent-to-treat analysis. Assessment of hypoglycemic endpoints only used data from those who received at least one dose of the trial insulins. Hypoglycemic endpoints were superior if the upper bound of the two-sided 95% confidence interval (CI) of the estimated rate ratio (ERR) was less than one. Hemoglobin A1c was considered noninferior if the upper bound of the one-sided 95% CI was no more than 0.4%.

Results: A total of 721 patients were randomized to treatment sequence (361 to the IDeg-first arm, 360 to the IGlar-first arm). Mean age was 61.4 ± 10.5 years, mean duration of diabetes was 14.1 ± 8.1 years, mean HbA1c was 7.6 ± 1.1%, 53.1% of participants were men, and 79.1% were receiving at least one or more oral antidiabetic medications. Seventy-eight percent of participants in the IDeg-first arm and 83% in the IGlar-first arm completed both treatment periods. Reason for dropouts were similar between arms.

There was a statistically significantly lower rate of overall symptomatic hypoglycemia with IDeg compared with IGlar (185.6 vs 265.4 episodes per 100 patient-year of exposure (PYE); ERR 0.70 [95% CI 0.61 - 0.80], p<0.001) during the maintenance phase, which also proved true for the rate of nocturnal symptomatic hypoglycemia with IDeg compared with IGlar (55.2 vs 93.6 episodes per 100 PYE; ERR 0.58 [95% CI 0.46 - 0.74], p<0.001). The proportion of patients who experienced a severe hypoglycemic episode during the maintenance period differed by 0.8% between IDeg and IGlar (1.6% vs 2.5%, ERR 0.54 [95% CI 0.21 - 1.42], P=0.35).

At the end of treatment period one, mean HbA1c was 7.06 ± 1.07% with IDeg and 6.9 ± 1.03% with IGlar (estimated treatment difference [ETD] 0.9% [95% CI - 0.04 - 0.23%], p<0.001). Mean HbA1c was 7.08 ± 1.23% with IDeg vs 7.11 ± 1.15% with IGlar (ETD 0.06% [95% CI -0.04 - 0.23%], p<0.001) at the end of treatment period two.

Conclusions: Results from SWITCH 2 show a 30% reduction in the rate of overall symptomatic hypoglycemia and a 42% reduction in the rate of nocturnal symptomatic hypoglycemia when comparing basal IDeg with IGlar. Mean HbA1c of IDeg remained noninferior to mean HbA1c of IGlar throughout both treatment periods. There was no significant difference in proportion of patients who experienced at least one severe hypoglycemic episode during the maintenance period.

Key Point: Basal IDeg was associated with less episodes of overall and nocturnal hypoglycemia and noninferior HbA1c control compared with IGlar.

Association Between Antipsychotic Agents and Risk of Acute Respiratory Failure in Patients with Chronic Obstructive Pulmonary Disease[4]

Anjoli Punjabi, Pharm.D., MPH
Broadway Family Medicine

Background: Chronic obstructive pulmonary disease (COPD) affects 210 million people and is the leading cause of mortality globally. COPD patients are particularly prone to acute respiratory failure (ARF) after COPD exacerbation. After an episode of ARF, as many as 80% of COPD patients are rehospitalized requiring mechanical ventilation. There have been multiple case studies of ARF occurring in COPD patients within 10 days of initiating a typical or atypical antipsychotic. However, population-based evidence for the association between antipsychotic use and ARF in COPD patients is lacking.

Objective: To determine if antipsychotic use is associated with an increased risk of ARF in those patients with COPD.

Study Design: The Taiwan National Health Insurance Research Database was utilized to conduct a population-based case-crossover study analyzing all patients with COPD (n=61620), who were newly diagnosed with ARF in hospital or emergency care settings, requiring intubation or mechanical ventilation over a 10-year period. Patients with prior ARF, lung cancer, and cardiogenic, traumatic, or septic ARF were excluded.

The use of antipsychotics during days 1 to 14 (case period) and days 75 to 88 (control period) preceding the ARF event were compared. This within-self comparison design was utilized to minimize interpersonal variation and control time invariant covariates. The 14-day period and 60-day buffer period were selected based on the short timeframe for ARF events following antipsychotic use in the case reports and the and half-lives of depot antipsychotics, respectively. The antipsychotic class, route of administration, and dose were also considered.

Results: It was found that there was a 1.66-fold (95% CI, 1.34-2.05; p<0.001] increased risk of ARF in COPD patients taking antipsychotic medications regardless of antipsychotic class and administration route. Additionally, a dose-dependent risk of ARF associated with antipsychotics was identified, adjusted odds ratio of 1.35 [95% CI 1.19-1.52; p<0.001], which increased from a 1.52-fold risk for a low daily dose [95% CI 1.20-1.92; p<0.001) to a 3.74-fold risk for a high dose [95% CI, 1.68-8.36; P=0.001].

