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Research Updates

Breo Ellipta® and COPD: A review of the Salford Lung Study¹
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Background: Chronic Obstructive Pulmonary Disease (COPD) is one of the most common disease states encountered in primary care settings. Along with this, we know that uncontrolled COPD can lead to exacerbations requiring hospitalization, increased healthcare costs, significant morbidity and mortality, as well as overall decreased quality of life. With recent studies and the release of new medications for the treatment of COPD, it is easy to get caught up in the sheer number of medications available. Since the year 2011, there have been a total of 11 new FDA approved medications for the treatment of COPD; these medications include various long acting beta agonists (LABA's), long acting muscarinic antagonists (LAMA's) and inhaled corticosteroids (ICS).

Purpose: The Salford Lung Study is a recently published clinical trial seeking to demonstrate superiority of a new COPD therapy to standard of care. This study was conducted to evaluate the effectiveness and utility of Breo® (fluticasone furoate and vilanterol) in reducing COPD exacerbations in patients compared to current standards of care while specifically attempting to replicate "real world treatment settings" to further demonstrate its clinical utility.

Study Design: This study was designed as a randomized, open-label, clinical trial comparing the use of Breo®, fluticasone furoate 100 mcg combined with vilanterol 25 mcg delivered once daily via the Ellipta® device, against current standard of care for COPD. This could include the use of any available combination of LAMA's, LABA's OR ICS inhalers as deemed appropriate by the provider. This trial recruited patients 40 years of age or older with COPD that had at least 1 exacerbation in the past three years. Patients also had to be taking some form of ICS, LAMA, or LABA therapy to manage their COPD symptoms at the time of recruitment. These patients were followed over the course of one year. Their providers were allowed to make therapeutic adjustments including switching from the fluticasone/vilanterol group to usual care, but not vice versa. Enabling providers to make these changes, like they would in standard practice, was intended to replicate a "real world treatment setting". These patients were educated on how to use inhalers (both treatment and standard groups), as well as having their COPD symptoms assessed at baseline and at the end of the trial.

The primary outcome measured was mean annual rate of moderate or severe exacerbations requiring antibiotics, systemic glucocorticoids, or hospital admission. Secondary outcomes included analysis of symptoms (graded by the CAT score, a 40 point scale used to assess symptom severity), rates of primary care contact, and time to first exacerbation.

Safety outcomes were also analyzed, which included rates of pneumonia and other serious side effects.

Results: A total of 2799 patients were enrolled, of which 2269 were included in primary outcome analysis. The fluticasone/vilanterol group was found to have a mean of 1.74 exacerbations per year compared to 1.90 exacerbations in the usual care group ($P=0.02$). This difference between the fluticasone/vilanterol group and standard of care was considered to be statistically significant with an 8.4% reduction in exacerbations per year [95% CI, 1.1-15.2].

There was no statistically significant difference in time to exacerbation between the fluticasone/vilanterol group and standard of care HR 0.93 [95% CI 0.85-1.02]. Rates of primary care contact were 12.3% higher in the treatment group when compared to usual care [95% CI, 5.4 to 19.6]. Lastly, patients in the treatment group were more likely to decrease their CAT score by 2 points compared to usual care (OR 1.51; ($p<0.001$)). There were no statistically different trends in rates of adverse events or serious adverse events.

Conclusion: This trial succeeded in creating an environment that is similar to “real world treatment” settings through enabling providers to augment therapy as they normally would. That being said, this trial evaluating Breo Ellipta®, a new combination of fluticasone furoate and vilanterol against standard of care, did not demonstrate any clinically significant benefit over currently available treatment for COPD. The trial achieved a statistically significant improvement with regard to reducing rates of exacerbations compared to standard of care. Though statistically significant, the clinical impact of a rate reduction from 1.9 exacerbations per year to 1.7 is minimal.

Key point: New isn't always better. The convenience of a once daily inhaler like the Breo Ellipta® expands our drawer of tools to use in the treatment of COPD as a clinically equivalent treatment option to currently available treatment options.

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors (Annexa-4)²

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Background: The ability to reverse the action of direct oral anticoagulants (DOACs) is an ongoing topic of focus among both patients and providers. Idarucizumab reverses the effects of dabigatran (a direct thrombin inhibitor), but until recently, there was no agent available to reverse Xa inhibitors, such as apixaban and rivaroxaban. Factor Xa inhibitors are effective for stroke prevention and venous thromboembolism prevention

and treatment, but bleeding events are still a potential risk. Andexanet alfa is a recombinant human factor Xa decoy protein designed specifically to bind Xa inhibitors and reverse their effect.

Objective: To evaluate the effectiveness of andexanet alfa in patients with acute, potentially life-threatening, major bleeding.

Study Design: A descriptive preliminary analysis was performed for this ongoing single group, multicenter, prospective, open label study. Patients were included if they were receiving apixaban, rivaroxaban, edoxaban, or enoxaparin within the past 18 hours and had an acute major bleed defined as potentially life-threatening overt bleeding with signs/symptoms of hemodynamic compromise, or decrease in hemoglobin to pre-specified amounts, or an acute bleed in a major organ/critical area. Patients were excluded if they had surgery within 12 hours of presentation, pre-specified intracranial hemorrhage (depending on Glasgow Coma score or hematoma volume), survival expectancy less than one month, major thrombotic event in past two weeks, or had received warfarin, dabigatran, prothrombin complex concentrate, whole blood, or plasma one week prior to screening. A bolus dose of andexanet alfa was given over 15-30 minutes, followed by an infusion over two hours. Dosing was based on the specific Xa inhibitor taken. Overall, the doses used had shown at least 80% anti-factor Xa activity in prior studies. Two pre-specified populations were analyzed: a safety population (everyone receiving andexanet alfa) and an efficacy population (patients with baseline anti-factor Xa activity at least 75 ng/ml). The two primary outcomes included percent change in anti-factor Xa activity and rate of hemostatic efficacy 12 hours post infusion (based on imaging and other objective assessments). Anti-factor Xa activity and level of factor Xa inhibitor were measured within a 12 hour time frame. Outcomes and adverse events were collected during the following 30 days.

