Potential Overtreatment of Diabetes Mellitus in Older Adults with Tight Glycemic Control

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Background: Current recommendations from the American Diabetes Association and American Geriatrics Society endorse higher glycemic targets for elderly patients with multiple comorbidities, functional impairments, established diabetes complications, or limited life expectancy. In these patients intensive glycemic management is less likely to result in a benefit and is associated with an increased risk of harm. Those with tight glycemic control are more likely to have episodes of hypoglycemia, which has been associated with increased mortality, cardiovascular disease, falls and accidents, dementia, and diminished health-related quality of life.

Objectives: This study examined glycemic control among older adults with diabetes mellitus by health status to determine the prevalence of potential overtreatment of diabetes. It also evaluated the use of diabetes medications likely to result in hypoglycemia (insulin or sulfonylureas).

Study Design: The study was a cross-sectional analysis evaluating adults aged 65 years and older with diabetes from the National Health and Nutrition Examination Survey (NHANES) from 2001 through 2010. The sample was felt to be nationally representative of noninstitutionalized adults with diabetes. Participants were classified into three health status groups based on ADA/AGS framework for considering glycemic treatment goals. Categories included very complex/poor, based on difficulty with two or more activities of daily living (ADL) (difficulty performing tasks such as dressing, feeding, or walking without using any special equipment) or dialysis dependence; complex/intermediate, based on difficulty with two or more instrumental ADL (difficulty preparing one’s own meals, managing money, or housework chores) or presence of three or more chronic conditions (arthritis, congestive heart failure, lung disease, chronic kidney disease, coronary heart disease, stroke, or urinary incontinence), and relatively healthy if none of these were present. In this older population, outcomes were tight glycemic control (defined in this study as HbA1C <7%) and use of diabetes medications likely to result in hypoglycemia (insulin or sulfonylureas).

Results: 1288 older adults with diabetes were evaluated. The mean age was 73.2 years, and 20.8% were 80 years or older. More than one-third reported at least one ADL impairment, and more than one-third reported at least one instrumental ADL impairment. Of the study sample, 50.7% were categorized as relatively healthy, 28.1% as complex/intermediate health, and 21.2% as very complex/poor health. Overall, 61.5% had HbA1C <7%. This proportion did not differ across health status categories. Of note, 44.9% and 37.9% of patients with complex/intermediate and very complex/poor health had HbA1C <6.5%, respectively.
Of the older adults with HbA1C <7%, 54.9% were treated with either insulin or sulfonylureas, which was similar across health status categories. During the 10 years of the study, no significant trends were seen in the proportion of older adults with diabetes who had HbA1C <7%. Similarly, treatment with insulin or sulfonylureas in the complex/intermediate or very complex/poor health groups remained stable over time.

Conclusions: Despite unproven benefits and potential harms of intensive glycemic control in older patients with extensive comorbidities, most older adults with complex/intermediate or very complex/poor health status reached tight glycemic targets of HbA1C <7%, corresponding to 1.8 million US persons. Most patients with complex or very complex medical problems were treated with insulin or sulfonylureas, which could lead to severe hypoglycemia and poor health outcomes. Recognition of both the harms and benefits of glycemic control is important for patients and health care professionals to make informed decisions about diabetes treatment.

Key Point: A substantial proportion of older adults with diabetes are potentially overtreated.

**Less-Tight versus Tight Control of Hypertension in Pregnancy**

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Background: Hypertension in pregnancy is not uncommon: 1% of pregnant women have hypertension prior to pregnancy, 5-6% develop gestational hypertension without proteinuria, and in total almost 10% have hypertension. Blood pressure targets in this population are unclear. Previous randomized, controlled trials have been of moderate or poor quality, and were small trials. Some of these studies have shown a link between lower blood pressure goals and lower birth weight of the newborn; on the other hand, more strict control with beta-blockers has been linked to decreased respiratory complications in the newborn. Varying blood pressure goals have been recommended in guidelines from the American College of Obstetricians and Gynecologists, the National Institute for Health and Clinical Excellence, and a joint guideline from the American Heart Association and the American Stroke Association.

Purpose: As part of The Control of Hypertension in Pregnancy Study (CHIPS), this trial aimed to determine differences of maternal and fetal outcomes after tight versus less-tight blood pressure control.

