Cardiovascular Safety of Stimulants in Children with Attention-Deficit/Hyperactivity Disorder: A Nationwide Prospective Cohort Study*

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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: To examine whether stimulant use compared with non-use was associated with cardiovascular disease (CVD) in a general population of children and adolescents and in a subset population of youth diagnosed with attention-deficit/hyperactivity disorder (ADHD), and to examine a possible dose-response relationship in regard to such risk.

Study Design: Data for this longitudinal, prospective cohort study was collected from seven Danish national registries. The cohort observed included all children born in Denmark between 1990 and 1999. A total of 714,258 patients were followed. Lifetime data on CV risk factors, psychiatric and somatic diagnoses, prescription drugs, social factors, and demographics was obtained. Parental data regarding medical and socioeconomic background variables was also gathered. Subjects were excluded if they had a diagnosis of ADHD prior to age five. Stimulant treatment included purchase of a prescription for amphetamine, dexamphetamine or methylphenidate. Doses were compared using defined daily doses (DDD) of methylphenidate broken into three categories: (1) 0 to 15 mg/day, 15 to 30 mg/day, and > 30 mg/day. The primary outcome was defined as the child having a hospitalization, emergency department visit, or a clinic contact including a diagnosis code for CVD. Data on use and dose of stimulant medication was measured at three points: At the date of the CV event, and at three and 12 months prior to the event date.

Results: Subjects were observed for an average of 9.5 years. Of all 714,258 subjects studied, 5732 had a CV event resulting in a diagnosis of CVD. Stimulant use was found to increase risk of any CV event compared to non-use in the general cohort, adjusted HR of 1.83 (95% CI 1.10-3.04). Of the 8300 subjects with an ADHD diagnosis, 111 had a CV event. In this subset of study subjects, stimulant use was also associated with an increased risk for any CV event compared with non-use, adjusted HR of 2.34 (95% CI 1.15-4.75). Children prescribed > 30 mg of methylphenidate daily for 12 months experienced a greater number of cardiovascular events than non-users, adjusted HR 2.24 (95% CI 1.20-4.20);
however, when examining the dose at the time of the CV event, the highest risk was in the group of children being prescribed the lowest dose. 57% of children with stimulant-treated ADHD who also experienced a CV event, had a stimulant dose reduction within 12 months prior to the event. Only 30% of children without a CV event had a stimulant dose reduction within the last year (p = 0.0022). In addition, significantly more children with a CV event had discontinued stimulant treatment or had their dose reduced from high/medium to low (43%) versus children without a CV event (24%) (p = 0.017). There was no difference in risk of CV events between children with predisposing risk factors compared to children with no predisposing risk factors who were treated with the same dose of stimulant, adjusted HR = 2.46 (1.98-2.06).

**Conclusions:** Stimulant use was associated with an increased CV risk in children (HR: 1.83; 95%CI 1.1-3.04), and an increased risk in children with ADHD (HR: 2.34; 95%CI 1.15-4.75), although absolute risks were low. Results suggest a complex time- and dose-dependent relationship between CV adverse events and stimulant treatment; high doses of stimulant medications followed by a reduction in dose or discontinuation led to a greater number of CV events. The mechanism of this dosage phenomenon is unknown, however a possible biological explanation may involve alterations to cardiac sympathetic function via upregulation of dopamine transporters (DAT), which is inversely correlated with QTc interval.

**Key Point:** This large, retrospective cohort study showed increased risk of cardiovascular events in children treated with stimulants, including a concern that risk of a CV event may be higher after a dose reduction.