Results: Forty-seven patients were enrolled in the efficacy population and 67 in the safety population. Most were caucasian, average age of 77, and had atrial fibrillation as the indication for anticoagulation. All were noted to have a history of cardiovascular disease and thrombotic events. Sixty-three patients were taking apixaban or rivaroxaban. The other four patients were on enoxaparin. The mean time to administration of andexanet alfa was 4.8 hours. Gastrointestinal and intracranial bleeds presented at 49% and 42%, respectively, within the efficacy population. For patients on rivaroxaban, anti-Xa activity fell from baseline 277 ng/ml to 16.8 ng/ml after bolus administration (89% decrease). Post infusion, anti-factor Xa activity was 30.6 ng/ml. For apixaban, anti-factor Xa decreased from 149.7 ng/ml at baseline to 10.3 ng/ml post bolus dose (93%

decrease) and was 12.5 ng/ml post infusion. In the efficacy group, 79% of patients were found to have good or excellent hemostasis at 12 hours post infusion. Further broken down, 84% had good or excellent hemostasis with gastrointestinal bleeds and 80% for intracranial bleeds. After andexanet alfa administration, four patients went on to receive plasma, tranexamic acid or platelets. For the safety assessment, there were no infusion reactions or neutralizing antibody development. Twelve patients experienced a thrombotic event within the 30 day follow-up period, however, only three had restarted anticoagulation prior to the event. Overall, anticoagulation was resumed in 27% of patients during the 30 day follow-up. Of the 10 total deaths, six were due to cardiovascular causes.

Conclusions: The authors conclude that andexanet alfa administration rapidly and substantially reversed anti-factor Xa activity. As this was a preliminary evaluation, statistical analysis of outcomes was not performed. Rates of efficacy were similar in patients receiving apixaban and rivaroxaban.

Key Point: While a definitive conclusion on the clinical significance of andexanet alfa cannot be determined at this time, this study does support the potential for andexanet alfa to be an effective Xa reversal agent.

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older³⁻⁵

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Background: Herpes zoster results from the reactivation of latent varicella-zoster virus (VZV). The most common presentation is a dermatomal rash which appears between one to 14 days after reactivation. There is currently a live attenuated herpes zoster vaccine (Zostavax, Merck) approved by the United States *Food and Drug Administration* for use in adults 50 years of age or older. However, the Advisory Committee on Immunization Practices (ACIP), advises that the herpes zoster subunit vaccine (HZ/su) be routinely recommended for adults aged ≥ 60 years; this is due in part to limited long-term evidence demonstrating sustained efficacy if administered between 50 through 59 years old. A separate trial was conducted, ZOE-50, which demonstrated that the HZ/su vaccine had an efficacy against herpes zoster at 97.2%. However, only 24% of participants in ZOE-50 were over the age of 70 years. The authors analyzed the efficacy of the HZ/su vaccine against the herpes zoster virus in adults 70 years and older.

Objective: The aim of ZOE-70 trial was to analyze the efficacy of the herpes zoster vaccine, HZ/su, as compared with placebo in reducing the risk of herpes zoster among adults aged 70 years of age or older.

Secondary objectives included the evaluation of vaccine efficacy against postherpetic neuralgia among participants 50 years of age or older and the evaluation of vaccine safety and reactogenicity.

Study Design: The ZOE-70 trial was a randomized, placebo-controlled, blinded, phase 3 trial that was conducted in 18 countries across Europe, North America, Latin America, and Asia-Australia. Eligible patients included adults 70 years of age or older. Exclusion criteria included history of herpes zoster, previous vaccination against varicella or herpes zoster, or had an immunosuppressive condition. Participants received two doses of HZ/su or placebo (0.9% saline solution) administered intramuscularly into the deltoid muscle two months apart. The HZ/su vaccine is a novel herpes zoster subunit vaccine containing VZV glycoprotein E with an attached AS01B adjuvant system. This study and its authors were supported by GlaxoSmithKline, the manufacturer of the vaccine.

Results: A total of 13,900 participants were enrolled between August 2010 and July 2011. Data collection was completed on July 2015. The efficacy of the HZ/su vaccine against herpes zoster in participants 70 years of age or older was reported to be 89.8% [95% CI 84.2 to 93.7; $p < 0.001$]. Efficacy was reported to be 90.0% for participants 70 to 70 years of age and 89.1% for participants 80 years of age or older. Vaccine efficacy against herpes zoster was 91.3% in a pooled analysis of data from participants 70 years of age or older in ZOE-50 and ZOE-70 [95% CI, 86.8 to 94.5; $P < 0.001$]. Vaccine efficacy against postherpetic neuralgia was 88.8% for adults 70 years of age or older [95% CI, 68.7 to 97.1%; $P < 0.001$]. Vaccine efficacy against postherpetic neuralgia was 91.2% for adults 50 years of age or older [95% CI, 75.9 to 97.7%; $P < 0.001$]. The most common adverse events of the HZ/su group included injection-site and systemic reactions such as fatigue, myalgia, headache, shivering, fever and gastrointestinal symptoms. These symptoms were all noted within 7 days after injection. The reported incidence of serious adverse events was 16.6% in the HZ/su group and 17.5% in the placebo group. Immune-mediated diseases occurred in 11.3% of HZ/su participants and 1.4% of placebo participants. Death occurred in 6.1% of participants in the HZ/su group and 6.6% of the placebo group; according to the investigators, only one death was considered to be related to the trial intervention.

Conclusions: The ZOE-70 trial demonstrated that the HZ/su vaccination is capable of reducing the risks of herpes zoster and postherpetic neuralgia in the setting of adults 70 years of age and older. The study also supports that the adjuvant subunit HZ/su vaccine has a

reasonable safety profile with the most common adverse effect being injection-site reaction.

Key Point: This trial supports use of the investigational vaccine HZ/su for the prevention of herpes zoster in adults aged 70 years of age and older. This inactivated vaccine may be of particular importance to patients who cannot receive live attenuated vaccinations.

Direct Oral Anticoagulants and Renal Dosing⁶⁻⁷

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Background: Direct oral anticoagulants (DOACs) are non-vitamin K antagonists that have now been approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAf), the acute and extended treatment of venous thromboembolism, and the prevention of venous thromboembolism after total knee or hip replacement. DOACs are renally excreted, and therefore dosing recommendations are based on individual's renal clearance. FDA-approved package labeling provides dosing guidelines based on estimated creatinine clearance (CrCl) in mL/min estimated using the Cockcroft–Gault equation, which incorporates age, weight (measured and not ideal), serum creatinine, and gender, because this was the method used in all large randomized clinical trials to establish efficacy and safety. Most clinical laboratories use estimated glomerular filtration rate (GFR) instead of CrCl in their reporting. Estimation equations for CrCl and GFR are different in values associated with age, sex, weight, and race. The majority of individuals with NVAf are elderly. CrCl estimates will predict a steeper decline than GFR in older population. Therefore substituting GFR for CrCl raises the possibility of using incorrect dosing guidelines than recommended by the FDA.

Objective: The purpose of this study is to compare and determine the potential effects of substituting GFR estimates for renal clearance estimated using the Cockcroft–Gault method (CrCL-CG) in calculating direct oral anticoagulant dosing.