**Study Design:** This study was an open, multicenter, international, randomized, controlled trial. Women who had hypertension (with a diastolic blood pressure [DBP] of 90-105 mmHg if not on treatment for hypertension, or 85-105 mmHg if on treatment for hypertension), and were pregnant with a single fetus between 14 weeks, 0 days to 33 weeks, and 6 days of gestation were included. Hypertension included either preexisting hypertension (nonsevere and nonproteinuric with a DBP of 90 mmHg or higher before 20 weeks of gestation) or gestational hypertension (DBP of 90 mmHg or higher after 20 weeks of gestation). Exclusion criteria included systolic blood pressure (SBP) of 160 mmHg or higher, proteinuria, use of an angiotensin-converting-enzyme (ACE) inhibitor at 14 weeks gestation or later, maternal contraindication to the trial medications, pregnancy with multiple fetuses, a fetus with a major anomaly or abnormality, planned termination of the pregnancy, or previous participation in CHIPS. Mothers were randomized to less-tight blood pressure control with a target DBP of 100 mmHg or tight control with a target DBP of 85 mmHg. Labetalol was recommended in the study protocol as the drug of choice. ACE inhibitors, angiotensin-receptor antagonists, direct renin inhibitors and atenolol were not permitted prior to delivery. The primary endpoint included pregnancy loss (miscarriage, ectopic pregnancy, termination of pregnancy, stillbirth or neonatal death) or high-level neonatal care for more than 48 hours. Secondary outcomes included serious complications in the mother up to six weeks after childbirth or before the mother was discharged. Other analyzed outcomes included components of the primary and secondary endpoints, newborn complications, severely elevated maternal blood pressure, and measures of fetal growth.

**Results:** In total, 493 women and fetuses/neonates were included in the less-tightly controlled group, and 488 women and fetuses/neonates were included in the tightly controlled group. Sample sizes were estimated prior to the trial to have an 80% power at 514 subjects per group, which was not met. The two groups’ characteristics were similar at baseline, with the exception that the less-tightly controlled group tended to be slightly further along in the pregnancy. Adherence was similar between the two groups (74.1% for less-tight and 73.4% for tight control, P=0.81). Blood pressure was higher on average in the less-tightly controlled group versus the tightly controlled group: 5.8 mmHg systolic difference (95% CI, 4.5-7.0, P<0.001) and 4.6 mmHg diastolic difference (95% CI, 3.7-5.4, P<0.001). Frequency of either pregnancy loss or high-level neonatal care (the primary outcome) was not statistically significantly different between the two groups. Other perinatal outcomes (neonates that were small for gestation age and frequency of respiratory

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**Key Point:** A substantial proportion of older adults with diabetes are potentially overtreated.
complications) were also statistically similar between the two groups. Serious complications in the mother were similar between the two groups, and no mothers died during the study period. Most commonly, the mother needed blood products, and serious complications were more common in mothers with preeclampsia. Severe hypertension was also higher in mothers in the less-tightly controlled group (P<0.001), but systolic and diastolic readings were similarly distributed between the groups. There was no difference between these results when hypertension type, gestational diabetes or perinatal mortality ratio were taken into account. Labetalol was in study protocol as first-line therapy, however only about two-thirds of women who required antihypertensives received labetalol.

Conclusions: The trial did not include enough subjects to reach power, so the study was too small to determine differences between the groups. Researchers concluded that aiming for a more strict versus less strict blood pressure goal did not affect outcomes in either the mother or the fetus/neonate, though there were more instances of severely elevated blood pressure in the less-tightly controlled group.

Key Point: Lower blood pressure goals in pregnant women may not negatively affect the mother or her fetus/neonate when compared to higher, less strict blood pressure goals. Larger randomized, controlled trials are needed to examine the effects of lower versus higher blood pressure targets during pregnancy.

Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents
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Background: Dual antiplatelet therapy after stenting is generally employed for two reasons. First, dual antiplatelet therapy is used to protect the stented segment against stent thrombosis from inflammation during the healing process. The second reason is to provide protection to the stented area against the development of further atherosclerosis and plaque rupture. With the development of drug-eluting stents (DES), the first reason is not as paramount as in the past. Yet, the second reason is still quite important. Dual antiplatelet therapy with a thienopyridine and aspirin for 12 months has demonstrated benefit in the setting of post coronary DES placement, prompting the American College of Cardiology/American Heart Association clinical practice guidelines to recommend 12 months of dual antiplatelet therapy for patients. However, the most effective duration of dual antiplatelet therapy after DES placement for preventing both stent thrombosis and myocardial infarction, while limiting bleeding risk, remains uncertain.

Purpose: The Dual Antiplatelet Therapy (DAPT) study sought to determine the benefits and risks of continuing dual antiplatelet therapy beyond one year after the placement of a coronary stent.

Study Design: The DAPT study was a prospective, multicenter, randomized, double-blind trial. Following a coronary stent procedure with a drug-eluting stent, patients were enrolled into the DAPT study. All patients received 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin. At 12 months, patients were randomized to continue receiving thienopyridine treatment or to receive placebo for another 18 months; thus, patients received thienopyridine for a total of 12 months or 30 months. All patients continued receiving aspirin dosed 75-325mg for the first 6 months and 75-162mg indefinitely thereafter. The primary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months (the randomized treatment period). The primary safety end point was incidence of moderate or severe bleeding (as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] criteria) from 12 to 30 months. Bleeding was also evaluated according to the Bleeding Academic Research Consortium (BARC) criteria.

Results: A total of 9961 patients were randomly assigned to continue thienopyridine treatment or to receive placebo. Of those who continued to receive thienopyridine therapy for 30 months, there was a significant reduction in the primary efficacy end points of stent thrombosis (HR 0.29 [95% CI, 0.17-0.48]; P<0.001; NNT = 100) and major adverse cardiovascular and cerebrovascular events (HR 0.71 [95% CI, 0.59-0.85]; P<0.001; NNT = 63). The rate of myocardial infarction was significantly reduced in the group that continued to receive thienopyridine therapy (HR 0.47 [95% CI, 0.37–0.61]; P<0.001; NNT = 50). The primary safety end point, moderate or severe bleeding, was increased with continued thienopyridine therapy per the BARC criteria and the GUSTO criteria (HR 1.61 [95% CI, 1.21-2.16]; P = 0.001; NNH 112), but no significant difference in severe bleeding alone between groups according to the GUSTO criteria. Death from cardiac causes was similar and rate of death from any cause was 2% in the group that continued thienopyridine therapy and 1.5% in the placebo group (HR 1.36 [95% CI, 1.00-1.85]; P=0.05; NNH = 200), which was perhaps related to a significant difference in the amount of cancer related deaths in the...
thienopyridine group, compared to the placebo group (31 vs. 14, P=0.02). An elevated risk of stent thrombosis and myocardial infarction was noted in both groups in the three months after discontinuation of thienopyridine treatment.

**Conclusion:** Dual antiplatelet therapy continued beyond 12 months of DES placement, compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events, but was associated with an increased risk of bleeding.

**Key Point:** There might be benefit for continuing dual antiplatelet therapy for longer than 12 months post DES placement, but this benefit must be weighed against potential bleeding risks.

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**Savaysa® (edoxaban), developed by Daiichi Sankyo**

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**Indications:** Edoxaban was approved by the FDA on January 8, 2015 for stroke prevention in non-valvular atrial fibrillation (AF) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Mechanism of Action:** Edoxaban is a selective, reversible inhibitor of factor Xa, similar to rivaroxaban and apixaban.

**Dosage and Administration:** For AF, DVT, and PE: 60mg tablet orally once daily. Treatment for DVT and PE should be started 5-10 days after initiating parenteral anticoagulant therapy. Edoxaban requires dose adjustment to 30mg daily for CrCl 15-50 mL/min and for body weight < 60 kg or concomitant P-glycoprotein use for prevention of DVT/PE. Do not use in AF if CrCl>95 mL/min due to decreased reduced efficacy as demonstrated in the ENGAGE AF-TIMI 48 study. In patients with a CrCL >95, a different anticoagulant should be used due to an increased rate of ischemic stroke. Use not recommended in moderate to severe hepatic impairment or if CrCl<15 mL/min.

