Background: The commercially available live-attenuated herpes zoster vaccine (Zostavax, Merck) confers only 51.3% immunity against herpes zoster in patients 50 years of age and older. Zostavax efficacy declines as age at vaccination increases and is contraindicated in immunocompromised patients. An experimental, recombinant subunit herpes zoster vaccine (HZ/su) has undergone phase I and II clinical trials in older adults where it has produced robust immunity and acceptable safety.

Primary Objective: In this phase III clinical trial, the primary objective was to assess whether two doses of HZ/su administered 2 months apart reduces the risk of herpes zoster in adults 50 years of age or older.

Study Design: This randomized, placebo-controlled, phase III study was conducted in 18 countries. It enrolled patients who were 50 years of age or older without a history of herpes zoster infection, herpes zoster vaccination or immunosuppression. A total of 15,411 patients were randomized, 1:1, to receive 2 doses of study vaccine or placebo and were followed for 30 months. Study groups were stratified based on age: 50-59 years, 60-69 years and 70 years or older. Unsolicited adverse events were recorded for 30 days after each dose. Severe adverse events were recorded for 12 months after each dose. Results: After randomization, 7698 patients received study vaccine and 7713 patients received placebo. After the follow-up period, 6 confirmed cases of herpes zoster were determined in the study vaccine group. In the placebo group, 210 confirmed cases of herpes zoster were determined. The relative incidence rate was 0.3 and 9.1 per 1,000 person years in the study vaccine group and placebo group, respectively. This produced an overall vaccine efficacy of 97.2% (95% CI [93.7-99.0%]), p<0.0001. Vaccine efficacy did not differ significantly between age groups. Both injection-site and systemic reactions occurred in both groups. The most common injection site reaction was pain. Pain occurred in 79.1% of patients in the vaccine study group and 11.2% in the placebo group. The most common system reaction was myalgia and occurred in 46.3% of vaccine study group patients and 12.1% of placebo study group patients. Serious adverse event rates did not differ between groups (1.1% in vaccine study group and 1.3% in placebo group). Adverse events did not appear to deter patients from receiving the second dose of vaccine.
Conclusions: In this study, HZ/su conferred robust immunity that did not decline with increasing age at immunization. The incidence of serious adverse events is low and appears to be similar to the rate in placebo. The large majority of injection-site and systemic reactions were considered mild-to-moderate and did not impact rates of patients receiving the second vaccine dose. In other phase I and II clinical studies, there is evidence of safety and efficacy in immunocompromised patients. The findings of this study are clinically relevant in that, if approved, this vaccine could confer robust immunity in patients at increased risk for herpes zoster infections and reduce associated morbidity and mortality, irrespective of age. More research must be conducted to guide practice in previously vaccinated patients, immunocompromised patients and patients with a history of herpes zoster infection.

Key Point: An experimental, recombinant subunit herpes zoster vaccine in phase III clinical trials confers 97% immunity to herpes zoster infection in patients 50 years of age and older and appears resistant to immunosenesence while providing acceptable safety. More research is required for use in immunocompromised patients as well as those who have been previously vaccinated or have suffered herpes zoster infection.

PSCK9 Inhibitors for the Treatment of Hypercholesterolemia^{3-10}
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Background: Two Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab (Repatha) and alirocumab (Praluent) have recently finished Phase 3 trials and are scheduled for FDA review in June 2015. On June 9th and 10th, 2015, the FDA’s Endocrinologic and Metabolic Drugs advisory committee recommended the approval of alirocumab and evolocumab for use in patients with primary hypercholesterolemia or mixed dyslipidemia. PCSK9 is a regulator for the expression of low-density lipoprotein receptors (LDLR). LDLR binds low-density lipoprotein (LDL) in circulation and causes it to be internalized through endocytosis. PCSK9 stimulates LDLR to be degraded which decreases the body’s capacity for removing LDL from circulation. Thus PCSK9 inhibitors allow for LDLR to be more prevalent which, in turn, decreases circulating LDL. {3} PCSK9 inhibitors were first pursued when it was noted that mutations in this gene could cause familial hypercholesterolemia (FH). {4} Treating high cholesterol levels is linked to a decrease in atherosclerotic cardiovascular disease (ASCVD). Statins are the current standard of care for people at risk for ASCVD events, but even on the highest intensity statins, many people were not able to meet their LDL goal (prior to specific goal levels being eliminated in the 2013 ACC/AHA guidelines). Also, there is a definitive group of patients that cannot tolerate statins due to side effects.

