Effect of Self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease

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Background: Stimulants have been shown to increase blood pressure and heart rate in children and adolescents with ADHD. Whether these changes result in clinically significant increases in cardiovascular (CV) events is unknown. A 2012 review article of observational studies found data to suggest an increased CV risk with use of stimulants in both children and adults; however, the reviewed studies had several limitations making it difficult to interpret the results. A relationship between time and dose of stimulants to the risk of adverse CV events is yet to be determined.

Objective: The Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups (TASMIN-SR) trial’s aim was to assess if self-monitoring and self-titration of antihypertensive therapy, as compared to usual care, can lead to lower systolic blood pressure in patients who have at least one high-risk condition, including diabetes, cardiovascular disease, or kidney disease.

Study Design: This trial was randomized, unblinded, and included 552 patients with a blood pressure of at least 130/80 mm Hg, who were being treated in 59 family practice clinics throughout the United Kingdom. Data collection occurred between March 2011 and January 2013, and patients had to be at least 35 years old, with a history of either diabetes, chronic kidney disease, stroke, or coronary heart disease to be included in the study. Those with terminal illness, who were homebound, or who were otherwise deemed unsuitable for this study by their primary physicians (e.g. patients with dementia) were excluded from this study. Patients were randomized to either receive usual care or self-management, which included both self-monitoring of blood pressure followed by self-titration of antihypertensive therapy. All patients were followed-up within one year. The self-management group received training on Microlife Watch BP Home, a validated monitor, and also saw their family physician to determine an individualized three-step plan to initiate or increase antihypertensive medications. The goal for blood pressure self-monitoring at home was 120/75 mm Hg based on the British Hypertension Society and the Joint British Societies Guidelines. The usual care patients had a routine blood pressure check, where medication and dose changes could occur. Thereafter, all decisions about blood pressure measurements and targets, as well as medication changes were made at the physician’s discretion.
The primary outcome was the difference in systolic blood pressure seen between the self-management and usual care groups. Questionnaires were used to measure quality of life, anxiety, and adverse effects in each group. To compare the amount of antihypertensive drugs used in each group, each drug dose was translated into a defined daily dose (a World Health Organization measurement which is an assumed average maintenance daily dose).

**Results:** Of all 552 patients who were initiated in the trial, 230 in the usual care group and 220 in the intervention group (a total of 81%) completed the 12-month follow-up. The mean baseline blood pressure was similar in the self-management and usual care groups at 141.1/80.5 mm Hg and 143.6/79.5 mm Hg, respectively. After one year, there was a greater reduction of systolic blood pressure in the self-management group, with a mean systolic blood pressure difference of 9.2 mm Hg (95% CI, 5.7-12.7) between the two groups. When multiple imputation for missing values was applied, a slightly smaller difference of 8.8 mm Hg (95% CI, 4.9-12.7) was demonstrated. A difference was also shown between groups at six months, with the intervention group having a mean systolic blood pressure 6.1 mm Hg (95% CI, 2.9-9.3) less than the usual care group. Both groups had an increase in the defined daily dose of antihypertensives, but the intervention group had a significantly higher daily dose of 3.34 (95% CI, 3.1-3.7) as compared to 2.61 (95% CI, 2.4-2.9) seen in the control group after 12 months. The quality of life was not different between groups, nor was the frequency of adverse events, including those that may be linked to antihypertensive therapy including dizziness, impotence, and rash.

**Conclusions:** In this twelve-month study, patients with elevated blood pressure who have a higher risk of cardiovascular disease, self-management of hypertension was shown to cause greater blood pressure reduction as compared to usual care. While a greater amount of antihypertensive therapy was prescribed in the intervention group, adverse events did not increase and quality of life was similar to the usual care group. In patients that are already at an increased risk due to high risk comorbidities, improved blood pressure control could be particularly important in reducing cardiovascular events.

**Key Point:** This randomized clinical trial showed that in patients with elevated blood pressure who also have either diabetes, chronic kidney disease or cardiovascular disease, self-management of hypertension leads to lower blood pressure as compared to patients receiving usual care.

**Concomitant Use of Anticoagulants and Amiodarone in Atrial Fibrillation**

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**Background:** Amiodarone is an effective antiarrhythmic medication commonly used for management of atrial fibrillation. Amiodarone has a well-documented drug interaction with warfarin that affects the metabolism of warfarin.

**Purpose:** This study sought to utilize the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial to assess whether there were differences in event rates and bleeding risks in patients taking warfarin or apixaban alone or in combination with amiodarone.