Conclusions: Antipsychotic medication use is associated with an acute and dose-dependent increased risk of ARF in patients with COPD. Future studies are required to confirm these observed associations.

Key Point: Clinicians should be cautious when prescribing antipsychotics to patients with COPD and avoid high doses if possible.

Subclinical Hypothyroidism: The When and Why of Starting Treatment[5-9]

Kristin Howlett, Pharm.D.
Park Nicollet Health Services

Background: Subclinical hypothyroidism is defined as an elevated thyroid stimulating hormone (TSH) with free thyroxine (T4) in the normal range, whereas overt hypothyroidism is defined as higher than normal TSH with lower than normal free T4. It has been estimated that 3-15% of the population has subclinical hypothyroidism by this definition. Higher rates of subclinical hypothyroidism are seen in females, elderly, and those with low iodine intake.

Current American Association of Clinical Endocrinologists/American Thyroid Association (AACE/ATA) guidelines recommend initiating treatment in patients ≤ 70 years old with subclinical hypothyroidism if TSH > 10 mU/L. For patients with subclinical hypothyroidism with TSH < 10 mU/L or those who are over 70 years old, guidelines suggest treatment decisions should be based on the individual factors of symptoms, cardiac risk factors and autoimmune involvement. Patients who are pregnant have alternative guidelines and are not included in this discussion.

Evidence: Studies have shown increased rates of depression, fatigue, weight gain, cold intolerance, constipation and reduced cognitive function, memory and quality of life in those with subclinical hypothyroidism as compared to age-matched controls. Interestingly, elderly patients (over 70 years of age), have reported fewer symptoms than younger patients which may be why they are often not treated for subclinical hypothyroidism based on lab results.

There have been few randomized controlled trials evaluating long-term treatment of subclinical hypothyroidism; however, the studies that exist point to increased symptoms and cardiovascular events in those with untreated subclinical hypothyroidism if the TSH >10 mU/L. In comparison, studies of elderly patients and those with only mildly elevated TSH have shown little benefit of treatment.

In regards to cardiovascular risk, a large meta-analysis of 11 prospective cohorts with over 55,000 subjects found patients with TSH levels of 10.0-19.9 mU/L had increased risk of fatal and nonfatal coronary heart disease events than patients within a normal TSH range, HR 1.89 [95% CI 1.28 - 2.80]. In contrast, no statistical difference was found among participants with TSH ranging from 7.0-9.9 mU/L or 4.5-6.9 mU/L. Other previous meta-analyses have associated increased risk of cardiovascular risk in those with TSH > 7.0 mU/L; however, benefit of treatment in this group is less clear and generally not recommended.

Discussion: Observational studies have shown lower risk of heart failure events, death from any cause and ischemic heart disease events among patients 70 years of age or younger with subclinical hypothyroidism and TSH > 10 mu/L when treated with levothyroxine. Since there is some evidence for increased cardiovascular risk at TSH > 7.0 mU/L, treatment may be considered if symptoms are present, although evidence is not as strong. There appears to be little benefit to treating those over 70 years old or those with mild elevations in TSH and normal free T4.

Clinical Impact:

<u>Initial considerations when subclinical hypothyroidism is suspected:</u>

- It is recommended to repeat TSH and T4 two to three months later to rule out a transient TSH increase prior to diagnosis. TSH levels may normalize within two years in up to 46% of patients with subclinical hypothyroidism and TSH < 7 mU/L.
- A one-time lab value of thyroid peroxidase antibodies can be used to determine the presence of an autoimmune cause which correlates to twice the risk of progression to overt hypothyroidism.
- Consider other factors that may increase TSH such as an acute illness or medications like amiodarone or lithium.

<u>Treatment considerations after diagnosis of subclinical hypothyroidism (with repeated TSH/T4 levels):</u>

	TSH < 10 mU/L	TSH > 10 mU/L
Age ≤ 70 yr	Recheck TSH in 6 months or consider a 6 month trial treatment if symptoms are present	Treatment recommended
Age > 70 yr	Treatment not recommended	Treatment generally not recommended, could consider 6 month trial if symptoms are present

The goal of therapy for patients receiving treatment for subclinical hypothyroidism is to achieve TSH within normal limits to lower cardiovascular risk factors and improve patient symptoms. Use caution to prevent over-suppressing TSH which can result in increased risk of atrial fibrillation, osteoporosis and fractures.

Proton Pump Inhibitors: Know When Short or Long Term Use is Appropriate[10-14]

Brittany Thelemann, Pharm.D.
New Ulm Medical Center

Background: Proton Pump Inhibitors (PPIs) are a common class of medications used to treat gastrointestinal (GI) conditions associated with acid overproduction. In recent months, there has been a focus on inappropriate uses and durations of PPIs. In one US study, only 39% of inpatients' prescriptions were compliant to guidelines. Not only are PPIs being overused, but they also carry risks for potential adverse effects. Clinical guidelines suggest PPIs may be associated with chronic kidney disease, fractures, *C. diff*, pneumonia, micronutrient deficiencies and dementia. These risks may result from not only long term use of PPIs, but short term use as well.