Evidence: PCSK9 inhibitors have shown a great deal of promise in their lipid lowering abilities in both FH and non-FH cholesterol elevations, as well as in patients who are intolerant to statins. In a study by Robinson et al, alirocumab was compared to placebo in patients with heterozygous FH, established coronary heart disease, or established coronary heart disease equivalent. Patients were kept on current statin therapy plus-or-minus other lipid lowering therapies. Alirocumab decreased LDL by 62% from baseline (p<0.0001), with a slight increase in injection site reaction, myalgias, and neurocognitive (deliria, confusion, memory impairment, disturbances in thinking and perception, etc. events. {5} In a different study by Sabatine et al evolocumab was tested against standard therapy alone. This was also while maintaining the patient’s current therapy. LDL levels for the evolocumab groups were decreased by 61% (p<0.001) from baseline with a slight increase in neurocognitive events. {6} In a meta-analysis by Navarese et al, PCSK9 inhibitors showed a statistically significant decrease in LDL levels (~50% decrease), increase in HDL levels (~6% increase), and decrease to total cholesterol levels (~31% decrease). {7} The meta-analysis by Navarese also showed a statistically-significant decrease in all-cause mortality and myocardial infarction (MI) with no increase in serious adverse events. {7} It should be noted that PCSK9 inhibitors are ineffective in those patients that do not express LDLR. Therefore, no benefit has been shown in patients who are homozygous for FH. {3}

Discussion: If approved, PCSK9 inhibitors are likely to be used primarily in FH patients as 2011 FH guidelines support the addition of further lipid lowering agents. FH management guidelines recommend to target at least a 50% reduction in LDL and an ideal LDL level should be <160mg/dL in these patients. {8} Thus, if patients are unable to reach these goals on maximum statin therapy (with or without other lipid lowering therapy), a PCSK9 inhibitor could be added to further reduce LDL levels.

Given the diversion from treating to LDL targets for non-FH patients in the current cholesterol guidelines, it is unclear when patients should be prescribed PCSK9 inhibitors if they do not have FH. {9} With early evidence suggesting some cardiovascular benefits, these medications may start to be added to medication regimens for patients with extensive ASCVD history or numerous cardiovascular risk factors. However, these indications may be slow to gain insurance coverage due to the high anticipated cost of the monoclonal antibodies. It is speculated that evolocumab will be available as a
140-mg biweekly subcutaneous injections and a monthly 420-mg subcutaneous injection. Alirocumab is expected to be available in biweekly subcutaneous injections of 75 mg and 150 mg. The costs for both medications could range from $5,000 to $12,000 per year.10

Clinical Impact: PCSK9 inhibitors are a novel target for treatment of hypercholesterolemia. They have shown strong decreases in LDL cholesterol and a recent meta-analysis of Phase 2 and 3 studies suggested a possible decreased risk in all-cause mortality and MIs. There have been no increases in serious adverse events. These inhibitors are yet to gain approval by the FDA, but they have been recommended for approval by an FDA advisory committee and will be considered by the FDA in July 2015. The place in practice for these medications remains to be seen since the cost will likely be prohibitive for wide spread use.

Association of Adverse Pregnancy Outcomes with Glyburide vs Insulin in Women with Gestational Diabetes 11
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Background: Uncontrolled hyperglycemia during pregnancy affects fetal development and neonatal adaptation. In 7% to 10% of women with gestational diabetes mellitus (GDM), routine lifestyle modifications are not adequate for treating GDM. Insulin is the only pharmacological treatment approved by the Food and Drug Administration (FDA) and endorsed by the American Diabetes Association (ADA) for the treatment of GDM in the United States. Alternative pharmacologic agents have limited data on safety and efficacy in this population. Limited evidence from three trials suggests that glyburide may increase risk of neonatal jaundice, hypoglycemia and birth trauma. Use of glyburide in GDM has increased drastically over the last decade and is currently widely used, however further evaluation of safety and efficacy compared to standard therapy insulin is needed.

Purpose: To estimate the risks of adverse maternal and neonatal outcomes in women with GDM treated with glyburide compared with insulin.

Study Design: This study was a retrospective cohort study of women with GDM identified in the Truven Health Analytics MarketScan Research Database from January 1, 2000 to December 31, 2011, a database that contains claims data from employer-sponsored private health insurance. Inclusion criteria consisted of women that had an International Classification of Diseases (ICD-9, ninth revision) diagnosis code for GDM prior to delivery, were continuously enrolled during the year prior to and three months after the delivery date, and had their first pharmacy claim for glyburide or insulin within 150 days of delivery. Women were excluded if they had an ICD-9 diagnosis code for Type 1 or Type 2 Diabetes, were < 15 years of age or > 45 years of age, or had diagnoses or procedure codes for pregnancy with multiple gestations. The cohort was limited to women with a first eligible pregnancy with GDM. Duration of glyburide or insulin treatment was defined as the number of days between the index date (150 days prior to delivery) and delivery date.