**Study Design:** The study utilized the patient population from the ARISTOTLE trial. Inclusion criteria for this trial consisted of patients with documented atrial fibrillation on two occasions that were separated by at least two weeks in the 12-month time frame prior to enrollment in the study. In order to qualify patients were also required to possess one or more of the following risk factors correlating with the CHADS2 score: symptomatic heart failure within past three months or left ventricular ejection fraction ≤ 40%; hypertension or diabetes requiring pharmacotherapy; ≥ 75 years of age; and previous stroke, transient ischemic attack or systemic embolism. Patients were excluded from the study if they had atrial fibrillation from a reversible cause, moderate or severe mitral stenosis, conditions requiring anticoagulation other than atrial fibrillation, stroke within the past seven days, requiring aspirin > 165 mg/day or combined aspirin and clopidogrel therapy, or renal insufficiency. The primary efficacy outcome measured was the incidence of stroke or systemic embolism. Secondary outcomes consisted of myocardial infarction or death classified as cardiovascular or nonvascular. In the ARISTOTLE trial, patients were randomized to receive warfarin or apixaban. Those patients on warfarin had a target INR of 2.0 to 3.0 and apixaban was administered in standard dosing of 5 mg twice daily or dose adjusted to 2.5 mg twice daily based on prescribing criteria. This investigation sought to assess endpoints in these patients who were concurrently administered amiodarone versus those not on amiodarone therapy. A propensity score was utilized during the randomization process to ensure appropriate matching of those patients with and without amiodarone therapy.

**Results:** Patients on warfarin and amiodarone were in the target therapeutic INR range 56.5% percent of the time.
versus 63.0% on warfarin alone (p<0.0001). For patients on amiodarone in combination with apixaban or warfarin, there was no statistically significant difference in rate of stroke or systemic embolism (1.24% vs 1.85% per year). There was also no significant difference in stroke or systemic embolism in patients on apixaban or warfarin alone (1.29% vs 1.57% per year). However, patients on amiodarone therapy combined with apixaban had statistically less all-cause mortality (4.15% per year) compared to those combined with warfarin therapy (5.65% per year). There was no statistical difference in all-cause mortality with apixaban or warfarin alone in the absence of amiodarone (3.43% vs 3.68% per year). Major bleeding was statistically less in the apixaban group compared to the warfarin group both alone (1.86% vs 3.06% per year) or in combination (2.18% vs 3.03% per year) with amiodarone.

The use of amiodarone and risk of major events was analyzed using a propensity score-adjusted analysis. Patients on amiodarone had a statistically significant increase in risk for stroke or embolism compared to those not on amiodarone therapy (1.58% vs 1.19% per year, p=0.0322). Patients on amiodarone tended towards an increased risk of all-cause death and cardiovascular death and noncardiovascular death; however this was not statistically significant. The propensity score-adjusted analysis found there were no significant differences in major bleeding or myocardial infarction. Conclusions: NOACs as a class of medications did not have any greater major or clinically relevant bleeding than conventional therapies in elderly individuals. NOACs were more effective than conventional therapy in reducing the risk of VTE or VTE-related deaths and in the prevention of stroke of systemic embolism.

Conclusions: Those patients on amiodarone therapy and warfarin were more likely to fall outside of the target therapeutic INR range. Amiodarone administration had a significant increase in the risk of stroke and systemic embolism. The use of either warfarin or apixaban in combination with amiodarone presented with similar rates of stroke, systemic embolism, mortality and major bleeding events versus warfarin or apixaban alone.

Key Point: Patients that use amiodarone and warfarin in combination are more likely to fall outside of the therapeutic INR range and may be at increased risk of bleeding or thromboembolic events. For those patients that require amiodarone therapy, the use of newer anticoagulants, such as apixaban, should be considered.

Hypoglycemia After Antimicrobial Drug Prescription for Older Patients Using Sulfonylureas
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Background: Sulfonylureas (SU) are commonly used in the treatment of type 2 diabetes. Despite their appearance in the Beer’s criteria as medications to avoid in the elderly, SUs are still commonly employed for this purpose in older patients. Hypoglycemia caused by SUs has been reported at a rate of 1.23 hospitalizations per 100 patients annually, resulting in significant morbidity and mortality. When SUs are concomitantly administered with some antimicrobials, increases in hospitalizations due to hypoglycemia have been shown in studies of Medicaid data.

Primary Aim: In a Medicare population in Texas, this study sought: 1) to estimate the frequency of hypoglycemic events in patients concomitantly prescribed glyburide or glipizide with one of 16 selected antimicrobials 2) to estimate the added Medicare costs of these events, and 3) to identify patient-specific risk factors for hypoglycemic events.

Study Design: A retrospective cohort study design was employed to evaluate Texas Medicare claims from 2006 to 2009 for patients older than 65 years. Patients included in the analysis were concomitantly prescribed glipizide or glyburide and one of 16 of the most commonly prescribed antimicrobials for this patient population. A prescription overlap of at least 1 day was required for study inclusion. Patients were required to have received Medicare A/B and D benefits for 12 months prior to and 14 days after prescription of an antimicrobial. Patients enrolled in health maintenance organizations (HMO) were excluded. Three non-interacting antimicrobials were selected as controls: azithromycin, amoxicillin and cephalaxin.

