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Research Updates

SGLT2 Inhibitors: A Systematic Review of Diabetic Ketoacidosis and Related Risk Factors[1]

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Background: Sodium glucose cotransporter-2 (SGLT2) inhibitors are recommended by the American Diabetes Association (ADA) for the treatment of type 2 diabetes as one of six second-line therapy options after initial therapy with metformin. In addition, they have been studied in combination with insulin as a potential option for treating patients with type 1 diabetes. These medications act by inhibiting SGLT2 in the renal proximal tubule, which decreases the renal threshold for glucose. This results in urinary glucose excretion and consequently lower plasma glucose levels.

In May 2015, the FDA alerted the public to a potential concern for diabetic ketoacidosis (DKA) with SGLT2 inhibitor use. Twenty cases of DKA were identified through adverse event reporting during the first 14 months that SGLT2 inhibitors were approved for use in the United States. Currently only minimal information is available regarding risk factors for the development of SGLT2 inhibitor-related DKA.

Objective: The primary objective of this review was to identify patient-specific factors contributing to the incidence of DKA in patients with diabetes treated with SGLT2 inhibitors.

Study Design: A comprehensive search of Medline, Cumulative Index to Nursing and Allied Health (CINAHL), International Pharmaceutical Abstracts and EBSCOHost Academic Search Complete was conducted by the investigators using specific drug-related and adverse effect-related combinations of search terms. A publication was deemed eligible for inclusion if it involved human subjects, was published in English, included patients with diabetes and was in the format of case series or case report. Case reports were analyzed using descriptive statistics.

Results: Thirty-four cases out of 36 individual case reports were included in this review with 25 cases involving patients with type 2 diabetes and nine cases involving patients with type 1 diabetes. The average age was 50.4 years, 18 patients (52.9%) were female and 16 patients (47.1%) were male, the average hemoglobin A1C was 8.85 +/- 1.76% and the average blood glucose at presentation was 265.6 mg/dL.

Common precipitating factors included patients who were diagnosed with type 2 diabetes and were subsequently found to have latent autoimmune diabetes of adulthood (LADA), patients who had recently undergone major surgery, which included gastric bypass, pancreatectomy, elective coronary artery bypass grafting, cholecystectomy and cervical surgery or patients who had decreased or discontinued insulin.

Of the 34 cases found, nine patients (36%) were diagnosed with latent autoimmune diabetes of adulthood (LADA) following the episode of DKA, seven patients (28%) developed DKA following major surgery and six patients (24%) stopped insulin.

Conclusions: In this review, episodes of DKA with SGLT2 inhibitor use were characterized by lower blood glucose levels and were often caused by a precipitating factor. The most common precipitating factors included patients who underwent major surgery, who were diagnosed with LADA and who had decreased or discontinued insulin.

Key Point: By understanding the etiology and precipitating factors of DKA with the use of SGLT2 inhibitors, clinicians can take the necessary precautions to reduce future events.

Exenatide Plus Pioglitazone Versus Insulin in Poorly Controlled Type 2 Diabetes[2]

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Background: A combination of a thiazolidinedione (TZD) and a glucagon like peptide-1 (GLP-1) agonist represent a potential alternative to insulin for the treatment of type 2 diabetes (T2DM) in patients who are poorly controlled. The combined mechanism of improving beta cell function from the GLP-1 and TZD, with additional increase in insulin sensitivity from the TZD, target major metabolic defects responsible for the progression of T2DM. Limited research has been done focusing on this combination of agents compared to insulin treatment.

Objective: To compare efficacy and safety of combination therapy with pioglitazone, a TZD, plus exenatide, a GLP-1, versus basal-bolus insulin regimens in patients with poorly controlled T2DM currently on metformin and a sulfonylurea.

Study Design: This open-label, single centered, randomized control trial split eligible subjects into two treatment arms; one to receive combination therapy of exenatide extended release (2 mg weekly injections) and pioglitazone (15 mg/day) and the other to receive insulin glargine and aspart as a basal-bolus insulin regimen. The study population included patients with T2DM aged 18-75 with HbA1c of >7.5% and currently on at least 1500 mg metformin daily plus a sulfonylurea (>4 mg glimepiride or >60 mg gliclazide). Subjects indicating evidence of retinopathy, albumin excretion >300 mg/day and major organ disease were excluded. Goal HbA1c was <7% for treatment unless hypoglycemia (blood glucose <60 mg/dL) was encountered. Those individuals on insulin were titrated to a fasting blood glucose (FBG) of <110 mg/dL with basal insulin. If HbA1c remained above 7% at this goal, 4-6 units of prandial insulin was added before each meal and titrated to a 2 hour post-prandial blood glucose of <140 mg/dL. Follow-up occurred monthly during the first 4 months and then bimonthly thereafter for a total duration of 18 months.

