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Research Updates

Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth[1-9]

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Background: Vaginal candidiasis affects an estimated 10% of pregnant women in the United States.1 Intravaginal topical azoles are considered first-line treatment in pregnancy, but oral fluconazole is used in cases of recurrence, severe symptoms, topical treatment failure.2 Oral fluconazole may also be used as initial treatment in accordance with patient preference.3 Available evidence regarding the safety of oral fluconazole use in pregnancy is unclear. Case reports have linked high-dose, long-term fluconazole in pregnancy with craniofacial, skeletal, and heart defects.3-7 The majority of epidemiologic studies examining the birth defect risk in maternal fluconazole exposure "were not large enough to examine individual birth defects or focused on birth defects overall."8 A recent population-based, case-control study of reported birth defects in the United States from 1997 to 2011 found fluconazole use was associated with cleft lip, cleft palate and d-transposition of the great arteries.8 Few studies have investigated the risk for spontaneous abortion and stillbirth after maternal fluconazole exposure and have found no association. Their combined sample of 1512 women may have lacked sufficient power to detect a moderate risk increase.9

Objectives: This study evaluated the association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth.

Study Design: This was a nationwide register-based cohort study including all pregnancies ending with a singleton live birth, stillbirth, spontaneous abortion, or other abortive outcome in Denmark from 1997 to 2013. Maternal exposures were obtained from national prescription registries. Cases of spontaneous abortion were defined as pregnancy loss from 7 to 22 gestational weeks and stillbirth was defined as pregnancy loss from 23 weeks. Records of abortive outcomes in gestational weeks 0-6 and oral azole antifungal exposure 4 weeks prior to pregnancy onset through week 6 of gestation were excluded.

Each fluconazole-exposed pregnancy was matched to up to 4 unexposed control pregnancies based upon propensity scores, maternal age, calendar year, and gestational age. A number of other comparators were analyzed to control for possible confounders. Each oral fluconazole-exposed pregnancy was matched to one topical azole-exposed pregnancy and one pivmecillinam-exposed pregnancy (a prescription-only penicillin used as first-line treatment of urinary tract infection during pregnancy in Denmark) to assess impact of vaginal candidiasis infection and systemic anti-infective treatment. Maternal fluconazole exposure during pregnancy was compared to exposure in the year prior to pregnancy onset. Cases of oral itraconazole exposure were examined in association with spontaneous abortion risk to explore the potential impact of a class effect. To investigate potential dose-dependent mechanisms, low (150-300 mg) and high (350-5600 mg) doses of fluconazole were compared.

Results: Fluconazole exposure demonstrated a significantly increased risk of spontaneous abortion (HR 1.48 [95% CI 1.23-1.77]). Increased risk of stillbirth in fluconazole-exposed pregnancies was not statistically significant (HR 1.32 [95% CI 0.82-2.14]). In other comparator groups, oral fluconazole-exposed pregnancies were at significantly increased risk of spontaneous abortion compared with topical azole-exposed pregnancies (HR 1.62 [95% CI 1.26-2.07]). Timing of fluconazole exposure in pregnancy did not affect risk of spontaneous abortion or stillbirth.

Table 1. Hazard ratios (HR) of Fluconazole Exposure in Pregnancy and Risk of Spontaneous Abortion and Stillbirth in a Matched Cohort

Oral Fluconazole Exposure Versus:	Risk of Spontaneous Abortion (HR)	Risk of Stillbirth (HR)
Unexposed Control Pregnancies	1.48*	1.32
Topical Azole Exposure	1.62*	1.18
Pivmecillinam Exposure	1.44*	2.38*
Fluconazole Exposure the Year Prior to Pregnancy	1.23	1.43
Itraconazole Exposure	1.16	Unpublished
High-Dose Oral Fluconazole	1.55	4.10*
Low-Dose Oral Fluconazole	1.47*	0.99

Conclusions: Use of oral fluconazole in pregnancy was associated with statistically significant increased risk of spontaneous abortion compared with risk among unexposed women and women with topical azole exposure. The overall rate of stillbirth was not significantly increased; however, sensitivity analysis implicates higher fluconazole doses may increase risk. A small number of itraconazole-exposed pregnancies left authors unable to conclude whether fluconazole findings were representative of a shared class effect.

Key Point: Until further investigation, oral fluconazole for vaginal candidiasis should be prescribed cautiously in women who are pregnant or may become pregnant in the near future.

Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial[10-12]

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Background: Smoking cessation continues to be an important issue to address with patients at every encounter given the morbidity and mortality associated with smoking.[2] Two pharmaceutical options frequently used for smoking cessation are combination nicotine replacement therapy (C-NRT) and varenicline (Chantix®). C-NRT and varenicline differ in the need for a prescription, cost, and monitoring requirements. Previous clinical trials and meta-analyses have shown superiority of both varenicline and C-NRT over other monotherapies, although the two options have not been directly compared in randomized clinical trials.

Objective: To compare the effectiveness of the nicotine patch, varenicline and C-NRT for smoking cessation.

Study Design: This study was a randomized, open-label trial that took place between May 2012 and November 2015. Patients were assigned to one of three treatment groups, nicotine patch monotherapy, varenicline or a combination of the nicotine patch and nicotine lozenges, for twelve weeks. Treatment also included six counseling sessions for all three groups.

Eligible patients were >17 years old, smoking ≥ 5 cigarettes per day, had a desire to quit but were not currently treated, and females were using birth control. Exclusion criteria included exhaled carbon monoxide levels < 4 ppm, end-stage renal disease on dialysis, prior suicide attempts within the last 5 years or current suicidal ideation, diagnosis of or treatment of psychoses in the last 10 years, moderately severe depression, untreated hypertension > 200/100 mmHg, current use of bupropion, hospitalization in the last year for stroke, myocardial infarction, heart failure or diabetes, use of other forms of tobacco more than twice in a week and the presence of specific cardiac abnormalities.