Results: Occurrences of concomitant glipizide and selected antimicrobial use were documented 68,186 times in 31,184 patients; occurrences of concomitant glyburide and selected antimicrobial use were documented 65,359 times in 30,411 patients. When compared to the cohort controls, use of glipizide with clarithromycin (OR 4.17-5.38), levofloxacin (OR 2.35-3.04) and SMTZ/TP (OR 2.78-3.58) was associated with higher hypoglycemic risk than glyburide with clarithromycin (OR 2.67-3.87), levofloxacin (OR 1.99-2.89) and SMTZ/TP (OR 1.63-2.37). Overall, clarithromycin (OR 3.96 [2.42-6.49]), levofloxacin (OR 2.60 [2.18-3.10]), SMTZ/TP (OR 2.56 [2.12-3.10]), metronidazole (OR 2.11 [1.28-3.47]) and ciprofloxacin (OR 1.62 [1.33-1.97]) were associated with greatest risk of hypoglycemia when prescribed with SUs. Contributing factors to hypoglycemia included concomitant use of multiple medications, with contributory factors

Contributing factors to hypoglycemia included concomitant use of multiple medications, with contributory factors

Discussion: This study found that the use of clarithromycin with either SU was associated with the highest risk of hypoglycemia compared to the cohort controls. The use of other antibiotics such as azithromycin, levofloxacin, and SMTZ/TP was also associated with increased risk of hypoglycemia. The results of this study highlight the importance of considering the potential for hypoglycemia when prescribing SUs in combination with certain antimicrobials.
patient factors included increased age, female gender, black or Hispanic race, high comorbidity and prior hypoglycemic events. From data collected, 13.2% of hypoglycemic events associated with SUs were caused by concomitant use of high-risk antimicrobials. These events resulted in $30.54 per prescription of an antimicrobial in added Medicare costs.

Conclusions: In older patients, antimicrobials most likely to cause hypoglycemia when used with glyburide or glipizide include clarithromycin, levoﬂoxacin, SMTZ/TP, metronidazole and ciprofloxacin. Use of this medication combination represents approximately 13% of hypoglycemic events caused by SU use and adds approximately $30 per antimicrobial prescription in Medicare costs.

Key Point: In patients older than 65 years, use of a SU with clarithromycin, levoﬂoxacin, SMTZ/TP, metronidazole or ciprofloxacin can increase risk of hypoglycemia anywhere from 1.5-fold to 4-fold. Depending upon the length of therapy and patient risk factors, consider holding the SU during antimicrobial therapy. For lower risk patients, educate on hypoglycemia symptoms and treatment.

The role of GLP-1 agonists in combination with insulin therapy in type II diabetes
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Background: Glucagon-like peptide-1, an incretin hormone causes an increase in glucose-dependent insulin secretion, a decrease in glucagon secretion, an increase in pancreatic beta cell growth and replication, slower gastric emptying, and a decrease in food intake. GLP-1 agonists, such as Victoza® (liraglutide) and Byetta ®(exenatide), work to treat type 2 diabetes by mimicking incretin hormone in the body1. According to the American Diabetes Association Standards of Medical Care in Diabetes—2014, GLP-1 agonists may be considered as second-line pharmacologic treatment for adults with type 2 diabetes2. Because of the mechanism of action of GLP-1 agonists, it has been postulated that in combination with basal insulin therapy, patients may experience significant glucose lowering, yet experience less hypoglycemic episodes and less weight gain.

Purpose: The purpose of this study was to assess the effect of combination treatment of a GLP-1 agonist and basal insulin therapy on glycemic control, incidence of hypoglycemia, and weight gain as compared with other anti-diabetic treatments.

Study Design: This study was a systematic review and meta-analysis of randomized controlled trials that utilized combination treatments of GLP-1 agonists and basal insulin compared with other anti-diabetic treatments. Inclusion criteria were studies that were published between January 1, 1950 and July 29, 2014. Endpoints to be assessed were glycemic control, incidence of hypoglycemia, and weight change. A random-effects model was then used to determine significance of the pooled data.