Study Design: In a retrospective analysis, differences in dosing recommendations from using GFR and CrCl were analyzed via simulation. The study population included adults aged 18 to 80 without medical exclusions from National Health and Nutrition Examination Survey (NHANES) 2011/12 and medically stable adults enrolled in research studies at University of California (very elderly, nursing home residents and excluded people undergoing dialysis, with active malignancies, or with hypercalcemia). Unpaired t-tests were used to analyze statistical difference between the two sample groups.

Relationships between CrCL-CG and GFR and between GFR estimates were examined using linear regression and the Lin concordance correlation coefficient.

Results: Mean estimates of renal clearance were lower in the research subject sample compared to NHANES sample. Estimates of CrCl and GFR according to all methods were highly correlated ($P < 0.001$), with stronger correlations between GFR estimates than between CrCl and GFR estimates. Substitution of GFR estimates for CrCL-CG resulted in failure to recognize needs for dose reductions of rivaroxaban or edoxaban in 28% of NHANES subjects and 47% to 56% of research subjects, even at lower clearances. At a CrCL-CG of less than 30 mL/min, GFR estimates failed to recognize indicated dosage reductions for dabigatran in 18% to 21% of NHANES subjects and 57% to 86% of research subjects. Edoxaban is not recommended at CrCL-CG greater than 95 mL/min due to increased risk of ischemic stroke, but GFR estimates misclassified 24% of NHANES and 39% of research subjects. After the correction for Body Surface Area (BSA), misclassification was reduced to 7% for NHANES and 14% in research subjects. Correction for BSA still did not reduce misclassification of subjects with CrCl rates of less than 30 mL/min or less than 50 mL/min for whom DOAC dose reductions would be recommended.

Conclusions: Substituting GFR estimates for CrCl can lead to failure in recognizing individuals with NVAf for whom lower doses of DOACs are recommended. Failure to recognize the indication for a DOAC dosage reduction and GFR based higher dosing can result in a greater risk of bleeding than seen in randomized clinical trials.

Key Point: Healthcare professionals including pharmacists should recognize the need for reduced dosing in elderly population by using estimated CrCl instead of laboratory reported GFR. In general, FDA recommendations based on estimates of CrCl and not GFR should guide DOAC dosing adjustments.

Equations used:

CrCL-CG = $(140 - \text{age}) \times \text{weight (kg)} / 72 \times \text{creatinine (mg/dL)}$; 1.0 mg/dL = 88.4 $\mu\text{mol/L}$, multiplied by 0.85 in women.

GFR (mL/min per 1.73 m²) = $175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

Modification of Diet in Renal Disease (MDRD) equation: $10 \times \text{GFR (mL/min per 1.73 m}^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

Two-level race Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: $11 \times \text{GFR} = 141 \times \text{min}(\text{serum creatinine}/j, 1) \times \text{max}(\text{serum creatinine}/j, 1)_{-1.209} \times 0.993 \times \text{age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$

Role of glucagon-like peptide 1 receptor agonists in management of obesity⁸

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Background: Many anti-obesity drugs have adverse effects that limit chronic use; several have even been removed from the market due to safety concerns. Glucagon-like peptide 1 (GLP-1) receptor agonists offer a novel treatment approach for obesity which may be safer and better tolerated than other alternatives. While liraglutide (Saxenda®) is the only GLP-1 agonist approved by FDA for chronic weight management, other GLP-1 agonists have also been studied for weight loss in patients with or without diabetes.

Purpose: This article provides a clinical review of published data, with a focus on data from clinical trials, on the weight loss effects of GLP-1 receptor agonists.

Study Design: A literature review was performed. MEDLINE database search publications from Jan 2000 – Apr 2016 using keywords such as *obesity, weight loss, glucagon-like peptide-1 receptor agonist, GLP-1*. Only articles in English that evaluated GLP-1 receptor agonist effects on body weight or BMI in humans were reviewed, with priority given to clinical trials that evaluated GLP-1 agonist effects in patients without type 2 diabetes (T2D).

Results: Liraglutide (LIRA): In patients with or without diabetes, mean weight loss (MWL) from LIRA 1.8 – 3 mg daily ranged from 0.2 – 8.4 kg in multiple randomized placebo-controlled trials (RPCTs) of 24 – 56 weeks ($p < 0.001$). The higher dose of 3 mg daily exhibited greater weight loss but also resulted in higher risk of gastrointestinal adverse effects.

Exenatide (EXE): In patients with or without diabetes, MWL from EXE 5 – 10 mcg twice daily and 2 mg weekly ranged from 1.6 – 3.1 kg in several RPCTs of 16 – 56 weeks (inconsistent statistical significance across trials). EXE therapy was also studied in combination with oral hypoglycemics (metformin, sulfonylurea, or thiazolidinedione) with most RPCTs demonstrating significant weight loss in EXE group.

Albiglutide (ALBI): HARMONY trials studied ALBI as an adjunct to metformin therapy for T2D, with weight as secondary outcome. In the randomized, placebo-controlled, comparator-controlled trials, MWL from ALBI 30 – 50 mg weekly ranged from 0.4 – 1.2 kg in 24 – 56 weeks and was significant only when compared to glimepiride 2 – 4 mg daily ($p < 0.0001$). HARMONY-7

suggested that LIRA 1.8 mg daily is superior to ALBI 50mg weekly for weight loss in 32 weeks.

Dulaglutide (DULA): In AWARD trials, DULA demonstrated safety and efficacy for T2D, with weight loss as a secondary outcome. In these double-blind, parallel-group trials, MWL from DULA 0.75 mg and 1.5 mg weekly dose ranged from 0.9 – 3.1 kg in 24 – 56 weeks. These results were statistically significant compared to placebo at 26 weeks ($p \leq 0.001$).

Other GLP-1 Agonists: Lixisenatide (LIXI) has been accepted for FDA review on T2D management. MWL (secondary outcome) from LIXI 20 mcg daily was statistically insignificant when compared to placebo, LIRA 1.8 mg daily, or EXE 10 mcg twice daily. Semaglutide (SEMA) is a once-weekly agent that is in the pipeline with promising results on glycemic control and weight loss from initial data of Phase 3 trial completed in Sep 2015.

Conclusions: Originally marketed for glycemic control in T2D, GLP-1 receptor agonists have been found effective for weight reduction in patients with and without T2D. LIRA is currently the only GLP-1 agonist approved by FDA for obesity treatment. Given positive results from other trials, more approved agents from this class are likely to be on the horizon.

Key Point: GLP-1 receptor agonists demonstrated weight loss as a primary or secondary treatment outcome with more benign safety profile compared to other anti-obesity agents. The most common adverse effects associated with GLP-1 agonists are gastrointestinal upset and with careful titration, these generally subside. In patients who have risk factors such as cardiovascular or hepatic compromise which prevent the use of other anti-obesity agents, GLP-1 agonists may be appropriate agents to explore with or without concurrent diabetes.