The primary endpoint of the trial was self-reported 7-day point-prevalence abstinence at 26 weeks post-target quit date confirmed by carbon monoxide levels (≤5 ppm). Secondary outcomes included abstinence from smoking at 4, 12 and 52 weeks, and initial abstinence, defined as abstinence of at least 24 hours in the first week of treatment. Withdrawal symptoms were also studied. The trial was designed to have greater than 80% power based on 26-week abstinence rates of 24% for the patch (n =227) and above 34% for the varenicline and C-NRT groups (n = 387 per group) as well as 80% power to

detect a difference in abstinence rates > 9% between the varenicline and C-NRT groups.

Results: A total of 1086 patients were included in the study. The majority of patients were white (67%) and about half were female. The mean age was 48.1 years and mean cigarette use was 17 per day. Previous use of medication for smoking cessation was reported by 70.6% of patients.

Abstinence rates at 26 weeks were 22.8% for the patch (n=241), 23.6% for varenicline (n=424) and 26.8% for C-NRT (n=421). Risk differences for each comparison were not statistically significant. At 52 weeks, abstinence rates were lower in each group compared to rates at 26 weeks and did not differ significantly between the three groups. The rate of initial abstinence was greater in the N-CRT group compared to the varenicline group (80.5% vs 68.2%). No interaction between dependence and treatment was observed. Withdrawal ratings were significantly lower in the C-NRT group and varenicline group when compared to monotherapy but there was not a difference between C-NRT and varenicline. Adverse events including vivid dreams, insomnia and nausea were more common with varenicline compared to the nicotine patch. Medication adherence rates at week eight were less than 50% for all groups.

Conclusions: Comparison of nicotine patch monotherapy, varenicline and C-NRT showed no difference in abstinence rates at 26 or 52 weeks. Smaller differences in cessation rates between treatment modalities were observed in this trial compared to previous meta-analyses conducted. Limitations of the present trial include recruitment of highly motivated participants, open-label design, and low adherence rates to study medications.

Key Point: The results of this trial showed no difference in abstinence rates between nicotine patch monotherapy, C-NRT or varenicline when used in addition to counseling sessions for 12 weeks. Other patient-specific factors should be evaluated when determining appropriate therapy for smoking cessation including past medical history, potential adverse events and cost.

Medical Marijuana and Migraines[13-14]

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Background: Naturally occurring phytocannabinoids from the cannabis plant can stimulate the endocannabinoid system in the human body. It is theoretically plausible that using medical marijuana to target receptors in this endocannabinoid system may help treat diseases such as fibromyalgia and migraines. Cannabinoids have been studied and are known to affect both serotonin and dopamine pathways.[1] However, there is no previous research studying the efficacy and safety of marijuana for migraine relief.

Objective: The purpose of this study was to evaluate the frequency of migraines in patients who were using medical marijuana.[2]

Study Design: This study was a retrospective, observational chart review of 121 adult patients, ages 18 to 89 years old, at two Gedde Whole Health medical marijuana clinics in Colorado from January, 2010 through September, 2014. The patients were referred to the clinics for treatment and/or prophylaxis of their primary diagnosis of migraine headaches, and patients were only included if they had at least one follow-up session. Demographic data as well as information about the type, amount, and frequency of marijuana use were collected. The primary outcome of this study was monthly migraine frequency with medical marijuana use. Secondary outcomes of this study included evaluating the type and dose of marijuana used, previous and adjunctive migraine therapies, and patient-reported positive and negative effects of the medical marijuana. Results were analyzed using a two-tailed paired t-test.

Results: Average migraine frequency decreased from 10.4 to 4.6 events per month ($p<0.0001$). Of the total patients in the study, 85.1% reported decreased migraine frequency, while 12.4% and 2.5% reported no change or an increase in frequency, respectively. Patients used various forms of marijuana, including vaporized (42 patients), topical (15 patients), smoked (65 patients), and edible (66 patients). Most patients (51.2%) used multiple forms for both treatment and prophylaxis, usually with daily use. Inhaled marijuana was often effective at eliminating acute migraines. The most common negative effects from marijuana therapy were reported with edible forms, which included somnolence and difficulty controlling effects in relation to timing and intensity of dose.

Conclusions: The frequency of migraines was decreased with medical marijuana use and inhaled marijuana was able to treat acute migraine headaches. Future prospective studies evaluating the effects from various forms of marijuana on migraine relief may help further determine its place in therapy, especially if in comparison to current treatments.

Limitations: This study was retrospective and did not have a direct comparator group, which limits the utility and applicability of its results. Many different types of marijuana were used, often in combination, which also

makes it difficult to detect differences among the different forms. In addition, over half of the selected patients did not follow-up, and information obtained from chart documentation was sometimes brief and inconsistent.

Key Point: Daily medical marijuana use may have the potential to help reduce the frequency of migraine headaches. However, more research is needed and there are other effective, federally legal therapies that can be used, such as beta-blockers and tricyclic antidepressants for migraine prophylaxis and 5-HT agonists for migraine treatment.

Fresh vs. Frozen FMT for recurrent and refractory *Clostridium difficile* infection[15-17]

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Background: *Clostridium difficile* infections (CDI) occur in the setting of colonic dysbiosis. Initial first-line antimicrobial therapy with metronidazole and vancomycin have respective eradication rates of 87% and 97%.[1] Their utility is limited by both increased incident and age progressive recurrence rates (25% to 65%), evolving microbial resistance (NAPI/B1/027), and broad colonic microflora insult.[1,3] Colonic microflora restoration by fecal microbiota transplantation (FMT) has emerged as an effective and reliable treatment for CDI not responding to current therapy.[1,2] FMT logistical and procedural complications include donor availability, on-site laboratory facilities for infectious agent and parasite screening, an unstandardized administration route (nasogastric, endoscopic, colonoscopic, and retention enema), an undefined infusion volume (dose size), and poorly compared stability (fresh vs. frozen).[1,2]

Objective: To determine if the efficacy and safety of frozen-and-thawed FMT is non-inferior to fresh FMT in the treatment of recurrent and refractory CDI.