Results: A total of 251 patients were randomized to combination (exenatide/pioglitazone) or insulin therapy (129 combination, 122 insulin). Baseline characteristics were similar between each group. For the primary outcome of HbA1c difference, there was a statistically significant difference in subjects receiving combination therapy compared to insulin at 6 months (0.7%, $p<0.0001$), 12 months (0.9%, $p<0.0001$) and 18 months (1%, $p<0.0001$). More subjects receiving combination therapy achieved HbA1c treatment goal of <7% versus those receiving insulin therapy ($P=0.003$). To determine efficacy of combination therapy in relation to baseline glycemic control, subjects were divided into equal groups based on their starting HbA1c (HbA1c >9.5% and HbA1c 7.5-9.5%). There was equally effective lowering of HbA1c in both HbA1c groups with no statistical difference in change of HbA1c at 3 months. Changes in HbA1c were also independent of age, sex, body mass index (BMI) and diabetes duration.

Baseline FBG was similar between combination therapy and insulin therapy groups (231 ± 8 mg/dL and 237 ± 7 mg/dL, respectively) and decreased rapidly after initiation of therapy in both groups but was not statistically significant at 6 months (107 ± 2 mg/dL for combination therapy and 105 ± 3 mg/dL for insulin). Mean body weight increased in both groups, but less with the combination therapy compared to insulin therapy (2.1 vs 4.2 kg, $p<0.0001$). Hypoglycemia was the most common treatment-related adverse event, reported by 66% of subjects with combination therapy compared to 91% of subjects with insulin therapy ($p<0.0001$). Mild peripheral edema was reported more in the combination therapy group (9.3% vs 3.4%) and five cardiovascular events occurred, all in the insulin therapy group.

Conclusions: Regardless of age, sex, BMI or baseline HbA1c, combination therapy of exenatide plus pioglitazone results in a robust reduction in HbA1c and less occurrence of hypoglycemia compared with insulin therapy. Further research with larger patient populations and longer follow-up will be important to apply these findings.

Key Point: This trial suggests that combination therapy of a GLP-1 and TZD represents a safe and effective alternative to basal-bolus insulin therapy in patients with poorly controlled T2DM.

Quetiapine Monotherapy for the Treatment of Posttraumatic Stress Disorder[3]

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Background: Posttraumatic stress disorder (PTSD) is a chronic, disabling illness that has been estimated to have a lifetime prevalence of approximately 7.8% in the United States. The prevalence of PTSD is higher in certain trauma populations, such as combat veterans. Psychotic symptoms, anxiety, mood disorders and substance use disorders are comorbidities frequently associated with PTSD. Currently, antidepressants are the first-line therapy for treatment of PTSD, with paroxetine and sertraline being the only FDA approved agents for the treatment of this illness. It has been shown that some patient populations, specifically male combat veterans, respond poorly to antidepressants. Several studies have shown some benefit of using second-generation or atypical antipsychotics either as monotherapy or adjunctive therapy in patients with PTSD.

Purpose: The purpose of this randomized, placebo-controlled, double-blind study was to determine the efficacy of quetiapine as monotherapy for the treatment of military PTSD. The primary outcome was the total Clinic-Administered PTSD Scale (CAPS) score. Secondary efficacy measures included subscales of the CAPS, which included re-experiencing, avoidance and hyperarousal, as well as other scores from other assessment tools.

Study Design: Patients were recruited from the Ralph H. Johnson VA Medical Center in Charleston, SC and the Raymond G. Murphy VA Medical Center in Albuquerque, NM. Male and female veterans between the ages of 18 to 65 years were recruited to participate in this study if they met the DSM-IV criteria for chronic PTSD. They had to be capable of giving informed consent and have a score of at least 50 on the CAPS. Psychotropic or herbal remedies were withheld for 1 week prior to randomization (2 weeks for fluoxetine) and during the course of the study, with the exception of rescue medications. Rescue medications included, chloral hydrate for insomnia or agitation and lorazepam for anxiety or agitation. Exclusion criteria included quetiapine sensitivity, use of psychotropic medications 1 week prior to randomization or during the study and medical conditions that would prevent safe administration of quetiapine or may exacerbate anxiety symptoms. Participants who met the eligibility requirements were given a 1-week, single blind placebo lead-in. Nonresponders were then randomly assigned to receive either double-blind quetiapine or placebo tablets for 12 weeks. The medication was administered in a fixed-dose titration based on clinical response and tolerability.

Results: Of the screened patients, 119 patients entered the single-blind placebo lead-in phase with 80 patients being randomly assigned to the quetiapine (n=42) or placebo (n=38) group. The majority of patients were male combat veterans, with no difference in the percentage of males between the two groups. Efficacy measures were conducted at weeks 2, 4, 8 and 12. There was a significant reduction in the CAPS total for patients receiving quetiapine compared to the placebo group ($F=2.88$ $df=4,240$ $P=0.03$). Additionally, the quetiapine group had greater improvement on the re-experiencing and hyperarousal CAPS subscales. Quetiapine did not significantly improve the avoidance/numbing subscale when compared to placebo. The final dose range for both groups was between 50-800 mg daily, with the average dose of quetiapine being 258 mg daily and the average dose for placebo was 463 mg daily. No patients dropped out of the treatment group due to lack of efficacy; nine patients dropped out of the placebo group for this reason. Adverse effects were typically mild and similar to safety patterns associated with quetiapine established in the past. No significant differences in safety were noted between the quetiapine and placebo groups.

Conclusion: Given the patient population included in this study, the findings suggest that quetiapine can be used as a single agent to treat military PTSD. Although quetiapine significantly improved CAPS score, most patients remained symptomatic. It is important for clinicians to offer additional psychopharmacological or psychotherapeutic interventions in addition to quetiapine therapy.