Evidence: Expert guidance is now available for duration of PPI therapy. Based on the results of Khan et al, guidelines recommend a treatment duration of eight weeks with standard (once daily) dose PPIs for gastroesophageal reflux disease (GERD). The study found that 80% of patients experienced healing of reflux esophagitis and symptom relief during the eight week duration. Appropriate lifestyle modifications for patients experiencing GERD symptoms is also an important consideration during therapy. Other appropriate indications requiring short term treatment include duodenal ulcers, gastric ulcers, and *H. pylori.* Lastly, patients in the ICU with risk factors should be given a PPI during their hospital stay for stress ulcer prophylaxis but discontinued upon discharge. Three large meta-analyses found that the risk of bleeding in the ICU is reduced by about 60% in patients receiving stress ulcer prophylaxis compared with those treated with placebo or no prophylaxis.

While short-term therapy is preferred, there are a few instances that require longer treatment durations. Long-term PPI therapy is appropriate for prevention of NSAID-induced ulcers in high-risk patients. The available evidence is strong, with consistent ulcer reductions of 50% in large RCTs, meta-analyses of RCTs and large observational studies in clinical practice. Patients on chronic anticoagulation at increased risk of a GI bleed (age > 65, concomitant use of corticosteroids and/or previous history of GI bleed) may also benefit from long term PPI therapy. While gastroprotection is generally not advised unless a concomitant antiplatelet or NSAID therapy is prescribed, a very recent retrospective cohort study by Ray et al found that PPI co-therapy is associated with reduced risk of warfarin-related upper GI bleeding. Other indications requiring long-term therapy include Barrett's esophagus, Zollinger-Ellison Syndrome, eosinophilic esophagitis and complicated/refractory GERD.

Discussion: PPIs hold strong evidence for efficacy which has led to their unfortunate overuse. It is important that providers balance risks and benefits of long-term PPIs. Despite the long list of potential adverse effects associated with PPI therapy, the quality of evidence for most of those risks has been consistently low because of studies' conflicting results. While PPIs are effective, there are other therapies available to manage GI conditions. Inadomi et al found that 33% of patients with uncomplicated GERD on PPI therapy were able to successfully transition to an H2 antagonist while another 16% were transitioned off acid suppression completely. In patients who fail or cannot be transitioned, providers should periodically re-evaluate patients on long-term PPIs to ensure patients are on the lowest dose sufficient to manage symptoms.

Clinical Impact: When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks. However, combating inappropriate long term use of PPIs is crucial. For example, PPIs used in the hospital to prevent stress ulcers should be stopped upon discharge. Additionally, H2 antagonists or antacids may be suggested to manage acid reflux symptoms instead of jumping to a PPI. If long-term treatment is necessary, consider benefits of continuous, intermittent or on-demand therapy. Lastly, if the decision is made to stop PPI therapy, suggest a taper over a few weeks to prevent acid rebound. First, reduce the dose (if not at the minimum dose per day). Then, extend the dosing interval to every other day and possibly every third day.

Is Chondroitin Sulfate a Safe and Effective Option for Patients with Osteoarthritis?[15-18]

Jacob Lenzmeier, Pharm.D.
CentraCare Health-Saint Cloud

Background: Osteoarthritis (OA) is the most common musculoskeletal disease affecting humans and a major cause of pain, loss of function, and disability among patients. Acetaminophen, a first line-agent for treating OA is often well-tolerated but has limited effectiveness in patients with more advanced disease. Other traditional therapy options such as non-steroidal anti-inflammatory drugs (NSAIDs) introduce several safety concerns, drug-drug interactions and comorbidity complications. With these limitations, patients may turn to alternative therapies such as glucosamine and chondroitin making it important for pharmacists to be familiar with these options allowing them to advise patients appropriately

about their use. The most recent clinical practice guidelines from the American College of Rheumatology in 2012 recommend against the use of chondroitin sulfate supplements due to a lack of complete evidence. Newer studies have been published suggesting chondroitin sulfate be re-examined for its use in OA.

Evidence: A randomized, double-blind, placebo-control trial of 604 patients demonstrated that pharmaceutical grade chondroitin sulfate 800 mg/day was as effective in reducing pain and improving function as celecoxib 200 mg/day and was superior to placebo in symptomatic knee OA given over a 6-month period. The visual analog scale (VAS) was used to measure pain and Lequesne's index (LI) was used as a composite assessment of pain and function. Compared to placebo, both treatments were superior as measured by the LI but celecoxib showed a significant difference at day 30 while chondroitin sulfate did not have this effect until day 91. Significant differences in the VAS were demonstrated in both treatment groups but not until day 182 for either. Minimal clinically important improvement was analyzed as a secondary outcome and did not reach statistical significance in either group as compared to placebo. No significant adverse effects were observed in any group, though abdominal discomfort occurred more frequently in celecoxib than the others.