**Effectiveness:** AF: A noninferiority study of edoxaban vs. warfarin was conducted with 21,105 participants with moderate-to-high-risk AF and an average follow up time of 2.8 years. The annualized rate of stroke or systemic embolic event was 1.5% in the warfarin group and 1.18% in the edoxaban group (97.5% CI: 0.63 to 0.99; P<0.001 for noninferiority, P = 0.02 for superiority).

DVT/PE: A noninferiority study of edoxaban vs. warfarin was conducted with 4921 participants presenting with DVT and 3319 with PE. Participants were randomized to warfarin or edoxaban after at least 5 days of initial therapy with enoxaparin or unfractionated heparin to compare the incidence of VTE recurrence within one year. Recurrence of VTE was found in 3.5% of patients taking warfarin and 3.2% of patients taking edoxaban (HR=0.89; 95% CI: 0.70 to 1.13; P<0.001).

**Safety:** Edoxaban provides a good alternative to warfarin and may become the new favorite Xa inhibitor on the block. It shows efficacy superiority in AF and reduced bleeding rates compared to warfarin, similar to apixaban, but also has the convenience of once a day dosing like rivaroxaban. With all three drugs being brand only and around the same price point ($400/month), they are significantly more expensive than warfarin, but edoxaban is offering robust patient assistance programs (copays of $4/month).

i. Major bleeding is defined by the ISTH as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

ii. Clinically relevant bleeding was defined as major (overt and associated with a decrease in hemoglobin of 2 g/dL or more, leading to transfusion of two or more units of whole blood or red cells, or contributing to death) or clinically relevant nonmajor bleeding (overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life).
Aspirin for Primary Prevention of Stroke and Heart Disease

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Background: The use of aspirin for primary prevention of stroke and coronary heart disease (CHD) is controversial. In May of 2014 the FDA released a public advisory against use of aspirin for primary prevention for heart attacks and stroke. The most recent guidelines to address use of aspirin in primary prevention have been published by the American Heart Association (AHA) in 2002, the U.S. Preventative Service Task Force (USPSTF) in 2009, the AHA/American Stroke Association (ASA) in 2011, and the American Diabetes Association (ADA) in 2015.

The AHA, ASA, and ADA generally recommend aspirin for primary prevention in patients, with or without diabetes, that have a 10-year cardiovascular disease (CVD) risk >10%. The AHA and ASA recommend against use if CVD risk is <6% and the ADA recommends against use if CVD risk is <5%. Those within 6-10% and 5-10%, respectively, require clinical judgement. The USPSTF’s recommendations in favor of or against treatment with aspirin change for different age groups. They balance different CVD risks with accompanying bleeding risks to account for differences in bleeding risk between sexes and different ages.

Three recent articles have addressed use of aspirin for primary prevention of stroke and CHD.

New Evidence: Hira et. al., examined data from the National Cardiovascular Disease Registry’s Practice Innovation and Clinical Excellence Registry to assess inappropriate prescribing of aspirin for primary prevention to patients with a CVD risk <6%. The AHA and ASA recommend against use if CVD risk is <6% and the ADA recommends against use if CVD risk is <5%. Those within 6-10% and 5-10%, respectively, require clinical judgement. The USPSTF’s recommendations in favor of or against treatment with aspirin change for different age groups. They balance different CVD risks with accompanying bleeding risks to account for differences in bleeding risk between sexes and different ages.

A recent randomized clinical trial from Ikeda et. al. evaluated use of aspirin 100mg daily or no treatment in 14,464 Japanese subjects aged 60-85 years with one or more CVD risk factors (diabetes, hypertension, or dyslipidemia). The primary endpoint was a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (MI). At 6.5 years no difference in the primary endpoint was found between the groups or any subgroup with any specific risk factor. There was a significant decrease in nonfatal MI (aspirin 0.30% vs no treatment 0.58%, NNT=358) and TIA (aspirin 0.26% vs no treatment 0.49%, NNT=435), while there was an increased risk of GI ulcer (aspirin 2.61% vs no treatment 1.24%, NNH=73) and GI hemorrhage (aspirin 1.41% vs no treatment 0.42%, NNH=102).

van Kruijfdijk et. al. reviewed data from the Women’s Health Study and attempted to develop competing risk models to predict absolute risk reduction of the combination of CVD, cancer, and major GI bleed in order to offset the risks and benefits of aspirin 100mg every other day for primary prevention in women >45 years of age. They found that benefit and risk of treatment both increased with age, but women aged >65 years may have a net benefit for treatment (15-year NNT=29 [95%CI, 12-102]).