Key Point: Quetiapine monotherapy is efficacious in the treatment of posttraumatic stress disorder.

Dual Antiplatelet Therapy Versus Aspirin Monotherapy in Diabetes Patients With Multivessel Disease Undergoing CABG[4]

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Background: CHEST guidelines currently recommend dual antiplatelet therapy (DAPT) of aspirin and a thienopyridine post-operatively in patients who undergo coronary artery bypass grafting (CABG) following acute coronary syndromes, but the risk of bleeding with DAPT is not known. Diabetes itself is a risk factor for graft failure and subsequent increases in perioperative and

long-term mortality in CABG patients. Given this increased risk, these patients are thought to benefit from DAPT in lieu of aspirin monotherapy for secondary prevention, but there is little evidence to support this.

Purpose: The purpose of this study was to evaluate long-term clinical and safety outcomes associated with DAPT versus aspirin monotherapy post-CABG in patients with diabetes and multivessel coronary artery disease.

Study Design: This study was a post-hoc, nonrandomized analysis from the FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial. In the FREEDOM trial, patients age 18 and older with diabetes mellitus and with greater than 70% stenosis were randomized to either CABG or percutaneous coronary intervention with drug-eluting stents. This study analyzed patients who underwent CABG and were taking aspirin 30 days post-operatively. The DAPT cohort included patients taking aspirin and a thienopyridine (clopidogrel or ticlopidine), and the aspirin cohort included patients using aspirin monotherapy. Patients using warfarin were excluded from this study The primary outcome was the FREEDOM trial primary endpoint of 5-year all-cause mortality, nonfatal myocardial infarction (MI) or stroke. Safety outcomes were major bleeding, blood transfusions and bleeding hospitalization. Secondary outcomes included vascular death, MI and CV hospitalization (unstable angina, MI, heart failure, chest pain, arrhythmia, peripheral vascular disease, stroke or transient ischemic attack). The two groups were compared using Fisher exact test.

Results: At 30 days post-CABG, 251 (31.6%) patients received aspirin alone and 544 (68.4%) patients received DAPT. The median (25th, 75th percentile) duration of clopidogrel therapy was 0.98 (0.23 to 1.91) years. There was no significant difference in the 5-year primary composite outcome between DAPT- and aspirin-treated patients (P=0.39). The secondary outcomes were similar for patients receiving DAPT versus aspirin monotherapy in subgroups with pre-CABG ACSs (P=0.88) and those with stable angina (P=0.42). There were no treatment-related differences between monotherapy and DAPT for major bleeding, (HR 1.0 [95% CI 0.50 - 1.99]), blood transfusions, (HR 1.09 [95% CI 0.5 - 2.34]) or hospitalization for bleeding, (HR 0.85 [95% CI 0.34 - 2.17]).

Conclusions: This secondary analysis of the FREEDOM trial found no significant differences in all-cause mortality, MI, stroke or bleeding outcomes for patients with diabetes who undergo CABG and received DAPT or aspirin monotherapy. However, this may be due to inadequate power because of a small number of events. Larger randomized, controlled studies need to be conducted to specifically evaluate the need for DAPT in patients with diabetes post CABG.

Key Point: Although the study found no difference in 5-year efficacy or safety outcomes, pharmacists should be carefully monitoring patients on DAPT or monotherapy for bleeds. Additionally, the results of this study question the need for DAPT in patients with diabetes who undergo CABG. This highlights the importance of pharmacists who can ensure that patients are using only medications that are indicated and effective. Between specialty and primary care providers, pharmacists can play a key role in ensuring the most appropriate use of medications, which in this case, may mean minimizing medication exposure. More research is needed to determine if DAPT is necessary. Until there is substantial evidence available and updated guidelines, pharmacists can assess these patients for the need for continued DAPT therapy as recommended by the guidelines, while keeping in mind that this new data shows there may not be added benefit.

Depression and Smoking Cessation: Evidence from a Smoking Cessation Clinic with 1-Year Follow-Up[5]

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Background: Despite noted harmful effects, smoking remains a prevalent habit today. Smoking is also more common in people with depression; among patients diagnosed with depression, smoking is twice as prevalent when compared to the general population. A recent meta-analysis found history of past major depression may impact and reduce a patient's ability to obtain and maintain abstinence from smoking. Also, reviews of several longitudinal studies have found that tobacco cessation may be associated with a decrease in self-reported depression levels. Research in this area is still considered weak because many studies surrounding tobacco cessation explicitly exclude smokers using antidepressants making it difficult to determine if depression impacts tobacco cessation efforts or if tobacco cessation can impact depression levels.

Purpose: There were two main purposes for this study. The first was to determine the association between baseline depression level and predicted tobacco abstinence with 1-year follow-up. The second objective was to assess the association between tobacco abstinence and change in depression from baseline level.

Study Design: This was an observational study using information gathered from a tobacco cessation clinic (Center for Tobacco Dependence at the General University Hospital) located in Prague, Czech Republic

from 2008 to 2014. Baseline and follow-up depression levels were measured using Beck's Depression Inventory (BDI-II). The clinic utilized nicotine replacement therapy (NRT), varenicline and bupropion SR as well as face-to-face counseling in clinic to encourage tobacco cessation success. Smoking abstinence was defined as those who reported to have smoked less than or equal to five cigarettes since their quit date and who recorded concentrations of ten ppm or below of carbon monoxide in exhaled air at follow-up visits. Patients who did not maintain smoking abstinent stature were not included in the analysis.