A Cochrane review of chondroitin sulfate analyzed 4,962 patients with osteoarthritis treated with chondroitin sulfate taken alone or with glucosamine sulfate compared to 4,148 patients treated with placebo or an active control across 43 randomized controlled trials. Only 4 trials examined chondroitin sulfate dosing of less than 800 mg/day. Trial durations varied from 1 month to 3 years and participants in the treatment groups achieved statistically significant and clinically meaningful improvements in their pain scores in studies less than 6 months with an absolute risk difference of 10% (95% CI, 15% - 6%) lower than the placebo group. Trials looking at doses of < 800 mg/day failed to demonstrate statistical significance though the number of patients analyzed was very low. Other outcomes such as physical function, stiffness, and grip strength did not achieve significant differences. Studies had a high level of heterogeneity, high level of bias, and overall level of evidence was low.

Discussion: Despite new studies making exciting claims about the use of chondroitin sulfate, the evidence continues to be ambiguous. Though statistical significance was demonstrated in the study comparing chondroitin to celecoxib, the chondroitin did fail to reach the threshold for clinical significance set by the study design. A significant difference is seen in the Cochrane review in pain scores for shorter durations (6 months or less) of treatment. The studies overall had a high level of variability and bias introducing greater potential for confounding factors such as concurrent glucosamine and breakthrough medication use. Additionally, this review only found significant results in pain scores but other factors such as physical function showed no difference leaving clinical implications inconclusive. No significant adverse effects or safety concerns were noted among any of the reviewed evidence.

Clinical Impact: The use of chondroitin sulfate is not recommended based on current clinical practice guidelines. However, if a patient is inquiring about the use of these supplements due to contraindications or lack of success with recommended pharmacologic therapies the risks of doing so are low. Patients should be educated about realistic expectations regarding the use of these products and understand that it may take months to see a benefit. The effects in using it beyond 6 months are not yet fully understood.

From the Pharmacy Press

Nonadherence to Osteoporosis Medication Initiation[19-23]

Kristen Ross, Pharm.D.
Fairview Pharmacy Services

Background: Osteoporosis is characterized by low bone mineral density leading to increased fracture risk. Approximately one out of every two people in the United States older than 50 years old is at risk for an osteoporotic fracture. The National Osteoporosis Foundation recommends pharmacotherapy, primarily bisphosphonates, to slow disease progression in at-risk patients. Despite evidence that osteoporosis medications significantly reduce fracture risk and subsequent morbidity and mortality, medication adherence has been suboptimal. Previous research has estimated that one-third to half of all patients do not take their osteoporosis medications as directed in a persistent and compliant manner. Identifying the characteristics of patients likely to be nonadherent and their reasons for being nonadherent may help healthcare providers appropriately educate patients in order to maximize adherence. Although previous research has investigated adherence to osteoporosis medications in terms of persistence and compliance, little is known about adherence in terms of initiation.

Objective: The purpose of this study was to identify reasons patients stated for not starting osteoporosis

treatment prescribed by their healthcare provider and patient characteristics that might predict nonadherence.

Study Design: Data originated from the Patient Activation after DXA Result Notification (PAADRN) study which was a double-blinded, randomized controlled trial investigating the effects of a patient-activation intervention on osteoporosis measures. The population consisted of patients aged 50 years or older presenting for DXA at three academic health centers in the United States between February 2012 and August 2014. The investigators focused on a subset of patients whose providers prescribed pharmacotherapy for osteoporosis or osteopenia based on their DXA results. Patients completed three interviews at baseline, 12 weeks, and 52 weeks after DXA. Several characteristics were measured including: demographics, health habits, osteoporosis knowledge using the "Osteoporosis and You" scale, DXA results, and FRAX risk. In addition, adherence to initiation of the medication was assessed by asking patients if their provider prescribed a new or different medication and whether the patient had started it. Those who stated that they did not start the medication were asked why as an open-ended question and interviewers categorized these patient reports. Adherers were compared with nonadherers and temporary nonadherers using Pearson chi-squared tests for categorical variables, F tests for continuous variables, and multivariable multinominal logistic regression. Nonadherers were defined as patients who decided not to take the prescribed medication at all. Temporary nonadherers included patients waiting until another procedure was performed, waiting to schedule an infusion appointment, or waiting to see whether the treatment would be covered by their insurance.