Results: A total of 2905 studies were identified, fifteen of which were included in the analysis. All fifteen trials were published between the years 2011 and 2014. The average trial duration was 24 weeks with a range of 12 to 36 weeks. At baseline, patients’ average hemoglobin A1c was 8.13%. Average body mass index at baseline was 32.9 kg/m2. Patients had been diagnosed with diabetes for an average of 12.2 years with a range of 7.9 to 17.1 years. The trials compared combination treatment of GLP-1 agonist and basal insulin therapy with a variety of diabetes treatment options including: GLP-1 agonist plus basal insulin plus oral anti-diabetic drugs, metformin, basal insulin plus one daily injection of bolus insulin, and intensive basal-bolus insulin therapy. All fifteen trials were pooled to analyze change in hemoglobin A1c with the various treatments. Results showed that combination therapy of GLP-1 agonist plus basal insulin resulted in a statistically significantly larger decrease in hemoglobin A1c than with any of the other treatment options. Fourteen trials were pooled to analyze the likelihood of patients reaching goal A1c of 7.0% or lower. For this endpoint, it was found that after using a sensitivity analysis to compare the combination therapy (GLP-1 agonist plus basal insulin) with basal-bolus insulin therapy, there was no treatment benefit to using the combination therapy. Eleven of the fifteen studies were then assessed to determine likelihood of hypoglycemic events. Here it was found that there was no significant difference in the relative risk of hypoglycemic episodes between combination therapy and other treatment options. As compared to other treatments, patients on combination therapy had a mean reduction in weight of 3.22 kilograms.

Conclusions: Combination treatment of GLP-1 agonist and basal insulin therapy is an appropriate treatment for patients with uncontrolled Type 2 diabetes due to their hemoglobin A1c lowering potential with low risk of increased hypoglycemia and weight gain.

Key Point: When used in combination with basal insulin therapy, GLP-1 agonists can reduce hemoglobin A1c and help patients with uncontrolled Type 2 diabetes maintain glycemic control without increasing their risk of hypoglycemia and causing weight gain.
Harvoni ® (ledipsavir/sofosbuvir) for Chronic Hepatitis C Infection – Gilead Sciences

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Indications: Combination ledipsavir and sofosbuvir for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

Mechanism of Action: Ledipsavir and sofosbuvir are both protein inhibitors of hepatitis C virus. Ledipsavir inhibits the NS5A protein and Sofosbuvir inhibits the NS5B protein, which are necessary for viral replication. Sofosbuvir is incorporated into the virus RNA and acts as a chain terminator.

Dosage and Administration: One tablet of Harvoni ® contains 90 mg of ledipsavir and 400 mg of sofosbuvir. The medication is taken orally once daily without regard to food. For patients who are treatment-naïve with or without cirrhosis treatment duration is 12 weeks. Treatment for patients who are treatment-experienced without cirrhosis is 12 weeks. Duration for treatment-experienced patients with cirrhosis is 24 weeks. An 8 week course can be considered for some treatment-naïve patients without cirrhosis with lower viral counts (HCV RNA <6 million I.U./mL).

Effectiveness: Three randomized control trials assessed the effectiveness of combination ledipsavir and sofosbuvir in patients with CHC for 8-24 weeks.

ION-1 was a randomized, open-label study in treatment-naïve patients evaluating combination ledipsavir and sofosbuvir compared to combination ledipsavir and sofosbuvir plus ribavirin. Patients were randomized to receive one of the two study regimens and also to either 12 or 24 week treatment durations. The primary endpoint was sustained viral response (SVR). Combination ledipsavir and sofosbuvir showed an SVR of 99% at 12 weeks which was equal to or higher than the SVR seen in other groups.

ION-2 was designed identically to ION-1 in patients who had previously failed treatment with peginterferon and ribavirin. In this study combination ledipsavir and sofosbuvir for 12 weeks has an SVR of 94% compared to 96% when ribavirin was added for 12 weeks. SVR was 99% in the ledipsavir and sofosbuvir group with and without ribavirin when treated for 24 weeks.

ION-3 was a randomized, open-label study in treatment-naïve patients evaluating combination ledipsavir and sofosbuvir, and combination ledipsavir and sofosbuvir plus ribavirin for 8 weeks compared to combination ledipsavir and sofosbuvir for 12 weeks. The 8 week regimens had an SVR of 94% and 93% respectively compared to 95% in the 12 week regimen.

Safety: Combination ledipsavir and sofosbuvir does not have any contraindications. Caution should be taken when administering this medication with known P-glycoprotein inhibitors due to the potential of lower drug concentration and reduced therapeutic effect. The most common adverse reactions noted in clinical trials were fatigue and headache, occurring in 13-18% and 11-17% respectively in three studies. Other side effects occurring in <10% of patients are nausea, diarrhea and insomnia. Combination ledipsavir and sofosbuvir caused non-serious elevations in serum concentrations of bilirubin, lipase, and creatinine kinase. Combination ledipsavir and sofosbuvir is a category B agent in pregnancy. Lactation information in humans is not known. No dosage adjustment can be recommended with renal impairment or failure due to limited data. No adjustment is necessary in geriatric patients. It is not approved for pediatric use.