Therapeutic Thoughts

Calcium and Associated Cardiovascular Health Risk⁹⁻¹⁴

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Background: Inadequate intake of calcium and vitamin D was addressed as nutrients of public health concern by the 2015 U.S. Dietary Guidelines Advisory Committee. In 2010, the Institute of Medicine (IOM) recommended a daily allowance (RDA) of 1000 mg and 1200 mg of elemental calcium for men and women older than age 50 years, respectively, and 1200 mg for men and women older than age 70 years for better bone health. The National Osteoporosis Foundation (NOF) recommends intake of the recommended dose from food sources, and if not possible, in the form of supplements. However, the long-term safety effect of calcium and vitamin D supplements have not been well established. In 2009, the U.S. Agency for Healthcare Research and Quality (AHRQ) published a report that suggested calcium intake may have an association with cardiovascular events. Since then, conflicting data has been published. To provide an evidence-based recommendation on the risk of calcium intake from food or supplements on cardiovascular outcomes, NOF and American Society for Preventive Cardiology (ASPC) together performed a systematic review and meta-analysis.

Evidence: In this meta-analysis, four randomized controlled trials, one nested case-control trial, and 26 cohort studies from 2009-2016 were included. These studies were peer-reviewed, English-language studies that included healthy adults (no more than 20% of participants had cardiovascular disease). Studies included patients with hypertension or age >60 years. *Randomized controlled trials:* None found statistical differences between groups who had received calcium (1000 mg/d) plus vitamin D (400-800 IU) or received calcium supplement (up to 1200 mg/d) alone in risk for cardiovascular disease (CVD) events or mortality. *Prospective cohort and nested case-control studies:* 15 studies assessed CVD mortality risk and 20 studies assessed stroke mortality risk with a total calcium intake of 200 - 2400 mg/d (from either food or supplement) at 8-30 years follow up. No consistent dose-dependent relationship was observed. Of these studies, one study showed that calcium intake greater than 1000 mg/d was associated with an increase in higher CVD mortality (RR 1.2 [95% CI 1.00 – 1.14]). Two studies showed that calcium intake greater than 1000 mg/d was associated

with higher total stroke mortality (RR 1.13 [95% CI 1.02 – 1.26]).

Discussion: The meta-analysis and current literature concluded that calcium intake within recommended tolerable upper intake range of 2000 to 2500 mg/d is not associated with CVD risks in generally healthy adults. Three out of 15 studies showed that higher calcium intake (>1000 mg/d) showed increased risk in CVD and cerebrovascular mortality. However, relative risk was minimal in spite of its statistical significance and may not be considered clinically significant. Also, each study included a limited number of patients who took >1000 mg. Most cohort studies assessed calcium intake by a food-frequency questionnaire, which assessed calcium source from both food and supplements. Since it was a self-reported questionnaire, documented daily calcium intake may not be accurate. Lastly, it is difficult to distinguish if the effect of calcium on CVD event is from use of supplement or total daily intake of calcium. Due to the fact that subgroup analysis on patients with high risk of CVD was not performed, the effect in patients with history of CVD or at high risk of CVD is still unknown. Future prospective cohort studies with validated assessment of dietary and supplement calcium intake and stratification of CVD outcomes based on participant's baseline risk of CVD is needed to further strengthen the recommendation.

Clinical Impact: Based on this meta-analysis, NOF and ASPC have now adopted a position that calcium with or without vitamin D intake from food or supplements has no relationship to the risk for cardiovascular and cerebrovascular disease and mortality in healthy adults. To adopt this statement to practice, it is important to assess a patient's calcium intake from both dietary and supplement sources and educate the patient not to exceed 2000 to 2500 mg/d. Given the studied patient population, the risk of association between calcium intake and CVD events cannot be ruled out in patients with a high risk of CVD at baseline.

Insomnia Disorder: Clinical Practice Guideline from the American College of Physicians¹⁵⁻¹⁸

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Background: Approximately 6-10% of adults have insomnia that meets diagnostic criteria. In addition to a significant cost to the United States healthcare system, insomnia takes a toll on the economy in terms of loss of workplace productivity, costing an estimated \$63.2 billion

in 2009. Insomnia disorder, as defined by the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, requires sleep problems that are chronic, persistent, and associated with daytime dysfunction. Insomnia disorder includes predominant symptoms of difficulty with sleep initiation, difficulty maintaining sleep, or early-morning waking with inability to return to sleep. Current definitions require these insomnia symptoms to occur at least three nights per week and have persisted for three months or more. Pharmacologic interventions are often prescribed for insomnia as first line treatment.

Evidence: The American College of Physicians (ACP) recently released a Clinical Practice Guideline on the Management of Chronic Insomnia Disorder in Adults in *Annals of Internal Medicine*. The guideline is based on a systematic review of randomized, controlled trials from 2004 to 2015 of psychological and pharmacologic therapies and evaluated outcomes included global outcomes assessed by questionnaires, patient-reported and intermediate sleep outcomes, and harms. The following recommendations to practitioners were highlighted in the guidelines.

Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence).

Although the evidence of most psychological therapies was limited, moderate-quality evidence showed that CBT-I improved remission, treatment response, sleep onset latency, wake after sleep onset, sleep efficiency, and sleep quality in the general population. Improvements were seen with various methods of CBT-I including in-person individual therapy, in-person group therapy, telephone-based modules, web-based modules, and self-help books; however, evidence was insufficient to determine the superiority of one CBT-I method over another. As expected, there were no adverse effects reported for psychological interventions.

Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacologic therapy in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful (Grade: weak recommendation, low-quality evidence).

In the review of pharmacologic therapies for insomnia disorder, two non-benzodiazepine hypnotics, eszopiclone and zolpidem improved short-term outcomes of sleep onset latency and total sleep time

(moderate-strength evidence). The orexin receptor antagonist, suvorexant, improved short-term outcomes of response to treatment, mean change in Insomnia Severity Index, sleep onset latency, total sleep time, and wake after sleep onset (moderate-strength evidence). Evidence of benzodiazepine hypnotics, melatonin agonist (ramelteon), and antidepressants was insufficient or low strength. Evidence was also insufficient to compare efficacy within or across pharmacotherapy classes or compared to behavioral therapy. In addition, a large placebo response was often noted in the studies. For example, in a trial evaluating as-needed zolpidem, 24% of participants randomly assigned to placebo were rated as "much or very much improved" on the Clinician Global Impression (CGI) scale.