Results: Of 100,879 women with GDM, 9173 women (8.3%) were treated with glyburide (n = 4982) or insulin (n = 4191). The mean duration of treatment was 50.4 days with glyburide and 54.1 days with insulin. Among those treated with glyburide, 406 had a change in therapy from initial treatment, with a majority transitioning to insulin (n=333). Only 45 women treated with insulin had a change from initial treatment, with a majority (n=31) adding or switching to glyburide. After adjusting for differences at baseline, newborns of women treated with glyburide were at an increased risk for neonatal intensive care unit (NICU) admissions (RR = 1.41; 95% CI 1.23-1.62), respiratory depression (RR = 1.63; 95% CI, 1.23-2.15), hypoglycemia (RR = 1.40; 95% CI, 1.00-1.95), birth injury (RR = 1.35; 95% CI, 1.00-1.82) and large for gestational age (RR = 1.43; 95% CI, 1.16-1.76), compared to those treated with insulin. Women treated with glyburide were not at increased risk for obstetric trauma (RR = 0.92, 95% CI, 0.71-1.20), preterm birth (RR = 1.06; 95% CI, 0.93-1.21), or jaundice in newborns (RR = 0.96; 95% CI 0.48-1.91). The risk of cesarean delivery was 3% lower in the glyburide group (RR = 0.97; 95% CI, 0.93-1.00).

Conclusion: Overall, there was an association between use of glyburide and increased risk of adverse events compared to insulin. Admissions to the NICU, respiratory distress, and large for gestational age were more likely to occur among newborns of women treated with glyburide. The results from this study are consistent with findings from previous studies and suggest that women with GDM treated with glyburide may not be achieving adequate glucose control. Limitations of this trial include lack of ability to ascertain stillbirths or neonatal deaths and lack of information on race/ethnicity and sociodemographic variables.

Key Point: This retrospective cohort study of women with private health insurance demonstrates newborns from mothers that were treated with glyburide within 150 days before birth were more likely to experience adverse outcomes than those from mothers treated with insulin.
Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction

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Background: Given that a number of individual NSAIDs have been shown to increase the risk of thrombotic cardiovascular events, multiple guidelines discourage NSAID use (with the exception of low-dose aspirin) in patients with established heart disease. However, these medications are still widely prescribed, as evidenced by a previous study in Denmark which showed 44% of patients were exposed to NSAIDs after myocardial infarction (MI). Current ACC/AHA guidelines recommend dual antiplatelet therapy (aspirin and clopidogrel) for up to twelve months after MI, and one agent thereafter. Some patients also have indications for vitamin K antagonist therapy, resulting in triple therapy. Concomitant use of NSAIDs and antithrombotic therapy can further increase bleeding risk, which poses another safety concern in addition to increased cardiovascular risk.

Objective: To examine the risk of bleeding and cardiovascular events among post-MI patients taking antithrombotic drugs, who also received NSAIDs.

Study Design: This observational study included patients identified by several nationwide administrative registries in Denmark who were 30 years or older, admitted with first-time MI from 2002-2011, and were alive for at least 30 days after hospital discharge. Using prescription claims data, subsequent treatment with aspirin, clopidogrel, or oral anticoagulants and their combinations, as well as NSAIDs, was determined. Ibuprofen 200mg was the only available over-the-counter NSAID in Denmark during the study period, therefore, any use of this NSAID was not included in the analysis. Patients were followed until one of the following events occurred: outcome of interest, emigration, death, or end of the study period (December 31, 2011). The primary outcome of interest was bleeding (admission or death from diagnoses of intracranial hemorrhage, gastrointestinal bleeding, bleeding from respiratory or urinary tract, and anemia caused by bleeding), and the secondary outcome was a combined outcome of cardiovascular death, nonfatal recurrent MI, and ischemic stroke, transient ischemic attack, or systemic arterial emboli. Crude incidence rates were calculated as number of events per 100 person-years, and hazard ratios were calculated using adjusted time-dependent Cox regression models.