Place in Therapy: Combination ledipsavir and sofosbuvir is considered a first-line therapy for patients with genotype 1 HCV regardless of previous treatment or presence of cirrhosis.

Cost: Wholesale acquisition price (WAC) = $1,125 per pill, for an estimated treatment cost of ~$94,500 for a 12 week treatment.
Antidepressant Use in Elderly
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Late-life depression is defined as occurrence of major depressive disorder in persons 60 years of age or older. As compared to adults with depression earlier in life, late-life depression is correlated to increased neurological abnormalities leading to an increased risk for subsequent dementia. Clinicians utilize the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) to diagnose major depression. A complicating factor in management of late-life depression is the higher rates of coexisting conditions and concomitant medication use, requiring for more careful evaluation of suicide risk and depression screening in this patient population.

The U.S. Preventive Services Task Force (USPSTF) recommends annual depression screening if appropriate treatment and follow-up is available to these patients. Evaluation of past history, warning signs of suicidality or worsening symptoms, and certain laboratory tests like blood count and thyrotropin measurement are required to make an accurate diagnosis and rule out other conditions that may initially present similar to depression.

Treatment options for late-life depression can include lifestyle changes, pharmacotherapy, psychotherapy, and brain stimulation. First-line treatments for late-life depression can involve either pharmacotherapy or psychotherapy, depending on patient preference and availability of psychotherapy. First-line pharmacotherapy are the selective serotonin-reuptake inhibitors (SSRIs), at a low starting dose (e.g. sertraline 25mg daily) and increase as tolerated. In randomized, controlled trials, SSRIs have been shown to be more effective than placebo in reducing depressive symptoms, defined as ≥50% reduction depression severity, rates ranged from 35 to 60% versus placebo rates of 26 to 40%. In addition, SSRIs also increase rates of remission, defined as minimal level of depressive symptoms, with rates of 32 to 44% versus 19 to 26% in placebo. Common adverse effects of SSRIs are mild, which include nausea and headache. Second-line treatment are the serotonin-norepinephrine reuptake inhibitors (SNRIs) used when remission is not obtained with SSRIs, though this class produces more frequent adverse effects as compared to SSRIs. Tricyclic antidepressants (TCAs) have efficacy rates similar to that of SSRIs but are less preferred due to their greater anticholinergic and cardiac side effects. Second-generation antipsychotic agents, olanzapine and aripiprazole, have been approved for adjunctive use in treatment-resistant depression. In a pooled subgroup analysis of three placebo-controlled trials involving mostly younger adults with aripiprazole augmentation, remission rates were higher as compared to placebo augmentation, 32.5% versus 17.1% respectively. However, longer-term safety and efficacy data in older populations are still needed.

The alternate first-line treatment for late-life depression is psychotherapy, either cognitive behavioral therapy or problem-solving therapy. However, caution must be used with application of this treatment to the general population as most studies of psychotherapy for late-life depression involved cognitively intact, educated, and white geriatric populations. In a meta-analysis of 23 randomized, controlled trials, cognitive behavioral therapy displayed high efficacy in reducing depressive symptoms, and was comparable to other psychotherapies. Problem-solving therapy effectively treats depressive symptoms in adults with coexisting executive dysfunction. In a trial with cognitively impaired populations, problem-solving therapy resulted in greater improvement in disability and higher remission rates as compared to supportive therapy. Electroconvulsive therapy (ECT) is the most effective treatment for severe depression, even in elderly patients. ECT should be considered for persons at high risk for suicidality, who are unresponsive to pharmacotherapy, have a deteriorating physical condition, or depression-related disability that prevents their ability to live independently. Remission rates of ECT vary from 30 to 50% in community samples versus 70 to 90% in open-label trials. Whether starting pharmacotherapy and/or psychotherapy, lifestyle changes are encouraged as adjunct to therapy, which involves increase in physical activity, improving nutrition, and increasing engagement in activities and social interactions.

After remission is achieved, continued treatment with either pharmacotherapy and/or psychotherapy has been shown to have significant benefit in reduction
of relapse rates, with the combination of pharmacotherapy and interpersonal therapy to be more effective than monotherapy.

Current data is lacking on efficacy, safety, as well as in long-term use of pharmacotherapy and psychotherapy in older populations to manage late-life depression. Most data available are from younger adults without cognitive deficits and a low risk of dementia. Further studies are needed to address the change in cognition in older adults as a confounding factor in late-life depression.

NSAIDs: A Potential Risk Factor for VTE?11
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Background: NSAIDs are one of the most widely used classes of medications. Clinical trials and meta-analyses have found an increased incidence of cardiovascular events (myocardial infarction, stroke, and sudden cardiac death) associated with their use. This is largely explained by an imbalance of thromboxane and prostacyclin. Arterial and venous thrombosis share a number of pathophysiological pathways however it is not known whether there is an increased risk of venous thromboembolism (DVT and PE) associated with the use of NSAIDs. More well known risk factors for VTE include certain conditions (immobility, pregnancy, cancer, Factor V Leiden, protein C or S deficiency) and medications (oral contraceptive, hormone therapy).