Study Design: The study was a double-blind, randomized, non-inferiority clinical trial conducted at six academic medical centers in Canada from July 2012 to September 2014 involving 232 participants. Participants were 18 years or older with a history of recurrent or refractory CDI. Patients with neutropenia ($<0.5 \times 10^9$/L), high peripheral white blood cell counts ($> 30.0 \times 10^9$/L), toxic megacolon, or only a single recurrence of CDI (unless the most recent episode became refractory to treatment) were excluded. Frozen-and-thawed samples were stored at -20°C for a maximum of 30 days. Fresh samples were delivered by enema within 24 hours of collection and frozen samples delivered by enema within 24 hours of thawing. The primary efficacy endpoints were safety and no recurrence of *Clostridium difficile* diarrhea at 13 weeks with up to two FMT and no utilization of antibiotics for recurrence.

Results: In the per-protocol population, clinical resolution occurred in 83.5% of patients in the frozen FMT group vs. 85.1% in the fresh FMT group (difference, -1.6% [95% CI -10.5% to ∞]; p=0.01 for non-inferiority). In the modified intention to treat population, clinical resolution rates were 75.0% vs. 70.3% in the frozen and fresh groups, respectively (difference, 4.7% [95% CI -5.2% to ∞]; p< 0.001 for non-inferiority). There were no observed differences in comparative safety between the two groups.

Conclusions: Frozen-and-thawed FMT is non-inferior to fresh FMT when delivered as an enema for recurrent or refractory CDI. There have been some higher cure rates reported in systematic reviews, although these reviews were retrospective, not controlled, and had variability in patient population and delivery of FMT.[2]

Key Point: Frozen FMT is non-inferior to fresh FMT, is stable (can be transported), reduces temporal donor and prescreening issues, and provides a suitable product for facilities lacking comprehensive screening capability. Due to the brevity of study times, long-term safety data is needed for all FMT.

Rates of Deintensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients with Diabetes Mellitus[18-21]

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Background: In everyday practice, the primary focus of blood glucose and blood pressure (BP) management is to intensify treatment until a target level is achieved, frequently A1c <7.0% or BP < 140/90 mm Hg. Overtreatment is common among older, medically complex patients, which can result in significant harm. Recently, the American Diabetes Association and American Geriatrics Society have begun acknowledging the potential harm in overtreatment resulting in very low BP and A1c levels. The JNC8 Guidelines for Management of High Blood Pressure have also made recommendations for lower BP targets in older adults. Despite these considerations, deintensifying treatment can be met with resistance from both healthcare workers and patients alike. In addition, there are no specific recommendations on deintensifying treatment in elderly patients.

Objective: To explore the rate of BP and blood-glucose lowering medicine deintensification in older adults with type 1 or 2 diabetes.

Study Design: This was a retrospective cohort study using data from the US Veterans Health Administration from January 1 to December 31, 2012. Cohorts included all active primary care patients 70 years or older with a diagnosis of diabetes receiving treatment for elevated glucose or BP control. In the BP cohort, patients were excluded if they were only receiving low-dose ACE or ARB monotherapy for BP control. In the A1c cohort, patients were excluded if they were only taking metformin for glucose control. Patients were then stratified based on baseline BP or A1c in the following categories: *very low BP*: systolic BP(SBP) <120 mm Hg or diastolic BP(DBP) <65 mm Hg, *moderately low BP*: SBP 120-129 mm Hg or DBP <65 mm Hg, *not low BP: SBP ≥130 mm Hg and DBP* ≥65 mm Hg, *high BP: SBP* ≥140 mm Hg or DBP ≥90 mm Hg, *very low A1c:* <6.0%, *moderately low A1c*: 6.0-6.4%, *not low A1c:* ≥6.5%, *high A1c:* >7.5%. Patients with *very low* or *moderately low* BP or A1c were considered to be receiving potential overtreatment. Life expectancy was also taken into account using the Charlson Comorbidity Index derived from VA administrative data. Higher scores correlated with lower life expectancy.

Results: 211,667 patients were included in the BP cohort. Of these patients, 25,955 (12.3%) received treatment to get to a moderately low BP level, and 81,226 (38.4%) developed very low BP. There was only a slightly higher rate of deintensification in patients with *moderately low* or *very low* blood pressure (16.0% and 18.8%, respectively) compared to those with a blood pressure that was *not low* (15.1%). 179,991 patients were included in the A1c cohort. Of these patients, 23,769 (13.2%) patients received treatment to a *moderately low* A1c, and 12,917 (7.2%) had a *very low* A1c due to treatment. There was only a slightly higher rate of deintensification in patients with *moderately low* or *very low* A1c (20.9% and 27.0%) compared to those with an A1c that was *not low* (17.5%). BP and A1c rarely increased to elevated levels in patients who were eligible but did not have a medication reduction. In the *very low* BP group, 28.1% of patients had persistently low BP levels with only 0.2% reaching a BP of 140/90 mm Hg or higher. In the *very low* A1c group, 16.9% of patients had a low A1c at 6 month follow-up, with fewer than 0.8% having an A1c of 7.5% or higher. Life expectancy was weakly associated with the rate of deintensification in all groups.

Conclusions: Deintensification of therapy following low BP or A1c is not common among elderly patients with diabetes. Whether deintensification leads to clinical harm warrants further investigation.

Key Point: Elderly patients who may benefit from deintensification of therapy regimens rarely receive this benefit. Harms of overtreatment have yet to be rigorously evaluated or included in clinical guidelines. It is important to always consider the risks and benefits of treatment, especially in vulnerable populations.

New Drug Updates

Basaglar® (insulin glargine injection) 100 units/mL, for subcutaneous use – Eli Lilly and Company[22-27]

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Indication and Classification: Basaglar® (insulin glargine injection) is a long-acting, 100 unit/mL human insulin analog. As the first insulin product approved as a "follow-on product" by the FDA, Basaglar was able to prove itself similar enough to Sanofi-Aventis's Lantus®, and use efficacy and safety evidence for Lantus® to support its approval. While the product is classified a biosimilar in other countries, United States (U.S.) law and Food and Drug Administration (FDA) regulation placed the product's approval in a separate process from biosimilar approval. Basaglar® has received approval for all indications listed for Lantus®.