Treatment harms reported in trials were judged insufficient or low strength, though observational studies suggested that use of hypnotics for insomnia was associated with increased risk for dementia, fractures, and major injury. FDA documents have reported that most pharmacotherapies for insomnia have risks for cognitive and behavioral changes, including driving impairment, and other adverse effects, and they advised dose reduction in women and in older adults.

Conclusions: There is evidence that CBT-I is an effective and safe first-line treatment strategy for patients with insomnia disorder. If a patient fails CBT-I or requires pharmacologic therapy for adjunctive treatment of insomnia disorder, eszopiclone, zolpidem, and suvorexant have all shown to improve short-term global and sleep outcomes for adults with insomnia disorder. However, the long-term efficacy of these pharmacotherapies are not known, and there seems to be a placebo effect for a large number of patients. The risks associated with these pharmacotherapies include cognitive and behavioral changes and may be associated with infrequent but serious harms such as fractures and major injury.

Clinical Impact: Most of the trials in these guidelines for treatment of insomnia disorder were small and short term. Minimum important differences in outcomes were often not established or reported. Therefore, the moderate evidence reported with CBT-I appears to be the best first-line treatment option available at this time. Larger studies with a longer study period are needed to more effectively analyze the benefits and harms of pharmacologic therapies for insomnia disorder.

LDL-C and Cardiovascular Risk Reduction¹⁹⁻²²

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Background: Low-density lipoprotein cholesterol (LDL-C) has frequently been used as a surrogate marker for cardiovascular (CV) risk, but there is discordance among the literature whether LDL-reduction itself has a protective effect. Robust evidence and guideline recommendations support the use of statin therapy for reduction of morbidity and mortality related to cardiovascular disease and its complications. The utility of non-statin lipid-modifying therapies and their impact on CV risk has remained unclear due to the lack of randomized clinical trials with cardiovascular endpoints.

Evidence: A recently published systematic review and meta-analysis evaluated the association between various LDL-lowering therapies and their effect on cardiovascular risk. The systematic review and meta-analysis included therapies that acted through upregulation of LDL-C receptors. This included four studies on diet, two on bile acid sequestrants, one on ileal bypass surgery, and one on ezetimibe. For this combined group, each 38.7 mg/dl LDL reduction was associated with a RR of 0.75 (95% CI 0.66-0.86, $P=0.002$) for major vascular events. These results were comparable to statins, in which a decrease in 38.7 mg/dl in LDL-C is associated with a relative risk (RR) of 0.77 (95% CI 0.71-0.84, $p<0.001$) for major vascular events, suggesting LDL-C reduction is the source of benefit regardless of treatment class.

For primary prevention trials in a combined analysis of statins and agents that upregulate LDL-C receptors, the

absolute rate of major coronary events was reduced by 1.5% for each 38.7 mg/dl of LDL-C reduction (95% CI 0.5% - 2.6%, $P=0.008$). There was a greater effect seen in secondary prevention trials, where the decrease was 4.6% per 38.7 mg/dl LDL-C (95% CI 2.9% - 6.4%, $p<0.001$).

Discussion: Results suggest that both statin and non-statin therapies are associated with cardiovascular risk reduction correlating with decrease in LDL-C levels if their action is by upregulation of LDL-C receptor expression. There was no significant difference between the amount of risk reduction per equivalent LDL-C effect in the statin group and the combined group of diet, bile acid sequestrants, ileal bypass surgery, and ezetimibe interventions, which may all be acceptable strategies for reducing cardiovascular risk. However, the non-statin were analyzed as a group, and not all clinical outcomes were designated as primary endpoints in the included studies. It should be noted that the meta-analysis excluded patients determined to have significant comorbidities including heart failure and chronic kidney disease, among others.

Clinical Impact: While guidelines have moved away from targeting specific lipid panel goals, LDL-C lowering still seems to show some promise for mitigating cardiovascular risk. This may provide a useful discussion point with patients when including them in decision-making, in terms of percentage risk reduction per LDL-C reduction. From the available evidence, statins remain the best-supported agents for reducing cardiovascular morbidity and mortality, but other lipid-modifying therapies should not be entirely discounted.

From the Pharmacy Press**Management of Hypertension in Ambulatory Care
Dialysis Patients²³⁻²⁹**

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Background: The prevalence of hypertension in patients with end stage renal disease (ESRD) is a commonplace – it affects roughly two-thirds of ESRD patients. The pathogenesis is theoretically simple – with renal failure, patients become fluid-overloaded and dialysis is needed. With hemodialysis (HD), the primary goal is to achieve target dry weight which is attainable with volume control. However, hypertension is multifactorial in ESRD including: fluid overload and sodium retention and activation of the renin-angiotensin system (RAS), sympathetic overactivity and arteriosclerosis. The National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDIGO) offers clinical

practice guidelines for the management of cardiovascular risk factors in dialysis patients. In addition to therapeutic lifestyle changes including a low-salt diet, KDIGO guidelines recommend pre-dialysis and post-dialysis blood pressure goals be $<140/90$ mmHg and $<130/80$ mmHg, respectively. It recommends longer dialysis sessions with frequency greater than three times weekly as needed to manage excessive fluid accumulation and maintain target dry weight. Anti-hypertensive pharmacotherapy also plays an important role in the management of hypertension and includes beta-blockers, calcium channel blockers and RAS inhibitors.

Evidence: Bakris GL et. al. published a narrative review looking at anti-hypertensive medication use concurrently with intensive HD to attain optimal blood pressure goals.

With the current standard of dialysis occurring three times per week, blood pressure increases during the interdialytic intervals in correlation with weight gain especially in elderly patients. Polypharmacy in ESRD patients is common and therapy with multiple anti-hypertensives treated to blood pressure goals may not be indicated if the primary cause of the problem is excess intravascular volume. However, with increased session frequency or increased duration of dialysis, euvolemia may be achieved with subsequent reductions in blood pressure.

In dialysis dependent patients, ambulatory and self-monitored blood pressures are more strongly associated with mortality risk when not at goal. Patients enrolled in the Frequent Hemodialysis Network (FHN) trials were randomly assigned to either the Daily Trial or Nocturnal Trial. The groups were further split into either conventional HD (control group) or short daily/nocturnal HD (experimental group). Both subsets in the experimental group, with shorter but more frequent HD sessions, showed decline in systolic blood pressures (SBP -10 mmHg in short daily, -8 mmHg in short nocturnal, pre-dialysis), as well as lower interdialytic weight gain. In the Following Rehabilitation, Economics, and Everyday-Dialysis Outcome Measurements (FREEDOM) study on short daily HD, the mean number of medications decreased from 1.7 to 1.0 in 12 months and the percentage of patients not prescribed anti-hypertensives increased 21% to 47%.