Evidence: A systematic review of the literature was done by Ungprasert, Srivali et al. using Medline, Embase, and Cochrane databases. Six studies (five case-control and one cohort study with a total of 21,401 VTE events) were included in their meta-analysis to evaluate the risk of VTE with NSAID use. For all NSAIDs (non-selective and selective), VTE risk was found to be statistically significant with a pooled risk ratio of 1.8 (95% CI 1.28-2.52). Three of the studies evaluated subjects taking selective COX-2 inhibitors which was also found to be associated with an elevated risk however it was not statistically significant in comparison to all NSAIDs (pooled risk ratio 1.99; 95% CI 1.44-2.75). Although this meta-analysis used high quality studies, publication bias was noted and high statistical heterogeneity was present (I2 95%).

Discussion: Available data suggest NSAIDs nearly double the risk of VTE however much of the evidence is limited and based on retrospective studies. Aspirin, an irreversible COX-1 inhibitor, has a role in VTE prevention which may indicate that the risk could primarily be due to COX-2 inhibition. More studies are needed to explore this association. Nonetheless this finding does raise some concern given the wide use of NSAIDs.

Clinical Impact: For now, we cannot say for sure that this is a cause and effect relationship as other potential patient characteristics can also contribute to VTE risk including underlying conditions and other medications. In clinical practice, we should be continuously reassessing and evaluating the ongoing need in patients taking NSAIDs given the many other risks that this class of medications possesses.

Improving outcomes for diverse populations disproportionately affected by diabetes:
Final results of Project IMPACT: Diabetes12
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Background: Diabetes is a complex disease and when poorly treated can lead to serious complications and increase risks for heart disease, stroke, blindness, neuropathy, amputation, renal disease, periodontal disease, and premature death. Because diabetes management is complicated, patients need access to a comprehensive team of health care professionals who work collaboratively to help manage all aspects of the disease. Previous studies on diabetes including APhA’s Asheville Project have documented the positive impact of pharmacists’ patient care services on clinical and economic outcomes. This project engages pharmacists as integral members of the health care team to improve diabetes outcomes in diverse communities.

Objectives: Project IMPACT (Improving Persistence and Compliance with Therapy): Diabetes is an APhA initiative that seeks to evaluate the impact of pharmacist integration into interdisciplinary health care teams on patients with diabetes in high-risk areas in the United States. Objectives are to expand a proven community-based model of care, improve key indicators of diabetes care, establish peer-to-
peer network mentoring, and establish a platform for change that will drive diabetes care.

**Study design:** The study was a multisite, observational, pre-post comparison study that included patients with diabetes in 25 underserved and at-risk communities. Communities were selected based on an application process that evaluated patient population, resources, information accessibility, team motivation and education, plan for incentive alignment, previously demonstrated success, and leadership. To be eligible for enrollment, patients had to have a diagnosis of diabetes, be newly initiated on diabetes therapy, or be maintained on diabetes therapy but poorly controlled (e.g. A1C>7%). Pharmacists were integrated into interdisciplinary care teams and provided customized diabetes education and medication consultation to patients. Changes in clinical performance measures including hemoglobin A1C, body mass index, blood pressure, LDL-C, HDL-C, total cholesterol, and triglycerides were assessed at baseline then according to practice guidelines for a period of one year. Also assessed was foot examination status, eye examination status, influenza vaccination status, and smoking status. Each patient served as his or her own control for comparative analysis.

**Results:** Participants included 1,836 patients affected by diabetes representing diverse ethnicities, insurance statuses, and social and economic backgrounds. Participant race/ethnicity included 41.4% white, 24.4% black, and 21.5% Hispanic among others, primarily uninsured or underinsured. Average participant age was 54.1 years. Patients had a mean of 5.2 visits with pharmacists, either one-on-one or in collaboration with other health care team members. Pharmacist patient care services resulted in a statistically significant and clinically relevant decrease in mean A1C levels (-0.8%). Other values fell by statistically significant amounts, but since their means were already below target at baseline, the improvement was not clinically relevant (LDL-C -7.1 mg/dL, triglycerides -23.7 mg/dL, total cholesterol -8.8 mg/dL). Changes in HDL-C and blood pressure were not statistically significant. Improvements were also seen in the number of patients not at target for other diabetes measurements: 72% received foot examinations, 51.7% received eye examinations, 41.7% received influenza vaccination, and 9.3% quit smoking. Of the communities involved, 92% intend to sustain pharmacists’ services.