Results: Objective one contained n = 3775 patients with 14.3% reporting mild depression and 15.4% reporting moderate/severe depression. Objective two contained n = 835 patients reporting tobacco abstinence at the one year follow-up period and were included in analysis for change in baseline depression. Objective one demonstrated that in comparison to patients without depression, those who scored in the mild depression category using the BDI-II tool, were less likely to be abstinent from smoking, odds ratio 0.71 [95% CI 0.58 – 0.87; P=0.01]. Participants categorized as moderate/severe depression were significantly less likely to cease from smoking, 0.51 [95% CI 0.41 – 0.63; p<0.0001]. In regards to improvement of depression in patients who reported continued abstinence from smoking, mean BDI-II scores from baseline to follow-up improved significantly from 9.2 to 5.3 [t(834)=14.6, p<0.001 using paired *t* test].

Conclusions: Patients undergoing smoking cessation treatment at a tobacco cessation clinic who were categorized as having mild to moderate/severe depression were less likely to be successful in obtaining abstinence from smoking at one year compared to individuals with no depression. Researchers also concluded that individuals with reported tobacco cessation success at one year reported an improvement in depression. This was true in patients identifying with mild to moderate/severe depression levels.

Key Point: Baseline depression levels may serve as a predictive tool for abstinence in individuals attempting to cease from tobacco use. Similarly, patients who have successfully abstained from tobacco use at a one-year follow-up may experience an improvement in measured depression levels.

Therapeutic Thoughts

SSRIs, SNRIs and Cardiovascular Risk[6-11]

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Background: There are known safety risks with selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), particularly in regard to cardiovascular safety. In addition, it is well established that patients with cardiovascular disease are more likely to suffer from depression. These patients tend to be on multiple medications and are at risk for drug interactions and side effects, most notably, QT prolongation. SSRIs and SNRIs can also affect clotting, blood pressure and other relevant factors in these patients. Better understanding the risks that these medication classes and individual drugs pose to patients can help guide optimal medication usage.

Evidence: Within the class of SSRIs, citalopram and escitalopram are associated with the highest risk of QT interval prolongation. Studies have shown that this risk is dose-dependent and results in a 5-10 mSec increase in QT interval when the dose of medication is doubled (p<0.05). Other SSRIs studied include fluoxetine, fluvoxamine and paroxetine, none of which have produced a clinically significant increase in QT interval in studies. Patients at high risk for symptomatic QT prolongation, manifesting as syncope and arrhythmias, include those with a history of heart attack, heart failure, congenital heart defects, hypertension, diabetes, sleep apnea, cocaine or amphetamine use and advanced age. SSRIs can also affect clotting through CYP2C19 interactions and blockade of $5\text{-}HT_{2A}$ platelet receptors. Fluoxetine and fluvoxamine are CYP2C19 inhibitors, increasing the risk of bleeding with warfarin and decreasing the efficacy of clopidogrel. Of the SSRIs, paroxetine, sertraline, escitalopram and fluoxetine have the highest affinity for the serotonin transporter and are most likely to decrease platelet activity, reduce clotting and increase bleeding risk.

Of the SNRIs, venlafaxine and duloxetine have the most data available for cardiovascular risks. In a case-control study, venlafaxine was not associated with an increased risk of sudden cardiac arrest, odds ratio 0.68 [95% CI 0.38 - 1.22]. A review of 42 placebo-controlled trials failed to show a clinically significant increase in QT interval with duloxetine. Duloxetine has a higher affinity for the serotonin transporter and may have an increased risk of bleeding over venlafaxine. Of note, SNRIs have a risk of hypertension and tachycardia and should be used with caution in patients with uncontrolled blood pressure, uncontrolled or advanced heart failure or recent history of heart attack or stroke.

Discussion: The literature suggests that for patients at high risk for symptomatic QT prolongation, citalopram

and escitalopram should likely not be first-line options. SSRIs and SNRIs with high affinity for the serotonin transporter, including paroxetine, sertraline, escitalopram, fluoxetine and duloxetine, increase risk of bleeding. Bleed risk should be taken into consideration when starting these medications.

Clinical Impact: Historically, cost and generic availability have driven prescribing practices for antidepressant agents. Now that generic antidepressant medications are available, individual risk factors, patient characteristics and concomitant medication use should be considered when choosing an antidepressant. Risk for complications such as bleeding or QT-prolongation vary even within classes of antidepressants. Since QT prolongation is dose-related, pharmacists should advocate for use of lowest effective dose, especially when taken with other medications that affect heart rhythm. Some of the highest risk medications include anti-arrythmics, macrolide antibiotics, fluoroquinolones and antipsychotics.