Mechanism of Action: Basaglar®, like any insulin, primarily works by increasing peripheral glucose uptake and by inhibiting hepatic glucose production. A euglycemic clamp study involving 91 healthy adults given a 0.5 unit/kg bolus subcutaneously indicated sustained glucose lowering effect over 24 hours with no pronounced peak and a maximum effect at a median time of 12 hours after injection. Pharmacokinetic profile as determined by serum insulin concentrations during this study confirmed these results. This gives Basaglar® a similar pharmacokinetic/pharmacodynamic profile to Lantus®.

Dosage and Administration: Basaglar® will be supplied only in a 5-pen box of 3 ml prefilled KwikPens. Pens should be refrigerated and can be stored at room temperature for 28 days used or unused. Recommended starting doses are approximately one-third of the total daily insulin requirements for patients with type 1 diabetes and 0.2 units/kg or up to 10 units daily for patients with type 2 diabetes. It can be interchanged unit

for unit with other forms of U-100 insulin glargine such as Lantus®.

Efficacy: Eli Lilly and Company, in pursuit of the approval of Basaglar®, was able to partially rely on efficacy data from Lantus®. In addition to Lantus® data, two trials comparing Basaglar® to Lantus® and another non-U.S.-approved insulin glargine 100 units/mL product both found Basaglar® to be non-inferior to the other products in the primary outcome of lowering of HgA_{1C} values. The ELEMENT 1 study looked at 535 adults with type 1 diabetes in a 24-week, open-label, active-controlled study with a 28-week extension; patients were randomized to mealtime insulin lispro plus one of the three insulin glargine products. The ELEMENT 2 study looked at 759 adults with type 2 diabetes in a 24-week, double-blind, active-controlled study; patients were randomized to one oral antidiabetic medication plus one of the three insulin glargine products. Included patients had been taking two oral antidiabetic medications and had HgA_{1C} levels between 7-11% (60.6% of patients, n=460) or two oral antidiabetic medications plus insulin glargine and had HgA_{1C} levels $\leq$ 11% (39.4% of patients, n=299).

Safety: Analysis of pre-specified safety endpoints from both the ELEMENT 1 and ELEMENT 2 trials was conducted. There was no statistically significant difference in rates of hypoglycemia, injection-site reactions, or adverse events between Basaglar® and other insulin glargine products. Only three endpoints reached a statistically significant difference: weight gain in ELEMENT 1, overall incidence of detectable insulin antibodies in ELEMENT 2, and serious adverse events in ELEMENT 2. However, none of the findings were consistent across both studies, nor appeared to be clinically meaningful differences.

Place in Therapy: Basaglar® will be available Dec 15, 2016 in the United States. Feel comfortable switching between Basaglar® and Lantus® without concern. Eli Lilly and Company has not set a price for the drug, but practitioners can expect it to be priced 10-20% below Lantus®, following European trends where both products have been on the market for the past year.

Therapeutic Thoughts

Treatment of Venous Thromboembolism[28-36]

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Background: The 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis CHEST guidelines, published in 2012, recommends those requiring treatment with antithrombotic therapy due to a venous thromboembolism (VTE) be treated with a vitamin K antagonist. Although dabigatran and rivaroxaban were approved prior to the publication of the 9th edition CHEST guidelines, their use was not widespread. The four direct oral anticoagulants that are now on the market, dabigatran, rivaroxaban, apixaban, and edoxaban, are changing the recommendations for treatment of VTEs. The American College of CHEST Physicians recently published an Expert Panel Report to update the recommendations on antithrombotic therapy for VTE disease.

Evidence: Results from phase III noninferiority trials of direct oral anticoagulants versus vitamin K antagonists for treatment of VTEs (acute DVT and PE) showed that dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to standard/conventional therapy.[3,4,5,6,7] The RE-COVER trial showed 30 patients treated with dabigatran (2.4% of all dabigatran patients) and 27 patients in the warfarin group (2.1% of all warfarin patients) reached the primary outcome of the 6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths [95% CI -0.8 - 1.5]; p<0.001 for the prespecified noninferiority margin; HR 1.10 [95% CI 0.65 - 1.84]. EINSTEIN-DVT and EINSTEIN-PE both showed noninferiority between rivaroxaban and warfarin (with enoxaparin) with respect to primary outcome of recurrent VTE ((36 events (2.1%) with rivaroxaban, vs 51 events (3.0%) with warfarin; HR 0.68 [95% CI 0.44 - 1.04]; p<0.001) and (50 events (2.1%) with rivaroxaban vs 44 events (1.8%) with warfarin; HR 1.12 [95% CI 0.75 - 1.68]; p=0.003) respectively. The AMPLIFY trial comparing apixaban to conventional therapy (subcutaneous enoxaparin followed by warfarin) showed the primary outcome of recurrent VTE in 59 (2.3%) of apixaban patients and 71 (2.7%) in conventional patients (RR 0.84 [95% CI 0.60 - 1.18]; p<0.001 for noninferiority). Comparing edoxaban to warfarin in the Hokusai-VTE trial showed noninferiority of edoxaban to warfarin with respect to the primary efficacy outcome of recurrent symptomatic VTE (130 (3.2%) of edoxaban patients vs 146 (3.5%) of warfarin patients; HR 0.89 [95% CI 0.70 - 1.13]; p<0.001 for noninferiority).

A systematic literature search was utilized on the above trials to indirectly compare the direct oral anticoagulants for treatment of acute VTEs, with a primary efficacy endpoint of recurrent VTE and primary safety endpoint of major bleeding.[8] Although these were not head-to-head trials comparing the efficacy of each drug against each other, the studies were deemed to be highly comparable due to study design and patient inclusion and therefore are indirectly comparable. The results showed similar efficacy in the derived estimated relative risk at preventing recurrent VTEs between the four drugs and standard therapy, with suggestion that apixaban is associated with less major bleeding and major or clinically relevant nonmajor bleeding compared to dabigatran or edoxaban and rivaroxaban, dabigatran and edoxaban, respectively.