**Conclusions:** Project IMPACT: Diabetes demonstrates that pharmacists working in community based diabetes care teams can significantly reduce A1C levels and other clinical markers of diabetes for patients of various economic, social, and insurance statuses in diverse communities across the United States.

**Key Point:** All patients, even those with barriers to appropriate diabetes care, may benefit from patient-centered, interdisciplinary health care teams that include pharmacists.

**HIV Screening in Community Pharmacies**

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**Background:** Human immunodeficiency virus (HIV) continues to be a current and future health issue in the United States. In 2010, 1.1 million people were infected with HIV, and as many as 18% were unaware of their infection. 50,000 new HIV diagnoses are reported annually. Under current practice, patients must visit a department-supported clinical care site (STI clinic, community health center, or emergency department), physician’s office, or HIV testing sites for testing. Patients’ use of these sites can be hindered by physical distance and social stigma. On the other hand, 70% of rural patients live within 15 miles of a pharmacy, and 90% of urban patients live within 2 miles. Pharmacies may be less stigmatizing and more convenient than some other testing sites. Pharmacies have the potential to become an important resource when it comes to HIV testing. This pilot program determines how to implement confidential HIV testing services in community pharmacies and retail clinics.

**Objective:** “The objective of this study was to test the feasibility of offering rapid, point-of-care HIV testing at community pharmacies and retail clinics.”

**Study Design:** In 2011, the U.S. Centers for Disease Control and prevention (CDC) awarded a 2 year contract to ASHLIN management group, Inc, to create a HIV testing model that could be used in pharmacies as well as in retail clinics. Testing locations were required to get a Clinical Laboratory Improvements Amendments of 1988 (CLIA) Certificate of Waiver. Staff training was completed...
through in-person meetings or webinars. These sessions provided recommendations for obtaining patient consent and how to deliver the rapid HIV testing results accurately, with cultural and social sensitivity. A curriculum was created to outline the procedures for administering rapid, point-of-care HIV tests, specifically on oral fluids. OraQuick Advance Rapid HIV-1/2 antibody was the test used. The length of time spent was recorded for pretest counseling, incubation while waiting for test results, and posttest counseling. Positive and negative test results were also recorded.

These procedures were implemented in two phases. Phase 1 involved 6 pharmacies in 2012. After these sites were trained, the training modules were refined and Phase 2 was started. Fifteen additional sites were added in Phase 2. In-store promotional flyers, local newspaper articles, flyers in customer bags, websites, and social media were utilized for promotion of the testing service.

Results: One hundred and six staff were trained at 21 sites from August 2011-July 2013. These sites consisted of 18 pharmacies, one retail clinic, one nurse-led HIV testing service at an Indian Health Service Clinic, and one multisite venue run by a school of pharmacy. Each rapid-testing site formed a relationship a local health department for patient referral confirmation testing after a positive result and assistance with local norms for HIV point-of-care testing. Out of a total of 1,540 HIV tests completed, 24 positive test results were collected. These patients were referred for confirmatory testing after counseling by a pharmacist or nurse practitioner. Of these 24 patients sent for confirmatory testing, 16 results were not reported back to the rapid-testing site, two were previously diagnosed with HIV, five were false positives, and one was confirmed as a new HIV infection. The time required to conduct the HIV test was also recorded. Pretest counseling/consent time had a median of four minutes (IQR: 2-7 minutes). The median time spent waiting for test results was 23 minutes (IQR: 20-30 minutes). Post test counseling median time was three minutes (IQR: 2-5 minutes), but this increased to 14 minutes with a positive test result.

Conclusion: The success of this pilot program indicates that rapid, point-of-care HIV tests can be completed in a pharmacy or in a retail clinic. One key factor for success in this environment was involvement of local health departments. This, active support from management at each site, as well as the training of pharmacists, nurses, and nurse practitioners can also facilitate a meaningful integration between different health systems and improve public access to testing. Pharmacies are convenient and non-stigmatizing places to perform point-of-care testing.

Key Point: With the proper coordination and training, pharmacies and retail clinics can perform point-of-care testing for HIV. They are convenient and non-stigmatizing places to perform point-of-care testing.

Drugs Associated with Adverse Events in Children and Adolescents
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Several pharmacists from the University of Illinois at Chicago College of Pharmacy set out to identify the medications most commonly associated with adverse events (AEs) in children aged 1-12 and in adolescents aged 13-18. To do this, they reviewed all case reports submitted to the FDA Adverse Event Reporting System from Jan. 1, 2007 to Aug. 27, 2012. 78,623 reports were filed, with 40% of the reports filed for children and 43% of the reports filed for adolescents resulting in serious outcomes (death, life-threatening episode, hospitalization, disability, or congenital abnormality).