Gout Treatment Controversy: Should We Use a "Treat to Target" Approach with Serum Urate Levels?[12-14]

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Background: An accumulation of excess urate crystals in joint fluid, cartilage, bones, tendons and bursas results in gout, one of the most common forms of inflammatory arthritis. This disease is characterized by extreme joint point as well as swollen joints. This disease has historically been primarily in older men, however it is more commonly being seen in younger men, as well as in women. Acute gout treatments are anti-inflammatory in nature, while recurrent gout flares are prevented with urate-lowering therapies (ULT) such as uricosuric drugs and xanthine oxidase inhibitors. Recent controversy has erupted related to the use of these therapies to lower uric acid levels, and in particular, to what, if any, goal serum urate level providers should be treating.

Evidence: American College of Physicians (ACP) released clinical practice guidelines related to gout in January 2017 utilizing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to form recommendations. These guidelines recognize that ULT reduces serum urate levels and that moderate-quality evidence suggests longer-term ULT reduces gout flares. However, they found insufficient evidence "regarding whether the benefits of escalating ULT to reach a serum urate target ("treat to target") outweigh the harms associated with repeated monitoring and medication escalation." Post-hoc observational and retrospective cohort study data has shown an association with urate levels less than 6.0 mg/dL and a reduction in gout flares at 12 months, but given that none of these trials were randomized controlled trials, it is difficult to ascertain whether underlying patient characteristics caused the flare reduction. This, combined with the fact that little is known about the balance of the benefits versus the harms and costs resulting from monitoring and increased treatment, led to no firm recommendations to utilize a treat to target strategy.

Guidelines from the American College of Rheumatology (ACR) published in 2012 contain recommendations that tend to resonate more with gout specialists but conflict with those from ACP. These recommendations were developed using expert panels with RAND/UCLA methodology and level of evidence was ranked by the American College of Cardiology's methods. ACR recommended that the goal of ULT is to achieve a serum urate level target at a minimum of less than 6 mg/dL in all cases. This recommended evidence was given a level of A, indicating it came from multiple large RCTs or a meta-analysis, however the guidelines do not directly reference the trials included when they make this designation. They further recommend that a lower target of 5 mg/dL may be considered based on signs and symptoms, giving this recommendation a lower level of B.

Discussion: ACR designation of level A with treat to target recommendation is in direct contrast with the ACP recommendations which were made due to lack of evidence. However, rheumatologists are the providers that are most directly involved with care of gout patients so they may have the strongest clinical experiences to base these recommendations off of. Sources of evidence and recommendations must often be considered in clinical practice as well. In this situation, the ACR maintained expert panels with a majority (51%) of members without a perceived conflict of interest. Conversely, ACP follows stricter protocols where no committee members may have any current ties to pharma. This difference in financial support may be something further to keep in mind when comparing the two guidelines. It is also important to keep in mind that ULT and its monitoring are not without cost and possible harm to patients. In this era of higher deductibles, more patients are forced to pay for lab work out of pocket and increased doses of medications typically have higher rates of adverse effects. Additionally, patients may have various personal preferences for taking additional medications and for minimizing risk of future flares which should be taken into consideration.

Clinical Impact: This is an area of care that likely will continue to evolve in the coming years given the ACP and ACR guidelines offer differing recommendations. More research would be helpful to further guide care in this area.Moving forward, clinicians will need to weigh

the two guidelines with patient characteristics when deciding on treatment goals.

American Diabetes Association 2017 Update: A Brief Review of New Evidence[15-20]

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The American Diabetes Association (ADA) closely examines scientific literature and makes recommendations to help treat diabetes consistently and effectively. The ADA recently released an update on the Standards of Medical Care in Diabetes. This document serves all shareholders of the diabetes community. A Professional Practice Committee completes an extensive literature search, evaluates the quality of new evidence and provides recommendations for review with the Board of Directors. Accepted recommendations are published on an annual basis. The following recommendations were emphasized in the 2017 update.

Assessing Comorbidities: A recent meta-analysis concluded that poor sleep quality and sleeping for long or short intervals can negatively impact blood glucose control in patients with type 2 diabetes. An increase of A1C weighted mean difference of 0.13% to 0.35% was reported in the three sleep abnormalities. Due to these findings, the ADA recommends assessment of sleep patterns, including duration, as part of the comprehensive review of type 2 diabetes patients. Other important comorbidities to assess and treat include autoimmune diseases, HIV, anxiety disorders, depression, eating disorders and serious mental illness as they can impede diabetes management.

Staging Type 1 Diabetes: Three distinct stages of type 1 diabetes can be identified. A clear link has been established between the presence of autoantibodies and progression to clinical hyperglycemia and diabetes. The first stage involves detectable levels of beta-cell autoantibodies; however, the patient is presymptomatic and blood glucose levels are normal. The second stage involves progression to dysglycemia. However, blood glucose levels and/or A1C are just below classic diagnostic criteria. The third stage is identified by standard diabetes hyperglycemia criteria and a patient presenting with clinical symptoms. Evidence is not available to recommend interventions for the first and second stages of type 1 diabetes.

Cardiovascular Considerations: Empagliflozin and liraglutide have been shown to reduce cardiovascular and all-cause mortality in patients with uncontrolled type 2 diabetes and atherosclerotic cardiovascular disease. The ADA recommends considering the addition of either of these drugs to standard care in patients with established cardiovascular disease (CVD). The EMPA-REG OUTCOME trial was designed for empagliflozin to attain an FDA-approved indication to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and CVD. When compared to placebo, empagliflozin demonstrated a relative risk reduction of 38% for cardiovascular-related mortality [95% CI 0.49 - 0.77; p<0.001] and 32% for all-cause mortality [95% CI 0.57 - 0.82; p<0.001]. These benefits have not been proven to be a class effect, so the recommendation is drug-specific at this time.