Results: Of the 7749 patients in the PAADRN study, 790 reported 12 weeks after DXA that their health care provider had prescribed a new or different osteoporosis medication. The demographics for this group were a mean age of 66.8 years, 87.2% female, and 84.2% Caucasian. Concerning adherence rates, 24.8% of patients reported that they did not start their prescribed medication. Of that percentage, 5.8% indicated only temporary nonadherence and 19% indicated that they decided not to take the prescribed medication at all. The only patient characteristic significantly associated with nonadherence was osteoporosis knowledge, with those having better knowledge being less likely to take their medications ($p<0.05$). The most common patient-reported reasons for nonadherence were fear of adverse effects (53.3%), a dislike of taking medicine (25.3%), and the belief that the medication would not help their condition (16.7%).

Conclusions: One in four patients who were prescribed osteoporosis pharmacotherapy declined treatment because they feared potential adverse effects, did not like taking medicine, or believed that the medication would not help their condition. These findings suggest that improved patient counseling on the potential adverse effects of osteoporosis treatment and the risk-benefit ratio may increase adherence rates.

Outpatient Antibiotic Stewardship: Intervention and Opportunities[24]

Lauren Turner, Pharm.D.
Fairview Pharmacy Services

Background: Antibiotic overuse and misuse has become a concern across health care. The federal government has mandated this issue a national priority. This has lead to the expansion of antibiotic stewardship programs (ASPs) across the continuum of care, including outpatient practice settings. However, best practices for outpatient ASPs are yet to be defined due to unique factors that drive inappropriate antibiotic use in this clinical setting.

Objective: To combat these challenges, evidence-based antibiotic stewardship (AS) interventions and opportunities have been identified to enhance AS in the outpatient setting.

Interventions: Several strategies that have demonstrated success in enhancing AS include: [1] auditing and feedback, [2] education, [3] clinical decision support (CDS) tools, [4] delayed prescribing, [5] guideline implementation, and [6] point-of-care (POC) testing. Each intervention is summarized to highlight opportunities for outpatient ASPs.

[1] *Auditing and Feedback*: Provider audit and feedback methods are important to motivate change in prescriber patterns. In order to provide feedback on antibiotic prescribing patterns, clinical practices could consider adding antibiotic use metrics to other clinical metrics. Evidence has shown that sustained quarterly provider feedback and education has vastly reduced broad-spectrum antibiotic prescribing.

[2] *Education*: A comprehensive education plan directed towards health care professionals and patients is imperative to the AS initiative, and to drive change within practice. Communication training for prescribers, as well as shared decision making between the patient and prescriber, have been found to demonstrate success in antibiotic use reduction. Additional patient education should focus on promoting wellness, vaccinations, and

community pharmacy-based disease management to minimize unnecessary office visits and reduce antibiotic misuse.

[3] *CDS Tools*: CDS tools, created from electronic health records, offer assistance with AS during antibiotic prescribing. Through electronic alerts, antibiotic order sets, and cascading questions, antibiotic drug therapy selection is guided more appropriately. CDS tools can also require prescriber justification when prescribing a non-recommended antibiotic. This will ensure guideline-driven antibiotic use.

[4] *Delayed Prescribing*: Also referred to as watchful waiting, delayed prescribing is an effective strategy to reduce antibiotic use. This can be completed by requesting the patient delay filling the antibiotic prescription for 24-48 hours, postdating the prescription, or contacting the patient after the encounter to re-evaluate the patient's clinical status and appropriateness of treating with an antibiotic.
[5] *Guideline Implementation*: Health care system-specific antibiotic use guidelines should be implemented for common outpatient infectious diseases. This will minimize unnecessary or inappropriate antibiotic use and combat antibiotic-resistant bacteria. These guidelines should take into account local resistance patterns, prescribing trends, and cost. Evidence has shown that prescribing guidelines are associated with improved antibiotic outcomes in the outpatient setting.
[6] *POC Testing*: An ideal opportunity to enhance AS and to influence appropriate antibiotic use is through POC testing. POC testing has been identified as one of the leading innovations to promote AS in the outpatient setting by identifying patients with a disease of interest, providing timely treatment with the recommended antimicrobial agents, and delivering supportive care when antibiotics are not warranted.

Conclusions: Antibiotic resistance is a tremendous public health issue and improving antibiotic use is a national priority. To address these concerns, driving ASPs across the continuum of care will lead to continual progression towards appropriate antibiotic use to counteract antibiotic resistance. Outpatient AS initiatives should be strategized, developed, and piloted to further enhance the ASP care model.

Accountable Care Organizations Don't Always Boost Medication Adherence[25]

Stephanie Swanson, Pharm.D.
North Memorial Health Northeast Clinic

Background: Accountable care organizations (ACOs) in the Medicare Shared Savings Program (MSSP) under the Affordable Care Act (ACA) are evaluated on performance through a variety of quality measures. Through 2014, almost half of these measures focused on cardiovascular disease and diabetes, specifically on disease control and medication use. Medication adherence has been identified as a tool to improve these measures as prescription drug spending is not included in the MSSP financial calculation.