**New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials**

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**Background:** The risk for thromboembolic events increases with age, including stroke related to atrial fibrillation (AF) and venous thromboembolism events (VTE). Along with heparin, Vitamin K antagonists have been the main choice in therapy for treatment and prevention of thromboembolic events. However, the limitations of warfarin are well-known to include food and drug interactions, plus altered drug distribution and pharmacokinetics in the elderly. New Oral Anticoagulants, or NOACs (dabigatran, rivaroxaban, and apixaban), have been approved in the recent years for prevention of and treatment for thromboembolic events as an alternative to warfarin, but their relative safety and efficacy in the elderly population is unclear. These agents require less lab monitoring compared to vitamin K antagonists. Less data however, is available regarding the safety and efficacy of NOACs in the elderly population.

**Purpose:** To evaluate the efficacy and safety of NOACs in elderly adults.

**Study Design:** Meta-analysis of randomized controlled trials (RCTs) of NOACs that included specific data on elderly participants comparing dabigatran, rivaroxaban or apixaban to conventional therapies. The efficacy outcome of interest was VTE or VTE-related death and stroke or systemic embolism. The safety outcome of interest was major or clinically relevant bleeding. The authors analyzed odd ratios (ORs) and 95% confidence intervals for each trial, and addressed publication bias, plus performed subgroup, sensitivity, and follow-up adjusted analyses.

**Results:** Ten RCTs were included in the final analysis with a total 25,031 elderly individuals. Five articles included rivaroxaban, three for apixaban and two for dabigatran. These trials included the treatment of acute VTE or PE, extended treatment for VTE, and AF and included specific data regarding the elderly.

In elderly adults over the age of 75 years, NOACs did not cause greater major or clinically relevant bleeding compared to conventional therapies (6.4% with NOAC vs. 6.3% with conventional therapies; OR=1.02, 95% CI=0.73-1.43). NOACs did not cause extra bleeding for treatment of acute VTE or PI, extended treatment of VTE or AF, but did in acutely ill medical individuals for thromboprophylaxis. Risk of stroke and systemic thromboembolism was lower in NOACS compared to conventional therapies (3.3% vs 4.7%; OR=0.65, 95% CI=0.48-0.87; ARR=1.4%, NNT=71). NOACs had lower risk of VTE or VTE-related deaths compared to conventional therapy. (3.7% vs. 7.0%; OR=0.45, 95% CI=0.27-0.77; ARR+3.3%, NNT=30). Rivaroxaban compared to conventional therapy did not cause any more major or clinically relevant bleeding than conventional therapy in the elderly (4.5% vs 4.5%; OR=1.18, 95% CI=0.64-2.19). Rivaroxaban was as effective or more effective than conventional therapy for the prevention of stroke or systemic embolism and VTE or VTE related death. Apixaban did not cause any greater risk of major or clinically relevant bleeding (5.1% vs 7.4%; OR=0.80, 95% CI=0.43-1.51). Apixaban’s efficacy in reducing risk of stroke to systemic embolism and VTE or VTE-related death was either no different or superior to conventional therapy. Dabigatran was noted to have limited data. Dabigatran’s risk of major or clinically relevant bleeding was not different from conventional therapy (9.3% vs 8.7%; OR=1.07, 95% CI= 0.90-1.28). Dabigatran was superior to conventional therapy in preventing stroke or systemic embolism (3.2% vs 4.3%; OR=0.75, 95% CI=0.58-0.96 ARR=1.1%, NNT=95).
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.

Key Point: NOACs may be an appropriate alternative to conventional anticoagulation therapies in older individuals. Although the meta-analysis suggests NOACs are just as safe and effective in individuals age 75 and over, it is important to communicate to patients and caregivers the bleeding risk that is inherently associated with these medications and that antidotes are not available at this time. Treatment with NOACs is not a “one size fits all” approach. The appropriate selection of NOACs and dose for the elderly population should be determined by age, renal function, liver function, history of bleeds and sites of past bleeds and other patient-specific health conditions.

Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes
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Background: The advent of continuous glucose monitoring (CGM) has allowed the development of bionic endocrine pancreatic systems that include both insulin and glucagon. Previously, the bionic pancreas had only been studied in the inpatient setting for a maximum of 48 hours. Large variations in meals and activity among patients present an additional challenge and the need to test these devices in the outpatient setting.