Results: A total of 88,662 patients were admitted with first-time MI from 2002-2011, and 61,971 were included in this study. At least one prescription claim for NSAID treatment after discharge was identified for 33.8% of patients. The median follow-up period was 3.5 years. The crude incidence rates of bleeding (events per 100 person years) were 4.2 events (95% CI, 3.8-4.6) with concomitant NSAID treatment and 2.2 events (95% CI, 2.1-2.3) without NSAID treatment, resulting in a number needed to harm (NNH) of 50. In the adjusted analysis, the risk of bleeding associated with concomitant NSAIDs was increased (HR, 2.02 [95% CI, 1.81-2.26]) compared with no use of NSAIDs. The crude incidence rates for the combined cardiovascular end point were 11.2 (95% CI, 10.5-11.9) with NSAID treatment and 8.3 (95% CI, 8.2-8.4) without NSAID treatment, resulting in a NNH of 35. In the adjusted analysis, an increased risk for the combined cardiovascular end point was associated with NSAIDs (HR, 1.40 [95% CI, 1.30-1.49]) compared with no NSAID treatment. An increased risk of bleeding and cardiovascular events was evident with concomitant use of NSAIDs, regardless of antithrombotic treatment, types of NSAIDs, or duration of use.

Conclusions: In patients who received antithrombotic therapy after MI, concomitant use of NSAIDs was associated with a significantly higher risk of bleeding and excess thrombotic events, even when only used short-term, when compared to those who did not use NSAIDs. Caution is warranted when prescribing NSAIDs for patients post-MI.

Key Point: This study showed there are risks of increased bleeding and cardiovascular events when NSAIDs (other than low-dose aspirin) are used in addition to antithrombotic therapy after MI. Educating patients and other clinicians on the risks of using these agents after MI is an important intervention pharmacists can make, whether in the inpatient, outpatient, or community pharmacy setting.

Prevalence of aspirin-exacerbated respiratory disease among patients with asthma: A meta-analysis

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Background: Aspirin-exacerbated respiratory disease (AERD) is a condition where inhibition of cyclooxygenase-1 (COX-1) induces airway reactions including rhinorrhea, bronchospasms, and laryngospasms. This condition has also been named the Samter triad. Patients with this clinical syndrome experience adult-onset asthma, nasal polyposis or chronic rhinosinusitis, and nonsteroidal anti-inflammatory drug (NSAID) intolerance or hypersensitivity. As a result of these complications, these patients have a higher frequency of systemic steroid use, emergency
Purpose: Due to varying reports on the prevalence of AERD across the population of patients with asthma, the authors performed a meta-analysis to clarify this prevalence.

Study Design: This meta-analysis was performed by searching for clinical trials which analyzed the prevalence of AERD across the population of patients with asthma, the authors included clinical trials in human subjects with the following characteristics only, 1) all subjects were adults, 2) intervention had to include patients with asthma, 3) comparator or control had to include patients with AERD, and 4) outcomes assessed had to specifically include prevalence.

Results: The authors’ initial search identified 1770 trials. After exclusion for a variety of reasons, 27 trials were ultimately selected for inclusion. All studies utilizing a questionnaire for prevalence determination yielded a prevalence rate of 7.3%; [95% CI (5.14 to 9.53)]. Prevalence among trials utilizing retrospective chart review was 5.5%; [95% CI (2.36 to 8.66)]. Those trials which used a combination of approaches reached a prevalence rate of 12.4%; [95% CI (4.04 to 20.67)]. When all trial results were taken together without regard to a specific method of assessment, a prevalence rate of 7.2%; [95% CI (5.26-9.03)] was yielded. Analysis was further performed by calculating a conglomerate prevalence rate among patients with severe asthma (14.89%; [95% CI (6.48 to 23.29)]) and nasal polyps (9.7%; [95% CI (2.16 to 17.22)]).

Conclusions: The authors of this analysis state that an overall prevalence of AERD among patients with asthma of 7.2% is much lower than reported in previously published work. This being said, this rate is still higher than what most primary care providers may expect. Importantly, the prevalence doubled among patients with severe asthma. The authors go on to suggest that both objective and subjective symptoms be evaluated when diagnosing AERD, as medications (such as leukotriene modulators or antihistamines) can lead to a false negative result. Objective measures might include a change in nasal inspiratory flow rate for Forced Expiratory Volume (FEV1).

While patient-completed questionnaires may be a useful tool for assessing symptoms and collecting medical history, the study authors address some concerns about their use in this setting. Anecdotally, they found that patients may not always recognize an association between NSAID use and worsening airway function even when they are directly asked about timing of doses and symptoms (recall bias). The questionnaires evaluated in the study oftentimes did not ask the patient to distinguish between a cutaneous versus a respiratory hypersensitivity reaction to an NSAID. Lastly, several of the surveys used did not specifically list aspirin as an NSAID, and many patients do not categorize aspirin as such.