Discussion and Clinical Impact: As seen in multiple clinical trials, intensive HD reduces blood pressure and the need for oral anti-hypertensives. Possible non-adherence due to pill burden and poor volume control make ESRD patients particularly challenging. Polypharmacy can be avoided especially if the intended pharmacotherapy does not correct the main problem of fluid overload with conventional HD. Pharmacists have a great opportunity to work in concert with primary care providers and nephrologists to manage chronic disease states like hypertension in dialysis patients.

FDA Update on the Risks of Fluoroquinolones for Sinusitis, Bronchitis, and Uncomplicated Urinary Tract Infections in Adults ³⁰⁻³²

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The Federal Drug Administration (FDA) recently announced a change in labeling requirements for systemic fluoroquinolones due to risk of serious adverse effects including peripheral neuropathy, tendonitis, and central nervous system effects. These adverse effects are generally considered to outweigh the benefit for

treatment of less complicated infections including acute sinusitis, acute exacerbations of chronic bronchitis, and uncomplicated urinary tract infections. Below includes a review of current treatment recommendations for these conditions.

Sinusitis

The 2012 Infectious Disease Society of America (IDSA) Clinical Practice for Rhinosinusitis indicates the most likely pathogens for sinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus aureus*. The first-line treatment for this condition is unaffected by the recent FDA announcement. For adults, the first-line treatment is amoxicillin-clavulanate 500/125 mg by mouth three times daily or 875/125 mg twice daily. In the event of beta-lactam allergy, the recommendation would be doxycycline 100 mg by mouth twice daily or 200 mg by mouth daily. In adults, treatment duration should last five-seven days. Macrolides including erythromycin, clarithromycin, or azithromycin, as well as trimethoprim/sulfamethoxazole are generally not recommended due to increasing rates of pneumococcal resistance. Although nasal irrigation can be recommended, current guidelines do not support the use of oral or topical decongestants or antihistamines as adjunct therapy for rhinosinusitis.

Bronchitis

Acute bronchitis is often viral, however, if bacterial it is most likely caused by the same pathogens as acute sinusitis including *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. Because of the overlap of common pathogens between acute bronchitis and rhinosinusitis, the same antibacterial regimens can be used to treat acute bronchitis in the community setting (see sinusitis above).

Uncomplicated Urinary Tract Infections

The most common pathogens for uncomplicated urinary tract infections include *Escherichia coli*, *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus* spp., or other gram-negative bacteria. First-line treatment therapy for non-pregnant females is trimethoprim/sulfamethoxazole 160/800 mg by mouth twice daily for three days. Alternative options include nitrofurantoin 100 mg by mouth twice daily for five days, or fosfomycin trometamine 3 g by mouth for one dose. In the 2011 IDSA Guidelines for Uncomplicated Urinary Tract Infections, fluoroquinolones were second-line treatment options. Alternative second-line agents include beta-lactams. One study showed cefpodoxime proxetil 100 mg by mouth twice daily for three days was equivalent to trimethoprim/sulfamethoxazole 160/800 mg by mouth twice daily for three days, with cure rates 98%

and 100% respectively four-seven days after therapy completion.

Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy³³

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Background: Nausea and vomiting occurs in up to 85% of pregnant women while the more severe and persistent problem of hyperemesis gravidarum (HG) is experienced by 0.3 to 3% of pregnant women. Although HG symptoms usually begin between gestation weeks six and eight and typically resolve before 20 weeks, this can have very serious impacts on the health of the mother and baby. Evidence for treatment of both regular nausea and vomiting in pregnancy and HG is limited and conflicting. This review published in JAMA sought to assess available evidence and to categorize therapies based on severity of symptoms.

Study Design: Two primary reviewers completed this systematic review by utilizing the American Heart Association scale to give studies an evidence grade from level A to C (A being the highest) and recommendation class of I, IIa, IIb, and III (I being most useful to III being harmful or least useful). Electronic databases were searched through June 8, 2016 for studies of interventions to treat nausea and vomiting in pregnancy or HG. Studies were excluded for patient recruitment later than 20 weeks of gestation, lack of relevant outcomes being reported, and classification as having a high or unclear risk of bias. The authors intended to perform a meta-analysis but high study heterogeneity prevented this so results were summarized narratively.

Results: From 13,075 identified titles, 222 underwent full review and seventy-eight studies (n= 8930 subjects) were selected for inclusion (sixty-seven randomized controlled trials (RCT) and eleven nonrandomized studies). Thirty-five RCTs were identified as having low risk of bias from which the authors assessed the treatments and categorized them into first, second, or third line as outlined below.

The first-line group of treatments are options that a woman may self-initiate when mild to moderate symptoms first appear such as lifestyle changes and non-prescription options. For options that met level A evidence, class IIa first-line recommendations, the review concluded that treatments of ginger, acupuncture, and vitamin B6 were associated with symptom improvement for mild cases. Nerve stimulation had unclear benefit, but treatment may be considered (level

B, class IIb), while acupuncture had unclear benefit (level A, class IIb).

The second-line group treats moderate to severe symptoms. All recommendations in this group were given class IIa rating by the authors with varying grades of evidence. Higher evidence (level A) was associated with dopamine receptor antagonists (metoclopramide and promethazine) and serotonin receptor antagonists (ondansetron) which were found to have symptom improvement in all levels of severity. Antihistamines (hydroxyzine alone and vitamin B6 with doxylamine) had more limited evidence (level B), showing improvement in mild-moderate symptoms. Level B evidence suggested psychotherapy with vitamin B6 had greater symptom reduction than vitamin B6 alone and that dextrose saline may result in greater moderate-severe symptom reduction than normal saline.

Corticosteroids are the mainstay of third-line treatments which are given in a hospital setting and are reserved for symptoms that are more severe and persistent. Corticosteroids have unclear benefits, but their use may be considered in severe cases (level A, class IIb). Additionally, transdermal clonidine is not currently an established and recommended treatment of HG but limited evidence suggests it may improve symptoms (level B, class IIb).

Discussion: This review separates therapeutic recommendations by symptom severity for guiding therapy in pregnant patients. In comparison with guidelines from the American College of Obstetricians and Gynecologists released in August 2015, this systematic review had similar recommendations overall. Some limitations include high study heterogeneity which prevented completion of a meta-analysis and overall low quality of evidence. Based on the patient population involved, the lack of reliable safety data for the mother and child may be the most significant limitation and may prevent completely generalizable use of these recommendations.

Key Point: Quality of evidence in treatment of HG and nausea and vomiting in pregnancy is low. It may be reasonable to consider use of ginger, vitamin B6, antihistamines, metoclopramide, and pyridoxine-doxylamine for treatment of nausea and vomiting in pregnancy. Ondansetron has been shown to improve symptoms in all severities of nausea and vomiting in pregnancy and in HG, and corticosteroids show benefit in severe cases.