Objective: A To compare glycemic control with an automated, wearable, bihormonal, bionic pancreas in adults and adolescents with type 1 diabetes mellitus compared to standard insulin-pump therapy in two distinct outpatient settings over a five day period.

Study Design: This article contains two separate studies: the Beacon Hill study (adults) and the Summer Camp study (adolescents). Insulin and glucagon were administered by the bionic pancreas device, which consisted of two separate pumps, one containing rapid-acting insulin and the other containing freshly reconstituted glucagon which was refilled daily. The bionic pancreas was controlled by an iPhone and connected to a CGM. The automatically adaptive algorithm of the bionic pancreas received data from the CGM and meal sizes inputted by the patient to control subcutaneous delivery of insulin and glucagon. Patients received therapy with the bionic pancreas for five days and received therapy with their own insulin pump for five days in a random-order, crossover design.

Results: 52 patients participated in the studies (20 adults and 32 adolescents).

Adults: The mean plasma glucose for the five-day period of wearing the bionic pancreas was 138mg/dl. Plasma glucose levels were <70mg/dl 4.8% of the time and <60mg/dl 2.3% of the time. Overnight, the mean plasma glucose was 125mg/dl, <70mg/dl 4.0% of the time, and <60mg/dl 1.7% of the time. There was no significant difference in the amount of carbohydrate interventions between the bionic pancreas period and the control period. On days two through five of the bionic-pancreas period, compared to the control period, mean plasma glucose on continuous monitoring was significantly lower (133 ±13 vs. 159+ 30, p<0.001), the percentage of time with a glucose level between 70-180mg/dl was higher, and the percentage of time with a glucose <70mg/dl or <60mg/dl was lower.

Adolescents: The mean glucose level was 138+18mg/dl during the bionic pancreas period and 157+27mg/dl during the control period (p=0.004). The percentage of time with glucose levels <70mg/dl was similar between the periods. There were significantly less carbohydrate interventions during the bionic pancreas period compared to the control period. The mean glucose level days two through five of wearing the bionic pancreas was significantly lower compared to day one, but there was no significant difference between the percentage of time with a plasma glucose <70mg/dl. Overnight, patients wearing the bionic pancreas had significantly lower mean glucose levels compared to the control period, and also a larger percent of time in the 70-180mg/dl range, with no significant differences in time with glucose levels <70mg/dl.

Conclusions: Compared to the conventional insulin pump, a wearable, automated, bihormonal, bionic pancreas improved mean glycemic levels, with less frequent hypoglycemic episodes, among both adult and adolescent patients with type 1 diabetes mellitus.

Key Point: The bionic pancreas therapy demonstrated better glycemic control compared to insulin pump therapy in the outpatient setting over a five day period in patients with type 1 diabetes. However, studies with a longer duration and larger sample size need to be completed to better demonstrate the safety and efficacy of the bionic pancreas.
Efficacy of Varenicline Combined with Nicotine Replacement Therapy vs Varenicline Alone for Smoking Cessation: A Randomized Clinical Trial

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Background: The use of tobacco increases complications in both respiratory and cardiovascular disease and contributes to several different cancer types. To improve health outcomes, one of the best interventions a health professional can make is encouraging smoking or tobacco cessation. Varenicline blocks the actions of nicotine at the nicotine cholinergic α4β2 receptor and is also a partial agonist. A nicotine patch also acts on the nicotine cholinergic receptor, similar to how tobacco smoke would act on this receptor. Previous studies have investigated the effects of both varenicline and nicotine replacement therapy (NRT) on smoking cessation but these were small studies with short durations. Although previous studies found the combination to be safe and well tolerated, they did not show a benefit using the combination together.

Objective: The purpose of this study was to assess the effectiveness and safety in smoking cessation of combination therapy with varenicline and nicotine patch versus monotherapy with varenicline.