Objective: To evaluate if the MSSP has been associated with changes in medication use or adherence for patients with cardiovascular disease or diabetes within ACOs.

Study Design: Data from Medicare claims and enrollment files from 2009 to 2014 were analyzed for a 20% sample of fee-for-service beneficiaries. A total of six drug classes (statins, angiotensin-converting enzymes and angiotensin II receptor blockers, beta blockers, thiazide diuretics, calcium channel blockers, and metformin) were evaluated for proportion of days covered (PDC) by filled prescriptions for any beneficiary that had at least one prescription filled of the identified drug classes during the time frame. The denominator for the PDC was 365 days or the number of days remaining in the year after the first prescription fill. The numerator was the total days of drugs in the class supplied in the year. A difference-in-difference approach and linear regression was used to compare the changes in medication use and adherence between ACO beneficiaries and those with local non-ACO providers. Differential changes were estimated separately for cohorts of ACOs entering the MSSP in 2012, 2013, and 2014.

Results: Overall, differential changes in medication use and adherence between the groups in all six drug classes were minimal and not statistically significant. There was a slight increase in thiazides among beneficiaries with hypertension in the 2013 entry cohort (adjusted differential change, 0.5 percentage point [95% CI 0.1-0.8 percentage points). There were also no significant differential changes in PDC, except for a slight increase in the PDC for beta blockers in the 2012 entry cohort (adjusted differential change, 0.3 percentage point; [95% CI 0.1-0.5 percentage points]) and metformin in the 2012 and 2013 cohorts (adjusted

differential change, 0.5 percentage point; [95% CI 0.1-0.9 percentage points] for both groups).

Conclusions: The investigators concluded that at this time, exposure to the MSSP has not been associated with meaningful changes in medication use or adherence among patients with cardiovascular disease and diabetes. Further studies need to be conducted to identify which components are most contributing to the benefit of ACOs and furthermore, understand the steps to success of these programs.

Innovative Models for Providing Clinical Pharmacy Services to Remote Locations Using Clinical Video Telehealth[26-27]

Briana Gray, Pharm.D.
St. Cloud VA Medical Center

Background: Almost half of U.S. veterans live in rural or highly rural areas and face significant travel time and costs to receive primary care services. These patients often have difficulties attending frequent appointments and building relationships with their providers, especially if they have complicated disease states. Veterans Affairs (VA) Medical Centers have implemented several forms of telehealth, as shown in Table 1, for veterans to reach Clinical Pharmacy Specialists (CPSs) more efficiently for primary care services.

Table 1: Telehealth Modalities Used in the VA Healthcare System

Modality	Description
Clinical video telehealth	Allows patients to come to a local VA outpatient clinic and see a clinical pharmacy specialist or other primary care team member in real time; the clinician may be located at a clinic or hospital hundreds or thousands of miles away
Home telehealth	Allows patients to connect to a clinic or hospital from their home using telephone lines, cellular modems, and cell phones for monitoring of symptoms and measurement of vital signs (with the help of a care coordinator)
Care coordination store-and-forward telehealth	Involves the acquisition and storage of clinical information (e.g., data, images, sound or video recordings) that can be forwarded to (or retrieved by) another site for clinical evaluation

[a]VA = Veterans Affairs.

Methods: Two team-based models were implemented through a telehealth hub based at the Boise VA Medical Center in Idaho with a focus to reach the largest rural areas in the Northwest United States. In the first model, the patient and nursing staff are located at one site and the remainder of the team is at a location other than the patient site. The clinical team members may be located at the same site or may also have a virtual relationship across different sites. In the second model, the patient and the majority of the care team are located at one site while the CPS is at a separate site. The latter situation is best to serve patients without a CPS at their site or clinic while the former serves as a virtual primary care team.

Results: Since 2014, the Boise VA Medical Center pioneered clinical pharmacy telehealth services in diabetes, hypertension, hyperlipidemia, tobacco cessation, and other chronic disease states. The program started with one half-time CPS and grew to six full-time CPSs each serving a panel of up to approximately 3,600 patients. They collaborated with 16 rural VA clinics across Alaska, Washington, Oregon, Idaho, and Montana, saw more than 1,200 unique patients, and achieved an overall patient satisfaction score of 96%. The CPSs completed consults limited to chart review in an average of less than one day and, if patients required a video conference visit, they were seen in an average of 6.4 days.

Discussion: Benefits to serving patients via telehealth include decreased overall costs for the patient, “face-to-face” video visits that allow assessment of patient appearance and body language, and the means to count the visit similarly to an in-person visit. Barriers include patient preference for in-person visits, the convenience of telephone visits (no hardware needed and fewer logistics), patient's’’ ability to adapt to the technology, and increased documentation (a telehealth consult must be placed for a patient to receive services).