Metformin and Vitamin B12: Metformin is associated with decreased biochemical levels of vitamin B12. A study published early last year reported a presence of low vitamin B12 (≤ 203 pg/mL) in 4.3% of patients taking metformin therapy compared to 2.3% of patients taking placebo after 5 years (P=0.02). After 13 years of metformin therapy, subjects were more likely to be low or borderline low (≤ 298 pg/mL) compared to placebo (20.3 vs 15.6%, P=0.02). The authors state that years of metformin treatment were associated with an increased risk of vitamin B12 deficiency. The ADA recommends considering periodic monitoring of vitamin B12 levels in patients taking metformin long-term. A deficiency may contribute to anemia or peripheral neuropathy, so the recommendation to monitor vitamin B12 is stronger in patients with these conditions.

Glycemic Targets in Pregnancy: Previously, the ADA has published different glycemic goals for patients with pre-existing type 1 or type 2 diabetes who become pregnant and those who are diagnosed with gestational diabetes. For simplicity, the goals are now the same for these two populations of women. The target for a fasting blood glucose level is ≤95 mg/dL, one hour post-prandial is ≤140 mg/dL and two hour post-prandial is ≤120 mg/dL. The ADA recognizes the need for individualized glycemic goals if a woman cannot achieve that level of control without experiencing hypoglycemia.

From the Pharmacy Press

Loperamide Abuse and Misuse on the Rise[21]

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Background: Loperamide is a nonprescription antidiarrheal medication, available over-the-counter since 1988. As a synthetic opioid, it inhibits the mu-opioid receptor and peristaltic activity in the large intestines, thereby enabling its antidiarrheal effect. At recommended doses, loperamide is rapidly metabolized and almost 50% of the administered dose is excreted unchanged from the body. At high doses, the drug may cause an opioid-like intoxication and recent case reports have identified individuals intentionally misusing and abusing the medication in an attempt to alleviate opioid withdrawal symptoms or induce a euphoric effect. At high doses of loperamide, severe cardiac events and death have been reported.

Purpose: The purpose of this study was to identify recent trends and outcomes in intentional misuse and abuse of loperamide in the United States as reported to the National Poison Data System.

Methods: The article defined the following terms as related to abuse and misuse. *Intentional exposures:* any use of the medication for self harm, whether suspected or confirmed, or recreational use such to gain a euphoric high. *Unintentional exposures:* any exposure, whether accidentally or environmentally related, including adverse reactions or therapeutic errors. Investigators reviewed all intentional cases reported to the National Poison Data System from January 1, 2010 to December 31st, 2015. Unintentional exposures were excluded from this study. All cases were deidentified. For each intentional case, the medical outcome was captured through follow-up and categorized as one of the following: no effect (no symptoms related to exposure), minor effects (some signs or symptoms that are minimally bothersome and rapidly resolved), moderate effects (more prolonged or pronounced and systemic), major effects (signs or symptoms that are life threatening) or death. When follow-up was not possible, cases were identified as "not followed." Cases of single-agent loperamide use and polysubstance (coingestions with another known substance) use were assessed individually. Simple linear regression was used to assess the annual trends in loperamide exposure and chi squared analyses were used to evaluate differences in categorical data.

Results: There were 1,736 total intentional cases of loperamide use reported to the National Poison Data System over the study period. The study found a rate of 37.7 more exposures each year [95% CI 32.5-42.9; $p<0.001$] with 201 exposures in 2010 and 383 in 2015, a 91% increase over five years. Single-agent loperamide use increased at a rate of 24.7 a year [95% CI 21.3-28.0; $p<0.001$] compared to polysubstance use with an increased rate of 13.1 a year [95% CI 10.7-15.4; $p<0.001$]. 19.2% of single-agent loperamide cases were found to have moderate to major adverse effects compared to 39.6% of polysubstance cases. A total of eight deaths were due to loperamide use only and seven of the eight deaths were considered intentional.

Conclusions: With a 91% increase in intentional loperamide abuse and misuse, health care providers should be aware of this significant problem. Although less than half of the patient cases were seen to have moderate to major adverse effects with loperamide use, health care providers should know that the risk of overdosing can lead to life-threatening events, such as death.

The Impact of Tobacco-free Pharmacy Policies on Smoking Prevalence[22-24]

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Background: Efforts to impact social norm around tobacco use from policy changes, such as creating smoke-free areas, setting age limits and imposing an excise tax on tobacco products, have shown to be effective in reducing smoking prevalence in the United States. Statistics showing that tobacco sales in pharmacies have increased by 23% from 2005 to 2009, while total U.S. cigarette sales decreased about 17%, urge the need to promote a tobacco-free pharmacy policy. So far, there are two states that have implemented such policy: California (CA) and Massachusetts (MA). San Francisco, CA first implemented the policy in 2008 and three cities in MA implemented the policy in 2009. To further advocate for the nation-wide implementation of the tobacco-free pharmacy policy, it is important to understand the impact this policy has on smoking prevalence.