Discussion: The AHA and ASA guidelines currently recommend against the use of aspirin for primary prevention of stroke and CHD in patients with a CVD risk <6%. The data from the National Cardiovascular Disease Registry suggests 13.9% of these patients are inappropriately receiving aspirin, which represents a huge opportunity for clinicians to align their practice with current guidelines. Per USPSTF recommendations some males aged 45-59 years and some females 55-59 years with CVD risk <6% may be appropriate for aspirin therapy based on their relative bleeding risk. Regardless, this would not likely account for all of the 11.6%.

Based on the results of the clinical trial by Ikeda et. al. the use of aspirin for primary prevention is not likely beneficial in the general population aged 60-85 years with one risk factor for CVD. A more thorough assessment of an individual patient’s risk should be completed before recommending aspirin. However, this trial was in a Japanese population with a smaller BMI and lower smoking rates than Western populations.

While van Kruijfdijk et. al. found that the benefit of aspirin use in women >65 years reasonably outweighed the risk profile as compared to other
groups, the NNT calculation provided was for 15 years, which may be greater than the life expectancy for some in this group. The risk model also accounted for a benefit seen from prevention of any cancer. Additionally, this group is at a much higher risk of bleed and the authors did not include non-major bleeds (any not leading to hospitalization) in their risk model. All of these issues make it difficult to make an assessment on the question of aspirin for primary prevention of CVD.

Clinical Impact: The new evidence discussed will not change current opinions on benefits or risks of aspirin for primary prevention of stroke and CHD. The Japanese trial does add support to current guidelines that treatment decisions should not be based on a single CVD risk factor (DM, age, HTN, etc.). All three articles suggest that clinicians should re-evaluate all patients currently taking aspirin for primary prevention of stroke and CHD, including those with diabetes. Anti-platelet therapy has significant risks and there should be a net benefit if it is to be recommended to patients.

In conclusion, clinicians can follow AHA/ASA guidelines to decide if a patient should receive aspirin for primary prevention. Alternatively, USPSTF recommendations can be utilized to individualize decisions made about risk versus benefit. Additionally, guidelines should align more to reduce confusion for clinicians attempting to weigh risk versus benefit of aspirin for primary prevention in patients without diabetes. For patients with diabetes, it is advised to follow the ADA’s 2015 guidelines for aspirin use.

Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline Kim Tran, Pharm.D. Community-University Health Care Center

Background: The Endocrine Society defines obesity as a disease in which focus should be placed on weight loss to improve health in patients with obesity-associated risk factors and comorbidities. Therefore, an Endocrine Society-appointed Task Force of experts was commissioned to formulate clinical practice guidelines for the pharmacological management of obesity using the best available evidence. The purpose of this guideline is to assist providers in the knowledgeable use of medications as an adjunct to lifestyle changes to promote weight loss and maintenance. Below, areas of the guideline with the strongest recommendations as well as highest level of quality are summarized.

Recommendations:
- Diet, exercise, and behavioral modifications must be included in all weight-loss regimens, regardless if pharmacotherapy or surgery was utilized. Obesity drugs should be used in conjunction with lifestyle change therapy to result in greater weight loss.
- In patients with uncontrolled hypertension, history of heart disease or seizures, sympathomimetic agents such as phentermine and diethylpropion should be avoided because these agents are associated with elevations in mean blood pressure and pulse rate. Instead, lorcaserin, a serotonin 5-HT2C receptor agonist, is a better choice for these patients.
- In patients with obesity and depression already taking a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), lorcaserin should be avoided due to the potential for serotonin syndrome. Instead, phentermine/topiramate or phentermine alone is a better choice.
- Pharmacotherapy should be continued if a patient’s response to a weight loss medication is deemed effective (weight loss ≥5% of body weight at 3 months) and safe. However, if deemed ineffective (weight loss <5% at 3 months) or if there are safety or tolerability issues during the course of therapy, the medication should be discontinued and alternative therapies considered.
- Evidence: Weight loss medications do not permanently change the underlying physiology of weight regulation. The weight loss effects of these medications are only sustained as long as they are taken. Gradual weight gain typically occurs when medications are stopped.
- In the management of patients with diabetes mellitus who are overweight or obese, weight-loss and weight-neutral medications should be used as first- and second-line therapies. Clinicians should discuss possible weight effects of glucose-lowering agents with patients, and when possible, consider agents that have been shown to promote weight loss or lead to minimal change in weight such as metformin, GLP-1 agonists (exenatide and liraglutide - of note, liraglutide is the only one FDA approved for weight loss), pramlintide, dipeptidyl peptidase IV (DPP-4) inhibitors, and α-Glucosidase inhibitors.
(acarbose and miglitol - though limited use due to GI intolerance).