Overall, health systems can utilize telehealth to decrease healthcare costs and expand services for patients in rural areas. Each form of telehealth provides quality care tailored to the patient’s situation in a timely manner and the patients adapted well to the new routes of service. Further studies are needed to show if improved accessibility also leads to improved clinical outcomes as expected.

Miscellaneous News

The Dawn of Automated Insulin Therapy[28-29]

Hannah Schmidt, Pharm.D.
FirstLight Health System

For years, developing an "artificial pancreas" to improve the quality and convenience of diabetes was a pipe dream. The hope was to create a device which would self-monitor blood glucose and adjust insulin based on readings, activity and carbohydrate intake. After tireless research, the dream of an automated insulin delivery system became a reality. The first ever automated Hybrid Closed Loop System, the Medtronic MiniMed 670G, was approved for ages 14 and older.

The MiniMed 670G straddles the line between insulin pump and automatic delivery system. While a full closed loop system would be purely automated, this system allows the user to switch between pump and automated mode. In pump mode, the user and clinician can adjust rates and boluses. In automatic mode, the user only inputs insulin to carbohydrate ratios and insulin action time. All other features, such as target glucose and basal rates, are controlled by system parameters. While the user can switch between modes, time in the automated mode should be optimized to improve control and outcomes.

Recent studies of the MiniMed 670G resulted in significant reductions across the board in A1C, and hyper- and hypo-glycemia, . It also increased time in target blood glucose range. At the end of the three month study phase the percentage of adolescents and adults with an A1C < 7% increased by 26.6% and 20.8%, respectively. Safety was assessed in these studies as well and resulted in no cases of severe hypoglycemia or DKA. Experts believe the advantages of this system, and future systems, will eventually replace the concept of basal and bolus insulin therapy by merging basal, correction and meal dosing together through automation.

To allow the device to accurately manage dose adjustments, a new and purportedly more accurate continuous glucose monitor was created. However, the system can operate with current continuous glucose monitors on the market. The MiniMed 670G is generally affordable as it is covered by most insurances for new users or for users with a device five years or older. With the system now available to order and it's glucose monitor set to release this fall, the importance of education on these devices is brought forth.

Understandably, the concepts of this new system create quite a learning curve for clinicians and users alike. To help clinicians better conceptualize these products, the CARE acronym can be used to decipher important characteristics. First is "CALCULATE", to determine which dosing parameters are calculated or fixed by the system versus which are modifiable by the user. Second is "ADJUST", how do users adjust the system based on hyper- and hypo- glycemia? Third is "REVERT", to make sure users optimize time spent in automatic mode, and know when to revert to the pump mode, such as during illness. Last is "EDUCATION", to make sure the clinician and user know what resources are available and how to access them. Combining both the CARE acronym with device manuals and manufacture guidance is important to help clinicians provide proper care and education to new users.

The development of the Medtronic 670G and future automated insulin delivery systems make for an exciting time in diabetes management. With this new technology on the horizon, now is the time for clinicians to begin to conceptualize the operation of these devices to better provide quality care to diabetic patients.

Economic Outcomes of First-Line Regimen Switching Among Stable Patients with HIV[30-31]

Roberta Dume, Pharm.D.
GuidePoint Pharmacy—Northern Pines Mental Health Clinic

The advancements in antiretroviral therapy (ART) for the treatment of HIV in the past few years show that what was once considered a terminal disease merely thirty years ago is now an effectively treated disease. While there have been countless studies analyzing the most effective therapy while minimizing side effects, the economic impact of these costly medications has also been recently studied.

Studies have looked at switching ART in patients who were not stable on their current regimen. This included those who had virologic failure (inability to maintain HIV RNA levels < 200 copies/mL) and those with sustained suppression (HIV RNA levels below lower limits of detection) but experiencing severe adverse reactions. Consequently, switching ART was warranted in these patients for the purpose of achieving the most effective and safe therapy. The economic implications of ART were not discussed at length in these studies because they were conducted before the recommended therapies were commercially available.

In a recent study that was published in the *Journal of Managed Care & Specialty Pharmacy*, patients stable on their current ART regimen were specifically targeted to critically assess the economic implications of switching to other therapies. The researchers found that overall, healthcare costs were 8.9% higher in patients who switched regimens, than those who remained on initially prescribed therapies. More specifically, these costs were directly related to higher pharmaceutical costs. It is important to keep in mind that this study did not focus on achieving cost-lowering changes. Reasons for changing from initial therapy included a number of factors: tolerance, convenience, adherence, allure of new drug to market, and cost.