Objective: To determine the impact of tobacco-free pharmacy policies by assessing association between the tobacco-free pharmacy policy and smoking prevalence among adults in CA and MA.

Study Design: This is a longitudinal, population-based, cross-sectional study that compared the adult smoking prevalence between cities that implemented a tobacco-free pharmacy policy (case group) versus cities without implementation (control group). The source of data for adult cigarette smoking prevalence was from the Behavioral Risk Factor Surveillance Survey (BRFSS) from 2005 to 2012 or 2013. To be eligible as case group, a city was required to have implemented a tobacco-free policy before December 31, 2011. In CA, only San Francisco met this criteria while 40 cities in MA qualified. Due to the small sample size, only descriptive comparison was used in CA. Generalized linear mixed model and matching-based analysis were used for MA to calculate the rate ratio. Data for MA was adjusted for the following confounders: local tobacco control policies, city-level demographic variables and unemployment rates.

Results:
California: There were similar decreasing trends in smoking prevalence from 2005 to 2012 in both groups. The smoking prevalence reduced from 13% [95% CI 11.2 – 15.4] to 12.3% [95% CI 10.2 – 14.9] in San Francisco, while it reduced from 19.3% [95% CI 16.2 – 23.3] to 18.1% [95% CI 15.3 – 21.6] in the control group. *Massachusetts:* The case group had a greater reduction in smoking prevalence than the control group from 2005 to 2013. The smoking prevalence reduced from 23% [95% CI 21.2 – 24.9] to 16.9% [95% CI 16 – 17.8] in the case group, while it reduced from 16.4% [95% CI 14.9 – 17.9] to 14.1% [95% CI 13.4 – 14.9] in the control group. From 2009 to 2013 (tobacco-free policy first implemented in 2009), the smoking prevalence in the case group decreased by 8.6%, while it slightly increased by <0.1% in the control group. Despite there being a decrease in smoking prevalence, when the data was adjusted to account for the overall decreasing trend of smoking prevalence over time, this decrease was found to be non-statistically significant with an adjusted rate ratio of 1.00 [95% CI 0.92 – 1.08] and P=0.992.

Conclusions: Tobacco-free pharmacy policies had a slight effect on reducing smoking prevalence in CA and MA, however these findings were not statistically significant. The study was limited in that only descriptive comparison was used in CA due to the small case sample size (n=1). San Francisco has the one of the lowest smoking prevalences in CA, making it difficult to detect the difference. Also, the study failed to assess the location of tobacco purchase which could have been another confounder attributing to smoking prevalence. Because reducing smoking prevalence at the population level requires multifactorial approach with long-term implementation, it is generally difficult to show the statistical significance on single policy implementation. Future research that examines the effect of tobacco-free pharmacy policy among cities with matched local and state tobacco control over a prolonged time span is needed.

Key Point: Currently there are only two states (CA and MA) that have implemented tobacco-free pharmacy policies. This study demonstrates some effect on reducing smoking prevalence with tobacco-free pharmacy policies. There may not be an immediate impact on reducing smoking prevalence with the implementation of this policy; however, banning tobacco sales in certain venues may have a significant impact on influencing the social norm around tobacco use and sale. For example, promoting pharmacy as a venue for a healthy lifestyle can play a significant role in this social change. Further research on the impact of this type of policy can encourage widespread adoption in different states.
completion.

Use of Vitamin E and C Supplements for Prevention of Cognitive Decline[25]

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Background: Medications for Alzheimer's Disease (AD) have been shown to have mild to moderate effectiveness in delaying cognitive decline. Past studies have suggested benefits in decreasing risk of cognitive decline with the use of vitamin E, vitamin C, beta-carotene and flavonoids (due to antioxidant effects), however methodology and results have been inconsistent. Currently, no medications are indicated to prevent cognitive decline or Alzheimer's Disease.

Objective: To evaluate the association of vitamin E and C supplement use with the incidence of all cause dementia, Alzheimer's Disease and cognitive impairment without dementia, over a follow-up timeframe up to ten years.

Study Design: This was a case control study using data from the first two phases of the Canadian Study of Health and Aging (CSHA). The CSHA was a national, multicenter, longitudinal cohort study on dementia that included samples of people age 65 or older who were randomly selected from the community or institutions in three phases over 15 years.

Community patients screening positive by the Modified Mini-mental State (3MS; score <78/100), all selected institutionalized patients, and a random sample of

community patients with negative 3MS scores underwent an additional 3MS, medical and family history collection and physical and neurological examination. Those with 3MS scores of 50 or more were further examined and tested, with independent diagnoses being made by a physician and neuropsychologist prior to a consensus diagnosis being reached. Patients not found to have dementia, AD or cognitive impairment without dementia, were given a risk factor questionnaire to complete.

Vitamin E and C use were assessed during the clinical examination or via risk factor questionnaire. Patients were asked to list all medications/supplements, however dose information was not requested. Phase 1 occurred from 1991-92 and Phase 2 from 1996-97. Covariates included smoking status, alcohol use, physical activity, use of NSAIDs, history of diabetes, vascular risk factors and education. Continuous and categorical variables were evaluated by student's t-test and Chi squared test, respectively. Cox proportion regression models evaluated associations between vitamin exposure and all cause dementia incidence.