Key Point: Considering the characteristics of AERD, including adult-onset asthma, nasal polyposis, chronic rhinosinusitis, and NSAID sensitivity, patients with any combination of these symptoms should be evaluated for the presence of the condition. This is especially true for patients with severe asthma and nasal polyps because there is increased frequency of diagnosis of AERD in this patient population. Clinician assessment and evaluation of patients with potential AERD appears to be most frequently linked to an accurate diagnosis, rather than utilizing patient-completed questionnaires or surveys.

Long-term Nicotine Replacement Therapy
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West Side Community Health Services

Background: Six-month rates of smoking cessation rarely exceed 20% when using nicotine patches for the standard 8 weeks treatment. An alternative option is to extend therapy. A previous large, randomized placebo-controlled clinical trial demonstrated that extending the use of nicotine patch to 24 weeks increased six-month smoking cessation rates to 32%. In addition, the Food and Drug Administration now supports extended use of nicotine patches due to the safety profile and evidence supporting its benefits. However, few data show the potential benefits of using nicotine patches beyond 24 weeks.

Purpose: This trial compared smoking cessation rates, adverse effects, and adherence between 8 (standard), 24 (extended), and 52 (maintenance) weeks of nicotine patch treatment.

Study Design: This randomized clinical trial studied smokers from Philadelphia and Chicago who were 18
years or older, smoked at least 10 cigarettes per day, and were interested in smoking cessation. Individuals who had a contraindication to nicotine therapy, a diagnosis of psychotic or bipolar disorder, were suicidal, were unable to communicate in English, or were pregnant, planning to become pregnant, or lactating were excluded. Subjects were randomly selected into the standard, extended, or maintenance treatment of nicotine patch therapy. All received 12 sessions of smoking cessation counseling. Each treatment arm was given 21mg nicotine patches daily which was decreased to 14mg or 7mg patches if the 21mg patch was too strong and patients exhibited signs of nicotine overdose. The primary endpoint was self-reported abstinence for 7 days before assessments at 24 and 52 weeks with CO breath levels < 10 ppm. Secondary endpoints included continuous abstinence, prolonged abstinence, relapse, and time to relapse.

Results: In total, 525 smokers were included in the study of which 48.2% were African American. With covariates controlled at 24 weeks, the results demonstrated more abstinent days (95% CI, 1.06-2.26; P = .02), greater abstinence (95% CI, 1.03-2.81; P = .04), delayed relapse (95% CI, 10.30-32.25; P < .001), and less days of smoking if not abstinent (95% CI, 0.06-0.82; P = .02) in the extended and maintenance treatment arms compared to the standard treatment arm. There was no difference in abstinence rates at 52 weeks in the maintenance treatment arm compared to the standard and extended treatment arms. There was also no difference between participants in the extended and standard treatment arms at 52 weeks. Adverse effects between standard, extended, or maintenance treatment arms were similar. Participants in the maintenance treatment arm reported lower adherence compared to the standard and extended treatment arms (3.94+2.5, 4.62+2.0, 4.7+2.4 patches/week, respectively; P = .003).

Conclusions: The study provided evidence that 24 weeks of nicotine patch can increase six-month abstinence rates, but by 52 weeks there was no difference in smoking cessation rates among any of the treatment length therapies. It also demonstrated nicotine therapy is safe for use up to one year.

Key Point: Long-term use of nicotine patch for 52 weeks is safe but its efficacy beyond 24 weeks of treatment is insignificant.

Corlanor® (ivabradine), developed by Amgen

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Indications: Ivabradine was approved by the FDA on April 15, 2015 to reduce the risk of hospitalization for worsening heart failure (HF) for patients with chronic, symptomatic, and stable heart HF, with an ejection fraction (EF) <35%, who are in sinus rhythm and have a heart rate (HR) of >70 beats per minute (bpm) and are optimized on beta blockers or have a contraindication to beta blocker use.

Mechanism of Action: Ivabradine lowers heart rate by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, which leads to inhibition of the I(f)-current responsible for the spontaneous pacemaker activity at the sinoatrial (SA) node. Contractility and ventricular repolarization are not affected through this mechanism.

Dosage and Administration: For heart failure, use the initial dose of 5 mg orally twice daily for 2 weeks, then adjust to reach a resting heart rate of 50-60 beats per minute (bpm). If heart rate is greater than 60 bpm, increase dose by 2.5 mg twice daily. If heart rate is less than 50 bpm or if symptomatic bradycardia, decrease dose by 2.5 mg twice daily. Do not exceed a maximum dose of 7.5 mg twice daily. Ivabradine is contraindicated in severe hepatic impairment. No data is available for use in CrCL of 15 mL/min or less. Start at a lower dose, 2.5 mg twice daily, if patient has a history of conduction defects or bradycardia that could cause hemodynamic instability.