Study Design: A double blind, placebo-controlled study randomized a total of 446 smokers from seven different health care centers in South Africa to either varenicline plus placebo patch (224 patients) or varenicline plus 15 mg nicotine patch (222 patients). The time frame consisted of 12 weeks of treatment and 12 weeks of follow-up. Patients were instructed to wear patches for 16 hours daily starting 2 weeks before the targeted quit date and continuing until 12 weeks after the quit date. Varenicline 0.5 mg once daily began one week before the target quit date. After 3 days it was titrated up to 0.5 mg twice daily for 4 days, was continued at 1 mg twice daily until week 12, and then was slowly tapered for the next week. Generally healthy patients ages 18-75 who smoked 10 cigarettes or more daily and were not abstinent from smoking for greater than 3 months during the previous year participated. Exclusion criteria included antidepressant use within the past year, a history of a psychotic disorder, severe chronic obstructive pulmonary disease, cardiovascular disease within the past 6 months, use of NRT in the past 6 months, and additional criteria located on page 156 of the original article. The primary outcome was the percentage of patients who were completely abstinent from smoking the last four weeks of treatment (weeks 9-12) measured via exhaled carbon monoxide levels. This was calculated via multiple imputation of the per protocol analysis which included 216 patients in the combination group and 219 patients in the varenicline and placebo group. Secondary outcomes measured abstinence at 6 months, continuous abstinence at weeks 9 through 24, and adverse effects.

Results: The per protocol analysis showed the combination group had a higher rate of continuous smoking abstinence at 12 weeks (55.4% vs 40.9%, OR 1.85, 95% CI 1.19-2.89, p=0.007) and 24 weeks (49% vs 32.6%, OR 1.98, 95% CI 1.25-3.14, p=0.004) than the varenicline and placebo group. Point prevalence abstinence rate at 24 weeks was also higher for the combination group (65.1% vs 46.7%, OR 2.13, 95% CI 1.32-3.43, p=0.002). The intention to treat analysis showed continuous abstinence at 12 weeks in 44.6% of patients for the combination group versus 31.3% for varenicline and placebo (OR 1.77, 95% CI 1.18-2.66, p=0.004). There were a similar amount of patients experiencing side effects in the combination group and the varenicline and placebo group for: nausea (27.3% vs 24.7%, respectively), insomnia (19.9% vs 15.1%), headaches (7.9% vs 10%), and depression (2.3% vs 1.4%). There were significantly more skin reactions in the combination group (14.4% vs 7.8%, p=0.03).

Conclusions: The combination of varenicline and the nicotine patch is more efficacious than varenicline and placebo for the goal of smoking cessation and has shown success with continuous abstinence from smoking 3 months after completion of combination therapy. The main difference in side effect profiles was a skin reaction to the nicotine patch. Future studies should be conducted to include a broader population of smokers who have more co-morbidities with other forms of NRT.

Key Point: The combination of varenicline and the nicotine patch is more efficacious with helping patients to quit smoking and has comparable side effects to patients taking varenicline monotherapy.
**Afrezza® (insulin human) Inhalation Powder – MannKind Corporation**

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**Indications:** Afrezza® (insulin human) Inhalation Powder is a rapid-acting, orally inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus. It was approved by the FDA in June of 2014 and is expected to be available in the United States by the first quarter of 2015.

**Mechanism of Action:** Afrezza® is regular insulin in a novel dosage form, and it exhibits established pharmacokinetics of regular insulin once in systemic circulation. The absorption of Afrezza® results in maximum serum concentrations at 12-15 minutes, although this did not result in a faster onset of activity; the median time to maximum effect was 53 minutes.

**Dosage and Administration:** Afrezza® should be administered via oral inhalation using the Afrezza® Inhaler and cartridges (4- and 8-unit dose cartridges available). A combination of cartridges may be necessary to achieve the required dose (i.e. two 8-unit and one 4-unit cartridges to provide a 20 unit dose). The cartridges should be kept refrigerated and must be used within ten days at room temperature and three days of being opened. Information on inhaler technique can be found in the Medication Guide.