Results: The total sample included 5,269 subjects. At baseline in phase one, 10.7% of patients had used vitamin C and/or E compared to 5.8% in the dementia group and 5.7% in the AD group ($p<0.001$). In phase two, 11.6% had used one or both vitamins compared to 7.8% in the cognitive impairment without dementia group ($P=0.001$). Individually, the 'no dementia' groups had statistically significant higher use of the vitamins compared to those with some level of impairment.

After adjustment for age, patients had a 40% decreased incidence of all-cause dementia receiving both vitamin E and C [95% CI 0.44 - 0.80], 47% decreased incidence for vitamin E only [95% CI 0.36 - 0.78] and 36% decreased incidence for vitamin C only [95% CI 0.45 - 0.91]. Adjustment for sex and education, as well as alcohol, tobacco, physical activity, NSAID use and cardiovascular risk factors also showed statistically significant reduced incidences in the combination and individual vitamin exposure groups. For incidence of Alzheimer's, age adjusted results showed 42% decreased incidence in the combination group [95% CI 0.40 - 0.82], 46% decreased incidence with vitamin E only [95% CI 0.34 - 0.85] and 43% decreased incidence in the vitamin C group [95% CI 0.36 - 0.88]. Statistically significant results of similar effect sizes were seen when adjusted for sex, education,alcohol, tobacco, physical activity, NSAID use and cardiovascular risk factors as well. Use of vitamin E and/or C showed a statistically significant decrease in the incidence of cognitive impairment without dementia when adjusted for age.

Conclusions: Vitamin E and C were associated with decreased risks of all cause dementia and Alzheimer's Disease. Various limitations include potential for recall bias, 22% of the subjects lost to follow-up due to death and various confounding factors including lack of dosing information.

Key Point: Vitamin E and C supplementation may have beneficial effects on reducing risk of all cause dementia and Alzheimer's Disease, however further studies are necessary to assess dosing, safety and effects in target populations.

Miscellaneous News

New Naloxone Doses[26-29]

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Forty-six individuals die from prescription opioid overdose each day in the United States. Naloxone is an opioid antagonist first approved in 1971 by the U.S. Food and Drug Administration (FDA) for use in opioid overdose reversals. New formulations of naloxone have been developed since 1971, including Evzio®, Kaléo Inc.'s autoinjector, and Adapt Pharma's Narcan® Nasal Spray. Evzio® was originally approved in April 2014 at the 0.4 mg dose while Narcan® Nasal Spray was approved in November 2015 at the 4 mg dose. Within the last six months, the FDA has approved two new doses of these products for use in the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. A rise in use of the potent opioid carfentanil has created concerns that lower doses of naloxone may not be sufficient to reverse the effects. On October 10, 2016 the FDA approved a new 2 mg strength for Evzio®. This represents a five-fold increase in dose from the previously approved dose. However, there are also concerns about using doses too high of naloxone which could lead to severe opioid withdrawal in certain individuals. On January 25, 2017 the FDA approved Narcan® Nasal Spray as a 2 mg formulation. This decreased dose is approved for use in opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for

accidental or intentional opioid exposure by household contacts.

There is limited data directly comparing these products. It remains unclear exactly how to determine which dose is optimal for each patient. It may be that patients at high-risk, such as those with a history of substance abuse or higher opioid doses ≥90 morphine milliequivalents daily, would require the higher doses of naloxone, whereas patients on lower opioid doses, such as those using up to 90 morphine milliequivalents daily, may need lower doses of naloxone. Regardless of the dose or route of administration, the duration of action for naloxone is limited. Individuals that may administer naloxone should be educated that emergency services should be contacted immediately after administration of the first dose. Once the opioid antagonist wears off, symptoms of opioid overdose, such as respiratory depression are expected to return.

Medicaid Recommendations for Pharmacist Scope of Practice[30]

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The Center for Medicaid and CHIP Services (CMCS) released a bulletin in early January encouraging states to expand the role of pharmacists to aid in timely access to necessary and/or time sensitive drugs for Medicaid beneficiaries. This increased scope of practice for pharmacists can be implemented through independent prescribing rights for pharmacists, collaborative practice agreements with licensed prescribers, or standing orders allotted by the state. Currently, forty-eight states and Washington D.C. utilize one or more of these methods to increase the practicing capacity of pharmacists.

Pharmacists can help address national public health challenges, including the opioid epidemic, through expanded scope of practice. Naloxone, an opioid-antagonist medication, can be administered to aid in the reversal of an emergent, potentially life-threatening narcotic overdose. Giving pharmacists the ability to prescribe naloxone proactively to patients at risk for opioid overdose may reduce the incidence of complications and mortality.

Other examples where pharmacists can improve drug access include the prescribing of tobacco cessation products and emergency contraception pills (ECP). While some of these products are available over-the-counter, prescribing abilities would eliminate the need to contact a prescriber, allow for third party billing of these products and, for ECP, ensure timely administration of the drug. Additionally, administration and third party billing of immunizations, including the influenza vaccine, by pharmacists in the community can increase vaccination rates which consequently may reduce infection rate and epidemics.

CMCS recognizes and encourages innovative roles for pharmacists. Expanding the capacity of the pharmacist to prescribe, adjust or monitor drug therapy for certain medications or conditions may improve public health and patient access to medications.

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