Discussion: Treatment guidelines are now recommending patients who require treatment for a VTE with a need for long-term therapy, which is considered to be the first 3 months of therapy, utilize dabigatran, rivaroxaban, apixaban, or edoxaban over a vitamin K antagonist.[2] With these four drugs having similar efficacy in preventing recurrent VTEs, individual patient characteristics should be taken into consideration when selecting a treatment agent. Adequate renal and hepatic function, drug-drug interactions, disease state interactions, body weight extremes, patient adherence, etc. should be considered when determining appropriate therapy. Guidance for the practical management of the direct oral anticoagulants in VTE treatment, published in 2016, discusses specific elements of patient profiles to consider and provides guidance on selection, initiation, and monitoring of these agents.[9]

Clinical Impact: The increased use of direct oral anticoagulants and evidence supporting the efficacy and safety in the treatment of VTEs has changed the recommendations of long-term therapy accordingly. Rivaroxaban, edoxaban, apixaban, and dabigatran are recommended over the use of vitamin K antagonists for the long-term (first 3 months) treatment of VTEs in patients without active cancer pending careful consideration of individual patient characteristics by providers and pharmacists.

2016 Updates to ADA and AACE/ACE Guidelines for Type 2 Diabetes[37-39]

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Originally approved in 1988 and updated annually, the American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" is intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.[1] The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) created the AACE/ACE Type 2 Diabetes Algorithm in 2013, which includes updates regarding new therapies, management approaches, and clinic data. AACE/ACE's updates to Type 2 Diabetes care recommendations are reflected in the January 2016 Executive Summary.[2]

The January 2016 update of the ADA's "Standards of Medical Care in Diabetes" gives guidance on tailoring treatment to specific populations, including recommendations for patients with food insecurity, cognitive dysfunction or mental illness, and HIV. Disparities related to ethnicity, culture, sex, socioeconomic differences of patients with diabetes are also discussed.[1] The AACE/ACE Type 2 Diabetes Management Algorithm continues to focus on the need to individualize therapy to the patient, especially due to certain patient populations being at higher risk for adverse treatment-related outcomes.[2] Diagnostic testing guidelines for diabetes are again addressed, as ADA 2016 recommends that no one test is preferred over another for diagnosis of diabetes. These tests include fasting plasma glucose, 2-hour plasma glucose after 75-g oral glucose tolerance test, and A1C criteria.[1]

AACE/ACE recommends that diagnosis of diabetes is best confirmed by one of three tests including established direct measures of plasma glucose (fasting plasma glucose, 2-hour post-prandial glucose and random plasma glucose). In the absence of unequivocal hyperglycemia, the same type of test should be repeated on a different day to confirm the diagnosis of DM because of glucose level variability. A1C is recommended as a secondary criterion, as it may be affected by non-glycemic factors and possibly unreliable in different ethnic groups. AACE/ACE recommends that A1C should be used only for the purpose of screening for prediabetes, and diagnosis of prediabetes should be confirmed with glucose testing.[3]

The ADA recommends testing for diabetes in all adults beginning at age 45 years, as well as asymptomatic adults of any age who are overweight or obese with one or more risk factor for diabetes. These risk factors include: physical inactivity, first-degree relative with diabetes, high-risk race/ethnicity

(African American, Latino, Native American, Asian American, Pacific Islander), women who delivered a baby weighing more than 9 pounds or with a history of gestational diabetes mellitus, blood pressure more than 140/90 mmHg or treated with antihypertensive(s), HDL cholesterol less than 35 mg/dl and/or triglycerides greater than 250 mg/dl, women with polycystic ovarian syndrome, hemoglobin A1c above 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing, other clinical conditions associated with insulin resistance (PCOS, acanthosis nigricans, NAFLD), and history of cardiovascular disease.[1] AACE/ACE 2015 recommendations for diabetes testing are similarly based on risk factors, but additionally recommends screening for diabetes in patients with metabolic syndrome, if taking antipsychotic medications or chronic glucocorticoids, and with sleep disorders in the presence of glucose intolerance.[3] ADA does note that these factors are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis.[1]

The AACE/ACE 2016 update includes a new section highlighting lifestyle therapy. Key components of lifestyle therapy include medical nutrition therapy, regular physical activity, adequate sleep, behavioral support, and smoking cessation including avoidance of all tobacco products.[2] The ADA 2016 guidelines continue to include a section for lifestyle and behavior modifications that now also ties in medication evaluation, patient engagement, ongoing care, nutrition and vaccinations.[1]

Both ADA and AACE/ACE included guidelines for obesity management in type 2 diabetes in 2016, citing the Look AHEAD study. Look AHEAD's intensive lifestyle intervention group (weight loss through decreased caloric intake and increased physical activity) participants experienced a mean weight loss of 4.7% (SE 0.2) at 8 years. Approximately 50% of intensive lifestyle intervention lost 5% and 27% lost 10% of their initial body weight at 8 years. The ADA 2016 has new recommendations related to comprehensive assessment of weight in diabetes and treating overweight and obese patients with behavior modification and pharmacotherapy.[1] AACE/ACE 2016 references the AACE/ACE Obesity Treatment Algorithm, which emphasizes a complications-centric model as opposed to a BMI-centric approach for the treatment of patients who have obesity or are overweight. Patients who will benefit most from medical and surgical intervention have obesity-related comorbidities that can be classified into 2 general categories: insulin resistance/cardiometabolic disease and biomechanical consequences of excess body weight.[2]

Recommendations for aspirin therapy for primary prevention continue to evolve. The ADA 2016 recommendations regarding aspirin therapy have changed to reflect the new evidence on ASCVD risk among women (heart disease and stroke risk is equivalent if not higher in women compared with men with diabetes), and include considering aspirin therapy in women at or above 50 years of age, instead of over 60 years; aspirin use may also be recommended in patients under age 50 years with multiple risk factors.[1] AACE/ACE has not updated aspirin recommendations since 2015, and advised that aspirin use may be considered for those at high cardiovascular risk (10-year risk >10%), although they cite that data from many clinical trials and observational studies on the use of low-dosage aspirin in the primary prevention of cardiovascular disease in patients with diabetes continues to be controversial.[3] Both the ADA and AACE/ACE recommend aspirin therapy for secondary prevention of cardiovascular events in diabetes patients.[1,2]