Effectiveness: The Systolic Heart failure treatment with I(f) inhibitor ivabradine Trial (SHIFT) study was a randomized, double-blind, placebo-controlled, parallel-group study, that was conducted in over 6,500 patients. The primary endpoint assessed the rate of the composite of cardiovascular death or hospital admission for worsening HF. Patients were included in the study if they were already on standard of care therapies, including beta blockers, had symptomatic heart failure with a left-ventricular EF of 35% or less, were in sinus rhythm, had a HR of >70 bpm, and had been hospitalized in the previous year for HF. Over a median follow-up time of 22.9 months, 24% of patients in the ivabradine group had either hospitalization or died due to HF, compared to 29%
of patients in the placebo group (HR 0.82, 95% CI 0.75-0.90, p<0.0001).

**Safety:** Significant adverse events that occurred in patients on ivabradine in the SHIFT study include bradycardia (10% vs. 2.2%), hypertension (8.9% vs. 7.8%), atrial fibrillation (8.3% vs. 6.6%), and luminous phenomena, or visual brightness (2.8% vs. 0.5%). Ivabradine should not be used in patients with acute decompensated HF, blood pressure <90/50 mmHg, resting HR <60 bpm prior to treatment, sick sinus syndrome, sinoatrial block, or 3rd degree AV block (unless a functioning demand pacemaker is present), pacemaker dependence, severe hepatic impairment, or if concomitant use of a strong cytochrome P450 3A4 inhibitor.

**Place in Therapy:** With a unique mechanism of action, ivabradine may be a beneficial complement therapy for patients already on standard heart failure therapies, including beta blockers, who have a HR of >70 bpm, to lower the risk of hospitalization due to worsening HF. However, cost may prove to be prohibitive for some patients, with a reported price point of $375 a month\(^1\), so further analysis of cost vs. benefit will be important.

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**Therapeutic Thoughts**

**Revisiting Anticholinergic Medications in the Elderly\(^{20-22}\)**

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**Background:** Anticholinergic (antimuscarinic) medications are used to treat various illnesses. Additionally, many medications have anticholinergic properties which manifest into adverse effects. The Beers Criteria of Potentially Inappropriate Medications lists agents that should be avoided in individuals ages 65 years and older, and this list includes anticholinergic medications. Altered pharmacokinetics and volume of distribution, plus increased permeability of the blood brain barrier amplify anticholinergic adverse effects in the geriatric population especially in those with dementia, delirium or decreased cognitive function. Despite the evidence, anticholinergic medications are frequently prescribed and used among the geriatric population.

Two recent articles address the use of anticholinergic medications and dementia.

**Evidence:** Gray et al. examined if long-term cumulative exposure to highly anticholinergic medications is associated with dementia. This was a prospective cohort study of 3434 adults ages 65 years or older (mean age 74.4 years) with no previous diagnosis of dementia. Prescription data from an integrated health care system was used to determine the cumulative exposure of highly anticholinergic medications 10 years prior to a diagnosis of dementia. Twenty–three percent of the population developed dementia during the study. Cumulative doses of anticholinergic medications were calculated based on previous 10 years of pharmacy data imputed into an equation to determine the Total Standardized Daily Doses (TSDD). A 10 year cumulative-dose response relationship was found for dementia or Alzheimer’s disease (P<0.001). Increasing exposure to anticholinergic medications was associated with increased hazard ratios for dementia; however this was not statistically significant. Patients who were diagnosed with dementia had the highest exposure to anticholinergic with an adjusted hazard ratio of 1.54 (CI 1.21-1.96) which was statistically significant.

In another recent study conducted by Mate et al., the authors’ objective was to determine the prevalence of anticholinergic medication use, load and predictors for use among community dwelling individuals age 75 and older in Australia. In this cross-sectional study, a nurse collected medication lists of the participants (n=1,044) at the participant’s home. Cognitive status was assessed using a subsection of Cambridge Examination for Mental Disorders of the Elderly (CAMCOG-R). The Anticholinergic Drug Scale (ADS) was used to determine anticholinergic load. Factors that are associated with a higher anticholinergic burden include polypharmacy (p=0.001), increasing age (p=0.018), CAMCOG-R dementia (p=0.003), depression (p=0.003), and lower physical quality of life (p=0.001). Individuals with dementia were found to take a significantly higher number of total medications than those without dementia (4.6 vs. 3.9 p=0.04) and were also found to have a higher anticholinergic load (1.5 vs. 0.8; p=0.002). Dementia patients took a higher proportion of level 1 (potentially anticholinergic) (p=0.002) as well as level 3 (markedly anticholinergic) (p=0.005) medications.
**Discussion:** The prevailing understanding related to cognitive impairment and anticholinergic medications, is that once the offending anticholinergic agent (s) is removed, cognitive impairment improves. The study by Gray et al. suggests that there may be an association with cumulative exposure of anticholinergic medications and dementia. Mate et al. suggests that medications with little anticholinergic properties may contribute to anticholinergic adverse effects via an additive effect. Increased awareness of medications with anticholinergic properties among health care professionals and older adults are needed to avoid adverse effects.