The top twenty medications, in order of prevalence, for both groups are: methylphenidate, infliximab, isotretinoin, montelukast, somatropin, etanercept, ibuprofen, lisdexamfetamine, drospirenone and ethinyl estradiol, adalimumab, acetaminophen, lamotrigine, oseltamivir, aripiprazole, atomoxetine, quetiapine, zanamivir, tacrolimus, levonorgesteral, and risperidone.

Several interesting trends also emerged from this analysis. Among the adverse events reported, adolescents were more than twice as likely as
children to experience a serious outcome vs a non-serious outcome associated with methylphenidate, montelukast, and drospirenone and ethinyl estradiol. Children were far more likely than adolescents to have serious outcomes related to isotretinoin and levonorgesterel. Similar AEs were seen in both groups, with the exceptions of isotretinoin and aripiprazole. Aripiprazole was more likely to cause suicidality in adolescents vs. somnolence and dystonia in children. Isotretinoin was more likely to cause inflammatory bowel disease and ulcerative colitis in adolescents compared to children who were more likely to experience hypocalcemia, convulsions, and neuroblastomas.

Similar medications to these have been found in similar studies as well. These numbers are absolute values, which makes it likely the prevalence of these medications has lead to them being top causes of AEs. Even though they may have a lower chance of causing AEs on a per exposure basis than other medications, they still clearly warrant a watchful eye from their pharmacist when being dispensed to children and adolescents based on the number of occurrences.

A Breath of Fresh Air on Inhalation Accessory Devices15-22

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The most common drug delivery method in the treatment of asthma and COPD is inhalation. Correct use of inhaled medication is imperative for efficacy of pharmacotherapy. Ergo, it is important to educate patients how to use metered dose inhalers (MDIs) properly. Spacer devices play an important role in chronic lung disease management. Spacer devices, commonly referred to as “spacers,” provide an area where the initial momentum of drug particles can subside after actuation of a MDI. As a result, drug particles enter the patient’s mouth more gradually, drug particles are more likely to reach the lungs and less drug particles are deposited in the throat. Spacers are generally compatible in connecting to most MDIs. However, there are multiple spacers on the market, several different designs, and often are not covered by insurance. Are spacers worth the added cost? What options are there? Which device is best?

Foremost, proper terminology is important. Traditional spacers comprise a tube that extends the distance between the MDI and the patient’s mouth. Valved holding chambers (VHCs) also extend the distance between the MDI and the patient’s mouth but have critical differentiating features described below. The two most prevalent VHCs commercial spacers are the OptiChamber Diamond® and the AeroChamber Plus® Flow-Vu®, ranging from $20-50 in cost (if ordered with facemask, ordering location, etc). These two VHCs have several important and similar features. Both VHCs have: an anti-static coating to reduce deposition of the drug in the spacer, a high flow whistle to facilitate patient training of proper breathing technique, a built-in one-way valve to prevent exhalation back into the chamber, and they dissemble for cleaning. These VHCs have been shown to reduce total drug exposure by increasing the fine particle fraction and nearly eliminating the output of large-size drug particles, which deposit in the oropharyngeal region.

Research suggests that VHCs improve overall performance in vitro compared to traditional spacers, corrugated spacers, and no spacers. Additionally, VHCs, such as the OptiChamber® and AeroChamber® devices help when inhalation is delayed after actuation, such as with patients who have poor inhaler technique. VHCs reduce the variability caused by the varying time between canister actuation, and start of inspiration and varying inspiratory flow rate. Furthermore, VHCs are preferred over spacers in patients with suboptimal technique because less of the dose is lost.

What if patients cannot afford a VHC? Commonly corrugated plastic spacers are given out for free at pharmacies and clinics. However, research has shown that while throat deposition is decreased with corrugated spacers, less drug reaches the lungs than compared to using a MDI without any spacer device. Certain “homemade” spacers, such as toilet and paper towel rolls, have been shown to increase the amount of drug in the respirable region of the lung compared to a MDI used without a spacer. Spacers made of out plastic bottles have greater variability and inconsistent medication delivery as compared to homemade spacers (e.g. toilet and paper towel rolls, rolled paper) due to the electrostatic charge of the plastic spacer, resulting in unfavorable drug deposition.

VHCs allow the drug to reach the lungs in patients with optimal technique and in patients with suboptimal technique. VHCs also have several features.
to improve inhaler technique. If a VHC is not covered by insurance or if cost is a concern for the patient, a toilet or paper towel roll may be more effective than no spacer. However, little research has been done studying toilet or paper towel rolls and concerns over maintaining a sanitary environment need to be addressed. Corrugated plastic spacers are the least effective and patients would be better off using no spacer at all. Importantly, educating and insuring that patients have proper inhaler technique is paramount. Proper MDI usage education has been shown to improve patient compliance, forced expiratory volume, and peak expiratory flow rate. Inhaler education and the choice of a proper spacer is an important role for pharmacists.

References