Miscellaneous News

Update on HPV Vaccine Schedule for Adolescents ³⁴⁻³⁶

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On October 19, 2016 the Centers for Disease Control and Prevention (CDC) announced a simplified vaccine administration schedule for the human papillomavirus (HPV) vaccine, to be adopted into practice immediately. In the year 2015, the CDC estimates that just over 65% of teens ages 13-17 received the HPV vaccine. The agency hopes to increase the vaccination rate by decreasing the number of total doses needed. Human papillomavirus can cause genital warts and cancer. Gardasil®-9 protects against nine different strains of this virus. Protection is provided against cervical, vulvar, and vaginal cancer in females, anal and throat cancer in both females and males, and penile cancer in males. Females and males are also protected against genital warts. The vaccine is noted to be particularly successful in preventing cervical cancer caused by HPV strains.

The change will affect adolescents ages nine through 14, and will decrease the number of vaccinations in the series from three to two. New recommendations state the vaccine can be given at zero and six months for the limited age group. This change differs from the original three-dose series requiring administration at initial, one to two, and six months.

The patient age groups eligible for the vaccine (ages nine through 26) remain the same. However, the vaccine is commonly given around the ages 11-12. ACIP evaluated several studies that concluded the two-dose schedule offers the same amount or better protection than the three-dose schedule in the selected age group. This means that a large number of eligible recipients may benefit from the convenience of one less trip to their healthcare provider. Hopefully, the increased in convenience will correspond with an increase in the number of patients fully vaccinated against HPV.

Advancement in Insulin Pumps ³⁷⁻³⁸

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New Insulin Pump Release:

On September 28, 2016, Medtronic announced FDA approval of its newest device: the MiniMed 670G. The MiniMed 670G system will be the third addition to the current list of Medtronic insulin pump products which currently include the MiniMed 530G and MiniMed 630G systems. The MiniMed 630G system in an insulin pump-and-monitor combination system that was released earlier in August 2016. The new MiniMed 670G is a hybrid closed-system insulin pump which is FDA approved for patients 14 years of age and older who have type 1 diabetes mellitus. Further studies are also underway to expand FDA approval beyond type 1 diabetes. The newer system, MiniMed 670G, will be available for patients in the spring of 2017. Patients who have purchased the MiniMed 630G system after August 11, 2016 are eligible to upgrade to the 670G for \$299 after its release. Patients who purchase the MiniMed 630G system before December 31, 2016 may be eligible for a free upgrade if they participate in the System Access program.

What's new? The older Medtronic system, MiniMed 630G, will suspend insulin release for 2 hours once blood glucose falls below a preset level, but the new MiniMed 670G system has the capability to suspend insulin when blood glucose is dropping to a predicted low, and will resume after blood glucose recovers. This is a huge benefit for patients who have hypoglycemic unawareness.

The automated-basal function allows the pump to automatically adjust basal rate throughout the day to improve blood sugars. This could potentially lead to better control and improved A1c. The basal rate will be adjusted based off of algorithms and blood glucose readings. The MiniMed 670G sensor is reported to have enhanced accuracy and performance in addition to a 7-day life, compare to a 6-day life with the MiniMed 630G sensor.

The new Medtronic MiniMed 670G has great potential for patients. Between the suspend function and the auto-adjusted basal rate, theoretically, patients will be able to have better control of their insulin and minimal hypoglycemic events. This innovative technology will allow patients to focus more on life, instead of making plans around their diabetes.

New Drug Updates

Adlyxin® (lixisenatide), developed by Sanofi-Aventis U.S. LLC³⁹

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Indication: Lixisenatide was approved by the Federal Drug Administration (FDA) in July 2016 to improve glycemic control in adult patients with type II diabetes mellitus (T2DM) in addition to diet and exercise.

Mechanism of Action: As a glucagon-like peptide-1 (GLP-1) receptor agonist, lixisenatide mimics endogenous human GLP-1 by improving insulin secretion in the presence of high blood glucose, decrease glucagon secretion, and slow gastric emptying to regulate appetite.

Dosage and Administration: The recommended dose is 10 mcg subcutaneously daily within one hour before the same meal daily for two weeks. On day 15, the dose should be increased to 20 mcg daily as tolerated. Missed doses should be given administered one hour before the next meal. Lixisenatide is supplied as two prefilled pens, a 10 mcg (50 mcg/mL) green pen and a 20 mcg (100 mcg/mL) burgundy pen. Each pen contains 15 doses of medication. Pens must be primed before first use and discarded in 14 days. Pen needles must be prescribed separately.

Effectiveness: The FDA approval of lixisenatide was due to the outcomes of the GetGoal clinical program, which included over 5000 patients in 13 international randomized control trials. These trials studied the effects of lixisenatide with diet and exercise alone and in addition to metformin, with and without other oral antidiabetic agents, and in addition to a basal insulin regimen. Notably, lixisenatide was not studied in combination with short-acting insulin regimens. Across the 13 trials, lixisenatide offered a 0.7% to 1% decrease

in HbA1c from baseline in 26 weeks. In two separate trials, lixisenatide was found to be non-inferior to the HbA1c lowering ability of exenatide 10 mg twice daily and insulin glulisine three times daily in addition to oral medications and/or basal insulin. Maximum weight loss observed over study periods was approximately 2.7 kg; however, this difference was not always statistically significant.

Safety: The ELIXA Cardiovascular (CV) Outcomes study was an international randomized, double-blind, placebo-controlled study of more than 6000 adult patients with T2DM and recent history of acute coronary syndrome. The primary composite outcome measure was time to first major adverse cardiovascular event (or "MACE+", which included CV death, non-fatal myocardial infarction or stroke, or hospitalization for unstable angina). Over a median duration of therapy of 22-23 months, lixisenatide was found to be non-inferior to placebo (non-inferiority margin 1.3, HR 1.02 [95% CI 0.89 – 1.17]) for MACE+ outcomes. Common side effects of lixisenatide include nausea, vomiting, diarrhea, headache, dizziness, and hypoglycemia ($\geq 5\%$). It is recommended to avoid use in patients with end-stage renal disease, pancreatitis, severe gastroparesis, or in combination with short-acting insulin.

Place in therapy: Lixisenatide may be considered as an alternative GLP-1 agonist to other in-class agents (e.g. liraglutide and dulaglutide) in addition to diet, exercise, and metformin for reduction of HbA1c in adult patients with T2DM. Liraglutide and dulaglutide are reasonable to consider prior to lixisenatide due to better weight loss and established improvement in MACE+ outcomes with liraglutide and convenient, once-weekly dosing with dulaglutide.