**Effectiveness:** A total of 3,017 patients with diabetes mellitus (1,026 with type 1 and 1,991 with type 2) were evaluated in four, phase three clinical trials. In one 24-week trial in patient with type 2 diabetes mellitus, Afrezza® was found to be superior to placebo in reducing HgA1C as well as the percentage of patients to reach their goal HgA1C. In the three other similar trials of 24-, 52-, and 52-weeks, Afrezza® with meals was compared to subcutaneous insulin aspart with meals, both treatment arms utilizing basal insulin. In two out of three trials the treatment arm met its primary, non-inferiority endpoint of the pre-specified <0.4% for mean reduction in HgA1C.

**Safety:** Afrezza® is contraindicated in patients with chronic lung diseases due to acute bronchospasm seen in this patient population; the FDA has subsequently issued a REMS program for acute bronchospasm. There was a small, but statistically significant, decrease of 40 mL seen in FEV1 during clinical trials; FEV1 measurements are recommended at baseline, six months and annually thereafter in all patients starting Afrezza®. In clinical trials the most common reason for discontinuation of therapy was cough, seen in 27% of treated subjects. Other adverse events were similar to fast-acting insulin, however Afrezza® showed lower rates of weight gain and hypoglycemia than insulin aspart in clinical trials.

**Place in Therapy:** Afrezza® may replace standard subcutaneous mealtime insulin in some individuals with both type 1 and type 2 diabetes mellitus. It is not a replacement for long or intermediate acting insulin and should not be used as monotherapy in patients with type 1 diabetes. Afrezza® should not be used in patients with asthma, COPD, or any other chronic lung disease.

**Cost:** Information is not available at this time.

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**Glucagon-Like Peptide-1 Receptor Agonists for Diabetes Mellitus: A Role in Cardiovascular Disease**

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**Background:** Diabetes is a major risk factor for cardiovascular disease, and these macrovascular complications remain the leading cause for mortality. Clinical trials using strict glycemic control have not been able to establish macrovascular benefits, as opposed to clear benefits to reduce risk of microvascular complications. Incretin therapies, dipeptidyl-peptidase IV (DPP-IV) inhibitors and glucagon-like-peptide-1 (GLP-1) receptor agonists, were developed as adjunct therapies to conventional diabetes treatment. Evidence thus far has not shown improved cardiovascular benefits with DPP-IV inhibitors, but studies are currently underway to assess these outcomes for GLP-1 agonists. GLP-1 agonists stimulate glucose-dependent insulin release from pancreatic β-cells, inhibit glucagon
secretion, and enhance insulin gene transcription and synthesis. GLP-1 also decreases GI secretions, mobility, and gastric emptying, and may decrease appetite and promote weight loss through effects on the hypothalamus.

**Evidence:** Studies have found considerable reductions in A1C without an increase in hypoglycemia. Reduced appetite and delayed gastric emptying have been observed, resulting in weight loss of 2.0-2.4 kg and 4.8 kg relative to placebo and insulin, respectively. Improvements in lipid profile and blood pressure have also been noted. There are several safety concerns with GLP-1 agonists such as pancreatic cancer, medullary thyroid cancer, and a small increase in heart rate. Prospective trials have found differing conclusions, and do not report increased risk of pancreatitis or pancreatic cancer.

**Discussion:** Large trials are ongoing to assess long-term cardiovascular safety and clinical outcomes of GLP-1 agonists. The lack of this data may explain why this class of medication is second line therapy after metformin. Current data is optimistic that GLP-1 agonists may have a role in patients with prediabetes and cardiovascular risk factors. This class of medications may also help reduce insulin doses or delay insulin initiation.