- Evidence: In the Diabetes Prevention Program (1996 to 1999), participants with impaired glucose tolerance who took metformin 850mg twice daily lost 2.1 kg compared to a weight loss of 0.1 kg for placebo. A retrospective analysis of exenatide (n=6280), sitagliptin (n=5861), and insulin (n=32,398), indicated that treatment with exenatide resulted in weight loss of 3 kg, sitagliptin resulted in loss of 1.1 kg, and insulin treatment saw an average weight gain of 0.6 kg. A meta-analysis of pramlintide vs placebo demonstrated a weight loss of 2.6 kg in subjects taking pramlintide.

- In patients with diabetes mellitus who are obese, ACE inhibitors, ARBs, and calcium channel blockers should be used as first line therapy for hypertension, rather than β-adrenergic blockers.

- Evidence: Angiotensin is overexpressed in obesity, contributing to obesity-related hypertension, providing evidence for use of ACE inhibitors as a first-line agent. ACE inhibitors and ARBs have not been associated with weight gain or insulin resistance. In a meta-analysis of body weight changes in a series of hypertension trials of at least 6-month duration revealed that body weight was higher in the β-blocker group (1.2 kg weight increase) as compared to placebo.

- A shared decision-making process with patients in whom antidepressant therapy is indicated should be used to discuss expected weight effect of the antidepressant.

- Evidence: SSRIs such as fluoxetine and sertraline have been associated with weight loss during acute treatment (4-12 weeks) and weight neutrality in maintenance phase (>4 months). Bupropion is the only antidepressant that consistently results in weight loss. Paroxetine, amitriptyline, and mirtazapine are antidepressants associated with weight gain. In the systematic review conducted in accordance with this guideline, weight gain was demonstrated with amitriptyline (1.8 kg) and mirtazapine (1.5 kg), and weight loss with bupropion (-1.3 kg) and fluoxetine (-1.3 kg).

- Weight-neutral antipsychotics should be used when clinically indicated.

- Evidence: A randomized trial investigating the effectiveness of five antipsychotic medications found that a weight gain of >7% from baseline occurred in 30% of those taking olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% of those taking ziprasidone. However, a review of nine randomized controlled trials found that ziprasidone produced less weight gain in addition to less cholesterol increase than olanzapine, quetiapine, or risperidone.

- Weight effects should be considered when choosing an antiepileptic drug (AED).

- Evidence: AEDs associated with weight loss are felbamate, topiramate, and zonisamide. Weight-neutral AEDs are lamotrigine, levetiracetam, and phenytoin. AEDs associated with weight gain are gabapentin, pregabalin, valproic acid, vigabatrin, and carbamazepine.

Clinical Impact: Clinicians are able to assist patients in health improvement through the knowledgeable prescribing of not only medications approved for chronic weight management, but also those used to manage chronic conditions. Agents with favorable weight loss profiles should be chosen to manage chronic conditions, in conjunction to lifestyle modifications.

Charitable Pharmacy Services
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Background: Studies show the underserved population’s decreased adherence to medications based on cost can significantly increase risk of acute care and long-term care admissions and even death. In general, medication adherence is linked to reduced hospital utilization and better health outcomes.

Objectives: The purpose of this study was to access the impact on charitable pharmacy services on the underserved Ohioan patient population. The researchers hoped to find an association between fewer patient reported hospital visits as a result of utilization of these charitable pharmacy services.