**Clinical Impact:** Recent publications have supported long-held concerns of the harms of anticholinergic drug therapy in the elderly. Pharmacists have a role to educate prescribers and patients on the potential adverse effects of anticholinergic medications associated with short-term and long-term use.

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**Potential Cost Savings of Medication Therapy Management in Safety-Net Clinics**

*23-24*

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**Background:** Treatment of chronic disease accounts for a major portion of health care spending in the United States and demands large quantities of state and national budgets for healthcare expenditures. Medication Therapy Management (MTM) has been shown to improve outcomes and reduce cost for the management of chronic disease. A Minnesota study of the Fairview health system showed a return on investment (ROI) of $1.29 per $1.00 of MTM cost. Other studies have shown MTM as a significant cost-saving service. As we move forward to advance the Institute for Healthcare Improvement (IHI) Triple Aim (improved outcomes, lower cost, and better patient experience) MTM has the potential to play a major role. This study focuses on the work of safety net clinics in Maryland which provide a significant amount of care for patients with chronic diseases.

**Objectives:** Evaluate potential cost savings based on estimated cost avoidance from MTM delivered through safety net clinics over a four year period.

**Methods:** Pharmacists provided face to face MTM services to patients across multiple safety net clinics and identified and resolved medication-related problems (MRPs). Each MRP was evaluated under the criteria of indication, effectiveness, safety and adherence and correlated with potential cost avoidance. Data from the Fairview study was used to assign a dollar amount in cost savings. Total cost avoidance was calculated by multiplying the prevalence of MRP by the cost for each avoidable medical service. Time spent delivering MTM was tracked using pharmacist billing codes and cost of pharmacist services was calculated at $57.33 per hour with 30% fringe benefits. Only time in direct patient care was used to evaluate the ROI.

**Results:** The primary outcome of the study revealed a reduction in one hospital visit per year, where the change in frequency prior to (2.36 times per year) and during utilization of CPCO services (1.33 times per year) was significant (p<0.001). Upon initiation of the CPCO services the number of patients who filled all of their prescriptions increased from 40.9% to 85.3% (p<0.001). The majority of patients felt they had a better understanding of how their medications helped manage their health conditions, more access to health care providers such as pharmacists, doctors and nurses, more control of their own health and that their overall health was better.

**Results:** Over the course of the study 246 patients with 2,099 medications received MTM services (average 8.5 medications and 4.8 conditions per patient). A total of 814 MRP’s were identified (average 3.3 per patient). The total cost of medical services avoided through MTM ranged from $115,220-$614,570 based on estimated health care savings and the overall cost of pharmacist time was $57,307.50. The study showed a ROI range of 1:5 to 1:25 for direct patient care MTM services.

**Conclusion:** While the study only accounted for pharmacist time providing direct patient care (excluding documentation, precepting, tracking outcomes, etc), the authors conclude that pharmacists providing MTM through direct patient care may reduce potential medical costs for chronic disease. While further studies are needed to validate this research, the study showed potential cost-savings for pharmacy services.
Key Point: Pharmacists providing face to face MTM services can show a positive ROI for cost avoidance and potentially reduce the cost of care for chronic diseases.

A Review of Potential Antidotes for the New Oral Anticoagulants

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Background: There are currently four new oral anticoagulants available in the U.S. [dabigatran, rivaroxaban, apixaban and edoxaban]. Large randomized controlled trials have demonstrated their superiority or noninferiority to warfarin for the prevention of stroke in non-valvular atrial fibrillation and for the treatment and prevention of venous thromboembolism. Their use however has been limited in part due to the lack of specific reversal agents in the event of a life-threatening bleed. Current reversal options include hemodialysis, charcoal, anti-fibrinolytics, and coagulation factor replacement. This review article discusses the current progress towards the development of potential antidotes.