**Is It Time to Add DPP4 Inhibitors to the List of Medications to Avoid in Our Heart Failure Patients?: A Meta-Analysis**

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**Cub Pharmacy**

**Background:** Developers of all newly approved medications for the treatment of diabetes mellitus are responsible for evaluating the cardiovascular safety of their product by carrying out clinical trials. The results of one such study, the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis in Myocardial Infarction-53 (SAVOR TIMI-53) trial found that saxagliptin did not increase the risk of major cardiovascular events, but did statistically significantly increase the risk of hospitalization for heart failure compared to patients treated with placebo.

**Purpose:** Considering the results of the SAVOR TIMI-53 trial, the authors of this meta-analysis sought to evaluate the available information on “treatment-emergent” serious adverse event cases of acute heart failure described in randomized clinical trials involving any dipeptidyl peptidase-4 inhibitors (DPP4i’s). The objective of the analysis was to determine whether or not heart failure exacerbation is an adverse effect of the class of DPP4i’s versus specific medications within this class.

**Study Design:** This meta-analysis was performed by searching for randomized, clinical trials comparing a specific DPP4i agent with either placebo or non-DPP4i anti-diabetic treatment(s) compiled in the databases of Medline, Embase, and Cochrane Central Register of Controlled Trials. Both published and unpublished trials were evaluated. Specific drug names included in the search were alogliptin, dutogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. In order to be included in the analysis, trials had to have been carried out for at least 24 weeks and involve patients with Type 2 diabetes. If a clinical trial involved the co-administration of DPP4i’s and either insulin, sulphonylureas, or thiazolidinediones, those results were evaluated separately. The authors of this analysis defined “treatment-emergent” heart failure exacerbation as any exacerbation “requiring hospitalization and/or was life-threatening or posing a permanent threat to patient’s integrity.”

**Results:** The authors’ initial search identified 109 trials. Upon a more thorough evaluation, some were excluded due to no results reported or if there was no classification of heart failure as a serious event. Ultimately, analysis of 37 eligible studies lead to a total of 448 cases of acute heart failure exacerbations during DPP4i treatment and 361 cases in the other groups. These data resulted in an odds ratio of 1.19 (1.03-1.37) and a p-value of 0.015 (<0.05). While 37 trials were evaluated, 89% of events were found in the only two trials which were designed to evaluate cardiovascular events and effects, the SAVOR TIMI-53 trial and the Alogliptin after acute coronary syndrome in patients with type 2 diabetes (EXAMINE) trial. Both of these trials had substantially larger subject numbers than any other trials included in the analysis. When the results of these two trials were taken together, a significant increase in risk was seen (p=0.004); however, no statistically significant increased risk was found when these two trials were excluded from results analysis. The increase in risk was also not significant when trials involving co-administration of DPP4i’s and either thiazolidinediones or sulphonylureas were excluded. After evaluating each drug within the DPP4i class separately, only saxagliptin was found to have a statistically significant increase in risk of
acute heart failure exacerbations (p= 0.024). This significance was realized due to the results of the SAVOR TIMI-53 trial, as the p-value rose above 0.05 when this trial was excluded.

Conclusions: The authors of the SAVOR TIMI-53 trial do not support the conclusion that heart failure exacerbations are a class effect, as they state their results may have been skewed due to multiple outcome testing. The authors of this analysis state that despite non-significant results in many of the individual trials evaluated, when analyzed collectively, the risk was statistically significant. This suggests that heart failure exacerbation leading to hospitalization may be a class effect for DPP4i’s rather than an adverse effect specifically associated with saxagliptin.

It is particularly important to evaluate the differences between the typical subjects enrolled in a cardiovascular versus non-cardiovascular trial, considering the majority of the events discussed occurred in the two cardiovascular trials evaluated. These subjects tend to be older, have longer disease durations, are at higher cardiovascular risk, have decreased renal function, and are often on multiple medications to manage disease states.