Study Design: The Charitable Pharmacy of Central Ohio (CPCO) opened in February 2010. It provided service to residents who were uninsured or under
insured and at or below 200% of the Federal Poverty Level who could not afford their medications.

A cross-sectional study was performed using face-to-face interviews which were completed by trained pharmacy students from January to March 2013. A random sample of patients was interviewed for questioning while they awaited the filling of their prescriptions. Patients were incentivized to complete the survey with a $5 gift care to a local grocery store. Inclusion criteria consisted of those patients 18 year of age or older, English-speaking and utilization of the CPCO program for at least three months. Exclusion criteria consisted of those patients who were unable to answer the questions on their own, inability to comprehend interview questions or unable to communicate due to cognitive impairment.

The study’s primary objective was hospital utilization for any duration which was self-reported by the patient both prior to and during utilization of CPCO services. Patients were also asked to estimate the prescribed medications utilized prior to and during the utilization of CPCO. Finally, patients were questioned about their perceived change in overall health status while utilizing the CPCO.

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

Conclusions: The results of the study showed a trend towards decreased patient reported hospitalizations, improved access to prescriptions and patient perceived improved health status. The researchers of this study aimed to have other health care systems to consider developing charitable pharmacy services for underserved populations.

Key Point: Charitable pharmacy services may play a role in minimizing hospitalizations, improving access to prescriptions as well as improving overall perceived health status for the underserved population.

Medical Marijuana: Policy Topic for 2015 APhA House of Delegates

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The APhA House of Delegates has policy language related to medical marijuana (MM) which dates from 1980. Due to some state-level acceptance of medical and recreational marijuana use, the House will consider updating their policy in March 2015.

APhA- Academy of Pharmacy Practice and Management: Margherita Giuliano, BSPharm, CAE

In the wake of recent legalizations of MM, pharmacy’s role is murky at best. Pharmacists in some states have taken the lead on MM implementation. The Connecticut Pharmacists Association (CPA) strongly advocated bringing medical marijuana to patients in need.

Due to this involvement, pharmacists in Connecticut currently have a critical role in the dispensing of MM. The physician authorizes a patient to be eligible to try medical marijuana based on a diagnosis and the pharmacist selects the product.

The CPA has supported the move to treat MM as a Schedule II controlled substance, rather than a schedule I. This allows the distribution of MM to mirror the system used for any Schedule II drug and allow drug tracking via the Connecticut’s Prescription Monitoring Program (PMP).

The successes in Connecticut come with lessons learned:
1. Pharmacists should be proactive with the legislation introduced. Be ready to take charge of this emerging area of pharmacy.
2. Insist medical marijuana is changed to a controlled substance. This allows for tracking through PMP.
3. Collaboration with a regulatory agency is key. All dispensaries must be told the same information.
4. Owning a dispensary is still illegal on a federal level.
5. Implementing pharmacists into the process can help fill the evidence-based hole around MM.
6. Dispensaries should be held to high production standards to ensure a homogenized product.
Recently, 31 states have passed laws allowing MM use and four now allow recreational use. Despite these state laws, at the federal level, marijuana is still classified as a schedule I substance and considered “high potential for abuse with no currently accepted medical use”. On top of this the prescribing procedure for MM typically differs from the traditional method, and many times circumvents the pharmacy-medical checks and balances.

The inconsistencies between federal law and state law and the different prescribing practices may lead providers to view dispensing and prescribing MM a dangerous career choice. If providers dispense or write for MM legally under state laws, they are still liable for federal criminal prosecution. Due to these stark differences, federal laws should be reexamined and coordinated with respect to marijuana use and distribution.

Another hurdle that must be overcome is the lack of appropriate research. MM is a natural product that has been used to treat severe nausea and vomiting associated with cancer chemotherapy, weight loss associated with HIV and cancer, glaucoma, and many other conditions. The majority of MM research is anecdotal and based on case reports. The studies that rigorously assess safety, efficacy, and long term use of MM are few and far between. It seems that the flurry of legalization of MM across the states stems more from public opinion, rather than scientific evidence. While public opinion is important, our society traditionally has not allowed use of drug products without scientific evidence. After studying MM, the development of standardized good manufacturing procedures, purity, potency, as well as other procedures for assuring quality, safety, and effectiveness must be developed. It would be redundant and inefficient for each state to create individual practices.