Based on new evidence for additional cardiovascular benefit for select diabetes patients, the ADA 2016 recommends adding ezetimibe to moderate-intensity statin in select patients.[1] The AACE/ACE 2016 guidelines also recommend ezetimibe for certain patients, citing the IMPROVE-IT results: the ezetimibe benefit was almost exclusively noted in the pre-specified diabetes subgroup, which comprised 27% of the study population and in which the relative risk of ASCVD was reduced by 14.4% ($p=0.023$).[2]

A further addition to the AACE/ACE 2016 section on lipid-lowering therapies is use of PCSK9 inhibitors in patients with clinical ASCVD who require additional LDL-C–lowering therapy.[2] The ADA guidelines also include recommendations for PCSK9 inhibitors as adjunctive therapy for patients with diabetes at high risk for ASCVD events who require additional lowering of LDL cholesterol or who require but are intolerant to high-intensity statin therapy, as they demonstrated an average reduction in LDL cholesterol ranging from 36% to 59%.[1]

Breathe Easier: Emerging Primary Care Strategies for Managing[40-44]

Asthma-Chronic Obstructive Pulmonary Disorder (COPD) Overlap Syndrome (ACOS)

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Background: Asthma has been defined as an inflammation of the airways (usually associated with allergies)[1] that is characterized by airflow obstruction and variable airflow limitation.[2] COPD is a progressive and preventable inflammatory condition characterized by persistent airflow limitation[3] in which small airways are obstructed by bronchoconstriction, excessive mucous, and breakdown of the alveolar tissue.[1] While the inflammatory mechanisms for the two conditions are usually different in etiology, pathologies can overlap with time, leading to the variable hybrid condition of persistent airflow limitation called, "Asthma-COPD Overlap Syndrome" (ACOS). ACOS's prevalence is approximately 15-45% of all people with obstructive airway disease.[1] The overlap syndrome is associated with declining lung function, increased exacerbations and hospitalizations, lower quality of life, increased morbidity and mortality, and increased total cost of care.[2,3,4]

Evidence: At present, there is no prospective, randomized controlled trial that evaluates the safety and efficacy of treatment options for asthma and COPD for the treatment of ACOS.[4] Most global guidelines address asthma and COPD as separate conditions only.[4] Patients with asthma have historically been excluded from COPD studies (and vice versa).[2,3,4] Inclusion and exclusion criteria for "ACOS patients" in existing trials have been inconsistent.[2,3] In the *New England Journal of Medicine*, Postma and Rabe conclude that "..it is almost impossible to determine the most effective therapy for the individual patient."[1] The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) authors collaborated in 2015 to provide the first ACOS guidance document to provide primary care and non-pulmonary specialists with interim direction (in the absence of evidence) to assess and treat ACOS.[2,3]

Discussion: Asthma and COPD specialists[1,4,5] (and the GINA and GOLD reporting groups)[2,3] avoid defining ACOS. Because of symptom variability, they address ACOS as a spectrum of phenotypes rather than a singularly-defined condition.[1,2,3] Such phenotypes may include patients with COPD with eosinophilia, or asthmatics with smoking histories who have developed permanent airflow limitation as a result.[5]

Empiric treatment with low-to-moderate dose inhaled corticosteroids (ICS) is recommended due to improved morbidity and mortality in asthmatics, followed by long-acting beta agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) therapy (avoiding LABA monotherapy or ICS monotherapy when asthma or COPD characteristics present, respectively).[2,3] Once-daily LABAs, LABA + LAMA combinations, and triple inhaler regimens (ICS + LABA + LAMA) may assist with convenience for patients.[5] Many experts suggest that biomarker-targeted therapy may be beneficial for many patients in the ACOS spectrum.[1,2,3,5] Non-pharmacological interventions as well as modifiable risk factors (e.g. smoking cessation), inhaler technique, adherence, and management of comorbid conditions should be supported for all patients with ACOS.[2,3] Referral is encouraged during treatment failure, when comorbidities impact treatment, or when other diagnoses must be considered.[2,3]

Clinical Impact: The 2015 GINA/GOLD ACOS guidance provides introductory insights into management of a complicated medical condition. More randomized, controlled trials are needed to evaluate ACOS phenotypic response[5] and to obtain a consensus definition of the condition.[2,3] Long-term prospective studies are needed not only to determine the role that biomarker-guided treatment plays in the management of ACOS, but to evaluate clinical outcomes from use of novel inhaler combinations.[2,3,5]

From the Pharmacy Press

Are pharmacists receiving appropriate compensation with the Medicare Resource Based Relative Value Scale?[45]

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Background: Pharmacists were not included in the Current Procedural Terminology (CPT) nomenclature used by providers to bill for their services, which was created in 1970. In 2002, the Pharmacist Services Technical Advisory Coalition

requested that pharmacists be included in the CPT billing codes and in 2005, CPT codes were created allowing pharmacists to bill for medication therapy management (MTM). In 1992, the American Medical Association (AMA) collaborated with the Centers for Medicare and Medicaid (CMS) to create the Medicare Resources Based Relative Value Scale (RBRVS) to respond to inconsistencies in billing for physician services. In 2005, MTM pharmacists were established as providers in the state of Minnesota and it was mandated that MTM services be covered if the beneficiary was a part of medical assistance. Due to this requirement, the Minnesota Department of Human Services (DHS) created an MTM Advisory Committee to create an RBRVS for MTM which based reimbursement on the patient's number of conditions, number of medications, and number of drug therapy problems.

Objective: This study aimed to compare the actual billing amounts through RBRVs versus time-based billing for MTM services through analysis of reimbursement claims, which were submitted between November 1st, 2007 and April 22nd, 2014 at a University of Minnesota, Duluth, based MTM clinic.

Study Design: A retrospective, single-centered study published by Hager and Gosser in January of 2016 reviewed claims submitted by the MTM clinic from a single payer that used RBRVS exclusively. Exclusion criteria included patients who had not signed the clinic intake consent form or if a patient was not seen face-to-face (as non-face-to-face visits were not billable). The time spent with each patient was found in the encounter note and was used to determine time-based billing claims. A paired t-test was used to compare the dollars billed for RBRVS versus time-based billing. Multivariate linear regression analysis was conducted to discern the average patient age, number of medical conditions, number of medications, and number of drug therapy problems (DTPs).