Key Point: Available information may point to a correlation between an increased risk of heart failure exacerbations with DPP4 inhibitors as a class, but remains insufficient to confidently make this association. It is possible that patient specific characteristics are more significant factors in influencing the risk of heart failure exacerbations. There may be cause for greater concern with the use of saxagliptin in patients at risk for heart failure exacerbations based on the SAVOR TIMI-53 trial. As always, it is important to weigh the risks versus benefits for individual patients when evaluating drug therapy.

From the Pharmacy Press

Prescription Medication Burden in Patients with Newly Diagnosed Diabetes: A SUrveillance, PREvention, and ManagEment of Diabetes Mellitus (SUPREME-DM) Study Sarah Amlin, Pharm.D. Community University Health Care Center

Background: Past studies on the medication burden in diabetes have looked at the number of antihyperglycemics prescribed to newly-diagnosed diabetics. They have not addressed the overall pill burden in newly-diagnosed diabetes or addressed common comorbid conditions that can also increase the amount of medication a patient is taking.

Objective: To quantify, using EMR records, the medication burden before and after diabetes diagnosis.

Study design: SUPREME-DM was a retrospective cohort study using patient demographics, diagnoses, medication, and laboratory data from six health systems between January 1, 2005 and December 31, 2009. A total population of 196,654 patients was identified. Inclusion criteria were age 20 or older, and having met laboratory or diagnostic criteria for new-onset diabetes. Diagnosis was made by one inpatient or two outpatient abnormal lab values, such as fasting plasma glucose >126, random plasma glucose > 200, A1c > 6.5%, or 2-hour, 75-g oral glucose tolerance test > 200, not during pregnancy.

Exclusion criteria were antihyperglycemic medication dispensed within the last two years or diagnostic laboratory values in the last two years. Medication burden was calculated based on the number of unique drug classes in dispensing data. Drug classes were based on AHFS Pharmacologic-Therapeutic Classification system, but antihistamines, anti-infectives, disinfectants, local anesthetics, diagnostic agents, devices, pharmaceutical aides, and vaccines were all excluded. The 12-month periods before and after diagnosis were considered. They further divided this data to quantify increases/burden in antihyperglycemics, antihypertensives, antihyperlipidemics, and mental health medications.

Data was analyzed for increase in overall medication burden, increases in medication burden within the selected drug classes, and increase in medication burden according to patient demographics.

Results: Medication burden was significantly different for pre-diagnosis (4.98 ± 4.05) and post-diagnosis (6.63 ± 4.14). Of this increase in medications, 81% was antihyperglycemics, antihypertensives, and antihyperlipidemics. This suggests an increased awareness of the cardiovascular risk associated with diabetes. Increases in mental health medications were predominantly antidepressants (58%). Demographic variables that were more likely to have a higher medication burden post-diagnosis include female gender, older age, white (non-
hispanic), obesity, and a higher A1c at diagnosis. Patients with higher A1c were also more likely to have a greater number of antihyperglycemic medications added. This study was not able to tell if dispensing data matched prescribing data, though they assumed, based on past studies, that the no fill rate for a newly diagnosed diabetic was low. It also could not differentiate between type 1 and type 2 diabetics.

**Conclusions:** A diabetes diagnosis increases medication burden in all patients. It is most likely to increase when patient is female, older, obese, or has a higher A1c on diagnosis. This medication burden is mostly the addition of antihyperglycemics, antihypertensives, and antihyperlipidemics. Cardiovascular risk is being recognized and preventative measures are being taken. This article briefly touches on the disparities that are found in prescribing for different ethnic groups, but does not make any conclusions or address it in the discussions.

**Key Point:** A new diagnosis of diabetes does increase a patient’s medication burden. It is most likely to increase the number of antihyperglycemic, antihypertensive, and antihyperlipidemic agents. An initial prescription for an antihyperglycemic agent should indicate to the pharmacist to look for an increase in other medications and assist the patient in handling their newly increased medication burden.