Evidence: Idarucizumab is a humanized monoclonal antibody fragment that selectively binds and inhibits dabigatran. Preclinical animal studies have shown that various single IV boluses of idarucizumab in test subjects receiving dabigatran completely reversed prolonged coagulant activity. Idarucizumab had no effect on warfarin activity in animal studies. In a phase 1 clinical trial, the safety and tolerability of idarucizumab was evaluated in healthy subjects receiving dabigatran 220mg twice daily. Idarucizumab doses of 1, 2, and 4 grams were well tolerated and did not elicit any immunogenic reactions. A phase 3 clinical trial is currently in progress, enrolling patients on dabigatran who experience uncontrolled bleeding or require urgent reversal for surgery or other procedures.

Andexanet alfa is a modified recombinant form of factor Xa and a potential antidote for factor Xa inhibitors. One study found andexanet alfa significantly reduced blood loss by > 85% in subjects treated with rivaroxaban. In a phase 2 clinical trial volunteers taking rivaroxaban 20mg daily were given IV andexanet alfa at doses of 210, 420, 600, or 720mg followed by a 240mg infusion. Anti-Xa activity and plasma concentrations of rivaroxaban decreased in a dose dependent manner. No thrombotic or serious adverse events were observed. In another trial, andexanet alfa at 210 and 420 mg decreased anti-Xa activity by 80% and > 90% respectively in the first two minutes after administration. Two phase 3 clinical trials are in progress to assess the efficacy of andexanet alfa in reversing the anticoagulant effects of rivaroxaban and apixaban.

Aripazine is a small synthetic molecule that binds directly with UFH and other anticoagulants including factor Xa and IIa inhibitors. Preclinical animal studies have shown decreased blood loss by > 90% in test subjects on rivaroxaban, apixaban, and dabigatran. In addition, aripazine completely reversed anticoagulant activity, measured by aPTT and anti-Xa, of apixaban and rivaroxaban in human blood ex vivo.

Discussion: Currently there are three antidotes being developed for the reversal of the new oral anticoagulants. Each antidote is at a different stage of development and all have had encouraging results from preclinical animal data. Idarucizumab and andexanet alfa seem to be well tolerated, effective at reversing coagulation measures, and do not exhibit procoagulant activity. Aripazine may potentially be capable of reversing multiple anticoagulants including UFH, factor Xa and IIa inhibitors. Although promising, further studies are yet to be conducted as in vitro and animal models may not predict efficacy in humans. Another limitation to the current studies is that the relationship between serum levels of the new oral anticoagulants and the risk of bleed has not been well established. Along the same lines, using coagulation lab measures as surrogate markers for bleeding is also not well validated with the new oral anticoagulants.

Clinical Impact: The new oral anticoagulants are an attractive alternative to warfarin because they require less monitoring, have more predictable pharmacokinetics and dynamics, and have proven to be as effective if not better than warfarin. Concerns regarding their safety is one factor that limits their widespread use given the lack of specific reversal agents. This however, may be changing in the near future. Certainly as with other conditions and medications, all things should be considered including but not limited to specific patient characteristics (renal function, medication adherence), cost, and the provider and patient experience.
‘Spice’ Increases Emergency Room Visits\textsuperscript{26-27}

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There has been a recent increase in emergency room visits and also calls to poison control centers around the United States (U.S.) due to a common street drug known as ‘spice’, which is a synthetic cannabinoid. This drug has contributed to adverse effects and deaths.\textsuperscript{26,27} Adverse effects from synthetic cannabinoids were first reported in 2009. Since then, the use of synthetic cannabinoid has spread across the country at an alarming rate.\textsuperscript{27} Reported cases of synthetic cannabinoid causing harm have quadrupled in 2015 compared to 2014.\textsuperscript{26} Adverse effects reported include: anxiety, violence, delusions, increased heart rate and blood pressure, nausea and vomiting, muscle spasms, seizures, tremors, increased suicidal ideation, and death.\textsuperscript{26,27}

‘Spice’ is a synthetic cannabinoid that is made to appear very similar to marijuana. The substance is then sprayed with a hallucinogenic chemical which abusers of the substance then smoke. The drug is imported into the US, usually from China, and new varieties are constantly evolving to try to skirt the DEA’s list of illegal drugs. The danger is that this substance can be 100 times more potent than marijuana. According to Mississippi’s health department, ‘spice’ was the cause of over 400 emergency department visits within the month of April 2015.\textsuperscript{26} Through May 14, 2015 poison centers around the U.S. received reports of over three thousand exposures to synthetic marijuana.\textsuperscript{27}

The prevalence of adverse outcomes attributed to synthetic cannabinoid use has been trending upwards since last year. It is important for health care providers to be aware of this and educate patients on the detrimental and potentially life threatening effects of synthetic cannabinoids if there are patients that are suspected to be abusing this substance.

References