Results: A total of 1024 claims were found by the MTM clinic during the study period; however, after applying exclusion criteria 525 claims involving 60 patients were analyzed. Average values were found to be: mean patient age of 62±9 years, mean number of medical conditions per encounter was 9±4, mean number of medications was 12±6, mean number of DTPs was 1±1, and mean patient encounter time was 47±18 minutes. The average billable amount per time-based billing was found to be \$111.83±\$34.55 versus the average billable amount for RBRVS was \$83.71±\$36.67. RBRVS was billed at a lower amount than time-based by an average of \$28.12±\$37.34 per encounter.

Conclusions: This study was limited in its scope as it was completed with a small, nonrandomized, retrospective sample of patients from one MTM clinic in Minnesota and, therefore, the results may not be valid for other MTM practices. The study concludes that the RBRVS used for MTM services in Minnesota should be reevaluated to ensure that it correctly aligns with the cost of resources required to provide these services.

Key Point: The current Medicare Resource Based Relative Value Scale method may not be providing full compensation pharmacists should receive due to the lack of alignment with the costs of providing medication therapy management to patients.

Miscellaneous News

Zika Virus: What's the Buzz About?[46-51]

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On Monday, February 1st 2016, the World Health Organization (WHO) declared Zika virus a global health emergency following concerning increases in the rates of birth defects and Guillan-Barre Syndrome (GBS).[1] Although originally discovered over 60 years ago in the country of Uganda, the most recent outbreak has occurred in the Western Hemisphere.[2] The virus is transmitted by the *Aedes* species of mosquitos that is found throughout South and Central America as well as some areas of the United States.[1] This species is also known to sometimes carry the Dengue and Chikungunya viruses.[2] It is primarily active during the day, but is also known to bite at night. Only about 20% of those infected with the Zika virus will experience symptoms. Typically mild, the symptoms of Zika virus include fever, skin rash, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms usually last around 2-7 days.[2] The most concerning, potential adverse health outcomes

include GBS and the birth defect, microcephaly. Babies born with microcephaly have smaller than expected heads and brains, which can be linked to seizures, developmental delays, intellectual disabilities, feeding problems, vision problems, hearing loss, and balance problems.[3] It is unclear when the highest risk for infection is for a pregnant woman or how long the fetus is susceptible to these outcomes once someone is infected.[4]

At this time there is no treatment or vaccine available against the Zika virus. Taking steps to prevent getting bitten by mosquitos and limit exposing the virus to others is the best defense at this time. Mosquito bite prevention includes a combination of wearing long-sleeved shirts, long pants, treating clothing with permethrin, and using insect repellent.[4] For pregnant women, safe repellant ingredients include DEET, picaridin, and IR3535.[4] Additionally, safe accommodations include those that provide air conditioning or screens on both doors and windows. At night mosquito netting should be used to help lower the risk of mosquito bites. Based on current evidence, it appears that the virus is present in the blood of non-pregnant females for about one week in those presenting with symptoms, but may persist in the semen of males for an unknown period of time.[4,5] Conception after viremia has resolved is not currently thought to lead to fetal infection, but the CDC is recommending women wait at least 8 weeks after their first symptoms before trying to get pregnant to minimize risks.[4,6] Because the role of sexual transmission is unknown at this time, condoms should be used to decrease the spread of infection to others for at least 6 months after symptoms started for men who are infected and 8 weeks for those who travel to an area with known Zika virus.[5,6]

As one of the most accessible healthcare professionals, it is important that our profession stays up to date on major public health concerns. With nearly daily updates, pharmacists and the public should refer to the Centers for Disease Control and Prevention (CDC) for the latest available information.

Avandia Restrictions Lifted[52-54]

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The controversy surrounding rosiglitazone appears to have finally been put to bed by the FDA. As of December 2015, all restrictions related to rosiglitazone-containing products have been lifted and the Risk Evaluation and Mitigation Strategy (REMS) has been eliminated.[1] The history of rosiglitazone has been filled with safety concerns and FDA restrictions since first coming onto the market in 1999.

In 2007, concerns about cardiovascular safety began to come into question. A meta-analysis of 42 clinical trials involving over 14,000 patients, mostly comparing Avandia to placebo, showed an increased risk of myocardial ischemic events including angina and myocardial infarction. There were three alternative studies comparing Avandia to other oral antidiabetic agents or placebo that failed to make the same connection. At that time, GlaxoSmithKline (GSK) agreed to add the black box warning that cautioned about the potential of cardiovascular risks.[2] In 2008, those prescribing and dispensing rosiglitazone were required to participate in a REMS program to ensure safe prescribing of the medication. In 2010, the FDA stated that rosiglitazone was to be restricted to “patients with type 2 diabetes who could not control their diabetes with other medications.”[3]

In 2013, the results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial demonstrated no elevated risk of heart attack or death in patients being treated with Avandia. This led to a recommendation that the REMS program and restrictions surrounding rosiglitazone be removed.[3] Finally, as of December 16, 2015, all restrictions regarding rosiglitazone and its prescribing, have been lifted.[1]