Despite the increase in legalization of MM throughout the country, the pharmacist’s role has not been clearly defined. Pharmacists will be interacting with marijuana users on a more frequent basis as this trend continues. Due to this, it is important for pharmacists to educate themselves on the subject. It is also important for pharmacists to be advocates for MM research, if not necessarily MM use in general.

Both practicing pharmacists and student pharmacists should be prepared to address our patient’s MM questions and concerns. Practitioners should understand this drug’s adverse effects, interactions, risks, and benefits. If not already included in curriculum, pharmacy students should be given training on MM to prepare them to care for their patients.

Pharmacist’s role in MM should be first to educate ourselves, and then educate our patients, and finally, support well conducted studies to broaden our knowledge base. Pharmacists need accurate data to support our recommendations and become a reliable source for MM drug information.

Overall, it is important for pharmacy to be directly involved in the implementation of MM. We should support continuing education and research on the topic to better serve our patients. As a profession, we should drive to resolve the inconsistencies between federal and state law.

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**Medication Therapy Management Interventions in Outpatient Settings: A Systematic Review and Meta-analysis**

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**Introduction:** Viswanathan et al set out to determine the impact of outpatient medication therapy management (MTM) interventions. Although the focus of MTM is to prevent and solve drug therapy problems, there are few large scale trials that demonstrate the outcomes of this service.

**Objective:** The objective of this systematic review and meta-analysis was to determine the effect of
MTM interventions on outpatients with chronic diseases.

**Outcomes:** The main outcomes in this meta-analysis included drug therapy problems, morbidity and mortality, quality of life, costs, health care use, and harms.

**Methods:** Of the 44 studies identified, there were 21 randomized controlled trials, four non-randomized controlled trials, and 19 cohort studies. The majority of these studies compared medication therapy management to usual care without medication therapy management.

**Results:** Outpatients that had medication therapy management scored statistically significantly higher in terms of medication appropriateness at 4.9 vs 0.9 points on the medication appropriateness index (P <0.001) based on a valid 10-item index of medication appropriateness. Patients with MTM were also significantly more adherent to medication regimens, as measured by the percentage of prescribed doses taken. Patients receiving MTM had a mean improvement of 4.6% in the percentage of prescribed doses taken. A final statistically significant outcome was medication dosing in that outpatients receiving MTM had significantly fewer medication doses. Patients receiving MTM had a mean difference of -2.2 medication doses (95% CI, -3.739 to -0.662). Researchers were unable to identify a statistically significant difference in other outcomes such as medication costs, number of outpatient visits and number and costs of emergency department visits.

**Conclusion:** Researchers concluded that evidence remains insufficient to determine the true value of MTM on most outcomes in the outpatient setting. Data remains limited and difficult to analyze in that current studies vary significantly in outcomes measured, study design and patient population. Also, MTM services vary considerably throughout the country, making it difficult to analyze and compare studies. As more research becomes available, the true value of MTM will become more evident.

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The National Governors Association released a statement advocating for the integration of pharmacists into the healthcare team, to help improve quality of care in rapidly evolving healthcare models. Pharmacists represent the third largest health profession, and are commonly associated with retail pharmacies, even though their roles have been evolving to meet patient medication needs.

Aging populations commonly have multiple chronic conditions and as a result have increasingly more complex medication regimens. Pharmacists are specifically trained to improve therapeutic outcomes and reduce healthcare costs. Direct patient care services are provided by interdisciplinary teams, commonly facilitated through a collaborative practice agreement (CPA) authorizing pharmacists to initiate/modify drug therapy for a specific patient.

Pharmacist involvement in the care team varies greatly across the country, but health care experts increasingly agree with studies that have demonstrated pharmacists’ ability to help improve chronic disease outcomes, reduce preventable adverse drug events and prescribing errors, and reduce costs. Several states across the country do enable pharmacists billing for their services through state and private health plans, even though formal recognition of pharmacists in the definition of providers is lacking by Medicare Part B. There are many opportunities to amend legislation in order to allow pharmacists to practice to the full scope of their license. The National Governors Association has created this document to empower states to strive to amend regulations governing CPA’s, provide compensation for direct patient care, and enable access to electronic medical records.

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