References

1. Vestbo J, Leather D, Diar Bakerly N, et al. Effectiveness of fluticasone furoate-filanterol for COPD in clinical practice. *N Engl J Med.* 2016;375(13):1253-1260.
2. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2016;375(12):1131-1141.
3. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med.* 2016;375(11):1019-1032.

- <http://dx.doi.org/10.1056/NEJMoa1603800>. doi: 10.1056/NEJMoa1603800.
4. Zostavax [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2/2016. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=30a0464e-e012-4c16-bc05-88f07e412203>. Accessed November 20, 2016.
 5. Centers for Disease Control and Prevention. *Shingles (Herpes Zoster)*. <http://www.cdc.gov/shingles/vaccination.html> Published May 1, 2014. Updated November 25, 2014. Accessed November 20, 2016.
 6. Schwartz JB. Potential Effect of Substituting Estimated Glomerular Filtration Rate for Estimated Creatinine Clearance for Dosing of Direct Oral Anticoagulants. *Journal of the American Geriatrics Society*. 2016;64:1996-2002.
 7. Jones GR. Estimating renal function for drug dosing decisions. *The Clinical biochemist Reviews / Australian Association of Clinical Biochemists*. 2011;32:81-88.
 8. Isaacs, D., Prasad-Reddy, L., & Srivastava, S.B. (2016). Role of glucagon-like peptide 1 receptor agonists in management of obesity. *Am J Health-Syst Pharm*, 73(19), 1493-1507.
 9. U.S. Department of Health and Human Services; U.S. Department of Agriculture. 2015-2020 dietary guidelines for Americans. 8th ed. December 2015.
 10. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Pr. 2011.
 11. National Osteoporosis Foundation. Calcium and vitamin D are essential for bone health. 2015. Assessed at <https://cdn.nof.org/wp-content/uploads/2016/04/Calcium-and-Vitamin-D-are-Essential-for-Bone-Health.pdf> on November 18, 2016.
 12. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: systematic review of health outcomes. Evidence Report/ Technology Assessment no. 183. (Prepared by Tufts Evidence based Practice Center under contract no. 290-2007-10055-I.) AHRQ publication no. 09-E015. Rockville: Agency for Healthcare Research and Quality. 2009.
 13. Chung M, Tang AM, Fu X, et al. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. *Ann Intern Med*. 2016. doi:10.7326/M16-1165.
 14. Kopecky SL, Bauer DC, Gulati M, et al. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: A clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. *Ann Intern Med*. 2016. doi:10.7326/M16-1743
 15. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165:125-133.
 16. Wilt TJ, MacDonald R, Brasure M, et al. Pharmacological treatment of insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians.
 17. FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). *U.S. Food and Drug Administration website*. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm>. 2013. Accessed November 2016.
 18. FDA requests label change for all sleep disorder drug products. *U.S. Food and Drug Administration website*. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm>. 2007. Accessed November 2016.
 19. Stone NJ, Robinson JG, Lichtenstein AH, et al. ACC / AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2014;1-49. doi:10.1161/01.cir.0000437738.63853.7a.
 20. Jacobson T, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. *J Clin Lipidol*. 2014;8(5):473-488. doi:10.1016/j.jacl.2014.07.007.
 21. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin use for the primary prevention of cardiovascular disease in adults. *J Am Med Assoc*. 2016;316(19):1997-2007. doi:10.1001/jama.2016.15450.
 22. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions. *J Am Med Assoc*. 2016;316(12):1289-1297. doi:10.1001/jama.2016.13985.
 23. Mailloux L, Haley W. Hypertension in the ESRD patient: pathophysiology, therapy, outcomes,

- and future directions. *Am J Kidney Dis.* 1998;32(5):705-719.
24. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis.* 2005;45:16-153. Doi: 10.1053/j.ajkd.2005.01.019
 25. Bakris GL, Burkart JM et al. Intensive hemodialysis, blood pressure, and antihypertensive medication use. *Am J Kidney Dis.* 2016;68(5):S15-S23.
 26. Inrig JK, Patel UD et al. Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. *Am J Kidney Dis.* 2007;50(1):108-117.e4. doi:10.1053/k.ajkd.2007.04.020
 27. Chertow GM, Levin NW et al. FHN trial group: in-center hemodialysis six times per week versus three times per week. *N End J Med.* 2010;363(24):2287-2300.
 28. Rocco MV, Lockbridge RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the frequent hemodialysis network nocturnal trial. *Kidney Int.* 2011;80(10):1080-1091. doi:10.1038/ki.2011.213
 29. Jaber BL, Collins AJ, Finkelstein FO et al. Daily hemodialysis reduces the need for anti-hypertensive medications. October 2009. <https://www.asn-online.org/api/download/?file=/education/kidney-week/archives/RW09Abstracts.pdf>. Accessed November 28, 2016.
 30. Abramowicz M, Zuccotti G, and Pflomm JM. Alternatives to fluoroquinolones. Published in JAMA from The Medical Letter. 2016; 316(13): 1404-1405.
 31. Chow AW, Benninger MS, Brook I, et. al. 2012 IDSA practice guideline for acute bacterial rhinosinusitis in children and adults. IDSA. 2012. doi: 10.1093/cid/cir1043.
 32. Gupta K, Hootan TM, Naber KG, et.al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious disease society of America and the European society for microbiology and infectious diseases. IDSA. 2010. doi: 10.1093/cid/ciq257.
 33. Mcparlin C, O'donnell A, Robson SC, et al. Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review. *JAMA.* 2016;316(13):1392-1401.
 34. Centers for Disease Control and Prevention. 2015 Adolescent Human Papillomavirus (HPV) Vaccination Coverage Report. <http://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/data-reports/hpv/reports/2015.html>. Published August 25,2016. Accessed November 28, 2016.
 35. Centers for Disease Control and Prevention. CDC Press Release. CDC recommends only two HPV shots for younger adolescents. <http://www.cdc.gov/media/releases/2016/p1020-hpv-shots.html>. Published October 19, 2016. Accessed November 18, 2016.
 36. Centers for Disease Control and Prevention. Vaccine Information Statements. HPV (Human Papillomavirus) Gardasil®-9 VIS. <http://www.cdc.gov/vaccines/hcp/vis/vis-statements/hpv-gardasil-9.html>. Published March 31, 2016. Accessed November 18, 2016.
 37. Kim J, Weispfenning R. Medtronic receives FDA approval for world's first hybrid closed loop system for people with type 1 diabetes. Medtronic. 2016. <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=2206594>. Accessed Nov 11, 2016.
 38. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, Kaufman FR. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. *JAMA.* 2016;316(13):1407-1408. doi:10.1001/jama.2016.11708
 39. Adlyxin ® [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2016.