References

1. Cotch MR, Hillier SL, Gibbs RS, et al. Epidemiology and outcomes associated with moderate to heavy candida colonization during pregnancy. Vaginal Infections and Prematurity Study Group. *Am J Obstet Gynecol*. 1998;178(2):374-380.
2. Eckert LO. Clinical practice: acute vulvovaginitis. *N Engl J Med*. 2006;355(12):1244-1252.
3. Tooley PJ. Patient and doctor preferences in the treatment of vaginal candidosis. Practitioner. 1985;229(1405):655-660.
4. Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet*. 1997;72:253-256.
5. Lee BE, Feinberg M, Abraham JJ, et al. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J*. 1992;11:1062-1064.
6. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol.* 2005;73:919-23.
7. Pursley TJ, Blomquist IK, Abraham JJ, et al. Fluconazole-induced congenital anomalies in three infants*. Clin Infect Dis*. 1996;22:336-340.
8. Howley MM, Carter TC, et al. Fluconazole use and birth defects in the national birth defects prevention study. *Am J Obstet Gynecol.* 2015. doi: 10.1016/j.ajog.2015.11.022
9. Molgaard-Nielsen D, Svanstrom H, et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67.
10. Baker TB, Piper ME, Stein JH, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *JAMA*. 2016;315(4):371-9.
11. Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses – United States, 2000-2004. MMWR Morb Mortal Wkly Rep. 2008;57 (45):1226-1228.
12. Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Rockville, MD: Dept of Health and Human Services; 2008.
13. Russo EB, Grotenhermen F, eds. Handbook of Cannabis Therapeutics: From Bench to Bedside. Binghamton, NY: Haworth Press; 2006:69–116.
14. Rhyne DN, Anderson SL, Gedde M, et al. Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population. Pharmacotherapy. 2016. [Epub ahead of print] doi: 10.1002/pharm.1673
15. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of clostridium difficile infection: a systematic review. *J Clin Gastroentrol*. 2014;48(8):693-701.
16. Lee CH, Steiner T, Petrof EO, et al. Frozen vs. fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent clostridium difficile infection: a randomized clinical trial. *JAMA*. 2016;315(2):142-149.
17. Lee CH, Steiner T, Petrof EO, et al. Frozen vs. fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent clostridium difficile infection: a randomized clinical trial. *JAMA*. 2016;315(2 Suppl 1):S1-19.
18. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. *JAMA Intern Med.* Oct 2015;175(12):1942-1949. doi:10.1001/jamainternmed.2015.5110.
19. Inzucchi SE, Bergenstal RM, Buse JB, et al. American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35(6):1364-1379.

20. Kirkman S, Briscoe VJ, Clark N, et al. Consensus development conference on diabetes and older adults. Diabetes in older adults: a consensus report. *J Am Geriatr Soc.* 2012;60(12):2342-2356.
21. James PA, Oparil S, Carter Bl. et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311(5):507-520.
22. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab*. 2015;17(8):734-41.
23. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015;17(8):726-33.
24. Hadjiyianni I, Dahl D, Lacaya LB, et al. The efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine. *Diabetes Obes Metab*. 2016. doi: 10.1111/dom.12628.
25. Linnebjerg H, Lam EC, Seger ME, et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies. *Diabetes Care*. 2015;38(12):2226-33.
26. FDA approves Basaglar, the first "follow-on" insulin glargine product to treat diabetes. Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm. Accessed Feb 20, 2016).
27. Basaglar® (insulin glargine injection), for subcutaneous use. Eli Lilly and Company. Revised 12/2015. Available from: http://pi.lilly.com/us/basaglar-uspi.pdf. Accessed February 20, 2016.
28. Guyatt G, Akl E, Crowther M, et al. Executive summary: antithrombotic therapy and prevention of thrombosis 9th ed: American College of CHEST Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(Suppl):7S-47S.
29. Kearon C, Akl E, Ornelas, J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016.
30. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342–2352.
31. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–2510.
32. EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287–1297.
33. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799–808.
34. The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406–1415.
35. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. *J Thromb Thrombolysis*. 2014;39(2):155–165.
36. Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016;41(1):206–232.
37. American Diabetes Association. Standards of Medical Care in Diabetes - 2016. *Diabetes Care*. 2016; 39(Suppl. 1):S1–S112.
38. Garber A, Abrahamson M, Barzilay J, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm- 2016 executive summary. *Endocrine Practice*. 2016;22(1): 84-113.
39. Handelsman Y, Bloomgarden Z, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2015. *Endocrine Practice*. 2015; 21(Suppl. 1): 84-113.

40. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. *NEJM.* 2015;373:1241-9.
41. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2015. http://www.ginaasthma.org/local/uploads/files/GINA_Report_2015_May19.pdf. Accessed February, 2016.
42. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2015. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed February, 2016.
43. Reddel HK. Treatment of overlapping asthma-chronic obstructive pulmonary disease: can guidelines contribute in an evidence-free zone? *J Allergy Clin Immunol.* 2015;136(3): 546-52.
44. Barnes PJ. Therapeutic approaches to asthma-chronic obstructive pulmonary disease overlap syndromes. *J Allergy Clin Immunol.* 2015;136(3): 531-45.
45. Hager K, Ren G. Retrospective analysis of billing at a standalone medication therapy management clinic. *J Health Syst Pharm.* 2016;73(2):78-82.
46. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. WHO Statement. World Health Organization.http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/. Accessed February, 2016.
47. Zika virus. WHO Fact Sheet. World Health Organization. http://www.who.int/mediacentre/factsheets/zika/en/. Accessed February, 2016.
48. Facts about microcephaly. Centers for Disease Control and Prevention. http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html. Accessed February, 2016.
49. Oduyebo T, Petersen EE, Rasmussen SA, et al. Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016. MMWR Morbidity and Mortality Weekly Rep 2016;65. http://www.cdc.gov/mmwr/volumes/65/wr/mm6505e2.htm. Accessed February, 2016.
50. Oster AM, Brooks JT, Stryker JE, et al. Interim guidelines for prevention of sexual transmission of Zika virus – United States, 2016. MMWR Morbidity and Mortality Weekly Report 2016; 65(5). http://www.cdc.gov/mmwr/volumes/65/wr/mm6505e1.htm. Accessed February, 2016.
51. CDC Issues Updated Zika Recommendations: Timing of Pregnancy after Zika Exposure, Prevention of Sexual Transmission, Considerations for Reducing Unintended Pregnancy in Areas with Zika Transmission. CDC. March 25, 2016. http://www.cdc.gov/media/releases/2016/s0325-zika-virus-recommendations.html
52. Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm477601.htm. December 16, 2015. Accessed February 18, 2016.
53. FDA Issues Safety Alert on Avandia. Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm. November 14, 2007. Accessed February 17, 2016.
54. FDA requires removal of certain restrictions on the diabetes drug Avandia. Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm. November 25, 2013. Accessed February 17, 2016.