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**Health Care Coverage under the Affordable Care Act – A Progress Report**

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The first open-enrollment period created by the Affordable Care Act (ACA) came to a close on March 31st, 2014. Despite the much publicized technical troubles of both state and federal marketplaces, 8 million Americans enrolled for health insurance through these platforms which exceeded the Congressional Budget Office’s (CBO) prediction. Three other enrollment avenues were also utilized as follows.

Starting in 2010, young adults were allowed to remain on their parent’s policy until they turned 26 years of age. A 2013 survey showed that 7.8 million young adults were enrolled in a parent’s plan that would not have been eligible to do so before the passage of the law.

Additionally, individuals were able to sign up for health insurance outside of the marketplaces directly through insurance companies. With added protection for those patients who would have been previously denied coverage or faced exorbitant premiums due to age or preexisting health conditions, it is estimated that an additional 5 million people may gain coverage in 2014 directly from insurers.

With the implementation of the ACA, Medicaid underwent its largest expansion since 1965 to include people with incomes of up to 138% of the poverty level. The federal government is covering 100% of the expansion costs for most states through 2016 with a gradual reduction in financing to 90% for all states by 2020 which will create an 800 billion dollar infusion into states through 2022. States opting out of Medicaid expansion are projected to leave nearly 5 million people uninsured. Since the launch of the ACA, 6 million people had enrolled in Medicaid or the Children’s Health Insurance Program (CHIP). Many found out that they were eligible through the marketplaces.

Taking into account all the coverage avenues, the authors estimated that 20 million Americans have gained coverage as of May 1st. More Americans are expected to gain coverage through their employers as the insurance markets for small businesses go into operation in 2015. The CBO now projects that the number of uninsured people will decrease by 26 million by 2017 due to the ACA.

The ACA successfully expanded coverage for millions of Americans in its first year, but the next great test for the United States health care system will be to develop and implement innovative approaches to health care delivery that provide greater quality at lower costs. The next open enrollment period will run from November 2014 through February 2015.
It is well documented that as many as one-third of all patients in the United States are currently taking natural, herbal, or alternative medicines. However, patients often do not disclose their use to healthcare professionals. One study reported that 70% of patients did not tell their healthcare provider about natural products they are taking before surgery, generally due to thinking the product was harmless and thus not a medication to bring up in pre-surgery appointments. That same study also found that some patients think healthcare professionals would be biased against alternative medication or that he or she would be judged on the use of these products. Natural products are often overlooked when assessing a patient’s health due to lack of studies on effectiveness, when in reality they could substantially affect outcomes. They can also have many drug interactions which can be of importance, particularly during surgical interventions.

Natural products can cause many adverse effects; in the surgical setting alone herbal medications have been observed to cause myocardial infarction, stroke, bleeding, decreased blood glucose, loss of blood pressure control, over- or under-sedation, organ transplant rejection and increased heart rate. Herbals can also affect the QTc interval, serotonin levels, and metabolism of medications used during surgery. The complete list of herbal medications implicated with outcomes that may affect surgery is too long to include in this article, however many of them are commonly used by patients, including garlic, high dose fish oil, ginkgo, saw palmetto, kava, coenzyme Q10, grapefruit juice, valerian, melatonin, glucosamine, chondroitin, ephedra, St. John’s wort and fenugreek.

A general recommendation that is supported by the American Society of Anesthesiologists (ASA) is that all herbal medications should be discontinued two to three weeks before surgery. Unfortunately, the ASA has no formal recommendation of its own. Supported in the study by Ang-Lee, et al., if the half-life of the product is known, it can be discontinued five half-lives before the time of surgery to ensure enough of the medication has been cleared from the body to be safe. However, many herbals have no good data on half-life, so this may not be a feasible suggestion.

In conclusion, due to the lack of studies and specific effects regarding herbal or alternative medications, caution should be used in patients taking them that require surgery. In addition, an accurate medication history should always be taken to ensure that providers are aware of any products a patient is taking on their own accord.

References