In light of the political turmoil and the uncertainty of government financial support in the healthcare system, this study poignantly addresses key issues around the economics of life-saving medications. We need to continue to provide effective ART that targets virologic suppression, while minimizing side effects. Cost management should be considered of equal importance in these patients due to access and affordability issues. Switching regimens in stable patients should be done only when clinically warranted.

References

1. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017; 377:644-657.
2. Dunn KE, Tompkins A, Bigelow GE, Strain EC. Efficacy of tramadol extended-release for opioid withdrawal: a randomized clinical trial. [published online July 12,2017]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2017.1838.
3. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA*. 2017:318(1):45-56. doi:10.1001/jama.2017.7117.
4. Wang MT, Tsai CL, Lin CW, Yeh CB, Wang YH, Lin HL. Association between antipsychotic agents and risk of acute respiratory failure in patients with chronic obstructive pulmonary disease. *JAMA Psychiatry.* 2017; 74(3):252-260. doi: 10.1001/jamapsychiatry.2016.3793
5. Peeters RP. Subclinical hypothyroidism. *N Engl J Med*. 2017 Jun 29;376(26):2556-2565.
6. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract.* 2012 Nov-Dec;18(6):988-1028.
7. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med.* 2017; 376:2534-44.
8. Rodondi N, den Elzen WP, Bauer DC, et al. *JAMA*. 2010 Sep 22;304(12):1365-74.
9. Chaker L, Baumgartner C, den Elzen WP, et al. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: An individual participant data analysis. *J Clin Endocrinol Metab*. 2015 Jun;100(6):2181-91.
10. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology*. 2017;152(4):706-715. doi: 10.1053/j.gastro.2017.01.031.
11. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - a position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016;14:179. doi: 10.1186/s12916-016-0718-z.
12. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. *Cochrane Database Syst Rev*. 2007;2. doi: 10.1002/14651858.CD003244.pub2.
13. Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology.* 2016;151(6):1105-1112.e10. doi: 10.1053/j.gastro.2016.08.054.
14. Inadomi JM, Jamal R, Murata GH, et al. Step-down management of gastroesophageal reflux

disease. *Gastroenterology.* 2001;121:1095–1100. doi: 10.1053/gast.2001.28649.
15. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):355-369. doi:10.1016/j.cger.2010.03.001.
16. Hochberg MC, Altman RD, April KT, et al. American college of rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* (Hoboken). 2012;64(4):465-474.
17. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the chondroitin versus celecoxib versus placebo trial (CONCEPT). *Ann Rheum Dis*. 2017;76(9):1537-1543.
18. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015, Issue 1. Art. No.: CD005614. DOI: 10.1002/14651858.CD005614.pub2.
19. Hall SF, Edmonds SW, Lou Y, et. al. Patient reported reasons for nonadherence to recommended osteoporosis pharmacotherapy. *J Am Pharm Assoc*. 2017;57(4):503-509.
20. Qaseem A, Forciea MA, McLean RM, et. al. Treatment of low bone density on osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(11):818-839.
21. Cosman F, de Beur SJ, LeBoff MS, et. al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10)2359-81.
22. Kathawala P, Badamgarav E, Ryu S, et. al. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clin Proc*. 2007;82(12):1493-501.
23. Cram P, Wolinsky FD, Lou Y, et. al. Patient-activation and guideline-concordant pharmacological treatment after bone density testing: the PAADRN randomized controlled trial. *Osteoporos Int*. 2016;27(12):3513-3524.
24. Dobson EL, Klepser ME, Pogue JM, et al. Outpatient antibiotic stewardship: Interventions and opportunities. *J Am Pharm Assoc* 2017;57(4):464-473.
25. McWilliams JM, Najafzadeh M, Shrank WH, Polinski JM. Association of changes in medication use and adherence with accountable care organization exposure in patients with cardiovascular disease or diabetes. *JAMA*. July 2017. doi:10.1001/jamacardio.2017.2172.
26. Perdew, C., Erickson, K., & Litke, J. (n.d.). Innovative models for providing clinical pharmacy services to remote locations using clinical video telehealth. *American Journal of Health-System Pharmacy*., 74(14), 1093-1098.
27. What is telehealth? *Department of Veterans Affairs.* (June 3, 2014). www.telehealth.va.gov
28. Messer LH, Forlenza GP, Wadwa RP, et al. The dawn of automated insulin delivery: a new clinical framework to conceptualize insulin administration. *Pediatric Diabetes.* 2017;1–4. doi: 10.1111/pedi.12535.
29. Garg SK, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. *Diabetes Technol Ther.* 2017 Mar;19(3):155-163. doi: 10.1089/dia.2016.0421.
30. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and- adolescent-arv-guidelines/0. Accessed Aug 28, 2017.
31. Rosenblatt L, Buikema A, Jerry Seare J, et al. Economic outcomes of first-line regimen switching among stable patients with HIV. *JMCP*. 2017;23(7):725-734.