Candesartan versus Lisinopril on Neurocognitive Function in Older Adults with Mild Cognitive Impairment

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Background: Observational studies suggest that angiotensin receptor blockers (ARBs) may provide protective effects on cognitive function in patients without impaired cognition. It is unclear whether this effect is due to overall benefits of blood pressure (BP) reduction or their specific mechanism of angiotensin type 1 (AT1) receptor blockade. It is proposed that selective antagonism at AT1 receptors allows for increased activation of angiotensin type 2 (AT2) receptors, which is associated with regeneration of neuronal axons, modulation of neuronal excitability, and reduced vascular inflammation. In addition, ARBs appear to provide greater reduction inflammatory markers compared to angiotensin-converting enzyme inhibitors (ACEIs).

Objective: To compare the impact of candesartan vs. lisinopril on cognitive function in patients ages 55+ with hypertension and mild cognitive impairment.

Study Design: This double-blind randomized controlled trial aimed to compare the effects of 12 months of treatment with an ARB (candesartan) vs. an ACEI (lisinopril) in patients ages 55+ diagnosed with mild cognitive impairment and hypertension. From June 2014 to December 2018, 176 patients were randomized from prior antihypertensive therapy to candesartan or lisinopril provided in identical oral capsule formulations. Medications were escalated to a maximum of 32 mg candesartan once daily or 40 mg lisinopril once daily to achieve goal BP <140/90 mmHg. Additional open-label antihypertensive therapies were added as needed following study protocol to attain goal blood pressure control. The primary outcome was executive cognitive function. This was assessed with the Trail Making Test (TMT) and the Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER) tool at baseline, 6 months, and 12 months. Secondary outcomes were episodic memory and microvascular brain injury. Episodic memory was measured with the Hopkins Verbal Learning Test-Revised (HVLT-R) at baseline, 6 months, and 12 months, and microvascular brain injury was visualized with magnetic resonance imaging (MRI) at baseline and 12 months. Patients were excluded if intolerant to any ACEI or ARB, diagnosed with dementia or any active medical or psychiatric condition deemed a safety risk by the study physician, had a systolic BP >200 mmHg or diastolic BP >110 mmHg, baseline serum creatinine >1.99 mg/dL, or baseline serum potassium >5.5 mEq/dL.

Results: Of 176 enrolled patients, 141 completed the trial, with no significant difference in dropout rates between groups. Both candesartan and lisinopril groups achieved similar BP control at the end of 12 months (mean systolic BP 134 vs 130 mmHg, P=0.2; mean diastolic BP 78 vs 77 mmHg, P=0.52). After adjusting for BP, race, additional antihypertensive drugs, and baseline cognitive test scores, candesartan was determined
to be superior to lisinopril in executive function measured with the TMT-Part B tool (effect size = -12.8 [95% CI -22.5 to -3.1]), but not with the EXAMINER tool (effect size = -0.03 [95% CI -0.08 to 0.03]). Candesartan was also found to be superior to lisinopril in some measures of the secondary outcome, including delayed recall (effect size = 0.4 [95% CI 0.02 to 0.8]) and retention (effect size = 5.1 [95% CI 0.7 to 9.5]). MRI scans showed a non-significant lower rate of white matter lesion accumulation with candesartan compared to lisinopril (effect size = -0.3 [95% CI -0.6 to 0]).

Conclusions: Overall, the results suggest that candesartan may have a greater impact on executive function and episodic memory in older adults with hypertension and mild cognitive impairment compared to lisinopril. These results indicate that candesartan’s neurocognitive protective effects may be independent of BP reduction. Further studies are required to determine if cognitive protection is a class effect of ARBs.

Key Point: Twelve-month treatment with candesartan was associated with protection of executive function and memory in older hypertensive adults with diagnosed mild cognitive impairment compared to lisinopril titrated to equivalent goal BP. It is unclear whether these findings may be attributed to ARBs as a class effect, and more research is needed to determine whether the impact on cognitive function is clinically significant.

The HPV Vaccine and The Associated Risk of Developing Invasive Cervical Cancer
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Background: Human papillomavirus (HPV) is one of the most common sexually transmitted infections and has been associated with genital warts, cervical lesions, oropharyngeal cancer, and anogenital cancer. The Centers for Disease Control and Prevention has estimated that annually 35,000 cases of cancer in men and women are caused by HPV infections. HPV vaccines have been shown to dramatically reduce the risk of developing HPV Infection, genital warts, and high-grade precancerous cervical lesions. Currently, evidence indicating prevention of invasive cancers later in life is limited.

Purpose: The purpose of this study is to analyze the association between girls and women who received the HPV vaccine and the risk of developing invasive cervical cancer.

Study Design: This study was a registry-based cohort study completed in Sweden using data from 2006 to 2017. The Swedish Total Population Register was used to identify females between 10 to 30 years of age who had no previous HPV vaccination or previous invasive cervical cancer. The participants were followed starting either on their tenth birthday or after January 1, 2006 and continued until either death, diagnosis of invasive cervical cancer, age 31 years old, or until December 31, 2017, whichever came first. Exposure to the quadrivalent HPV vaccine was determined using the Prescribed Drug Register and the National Vaccination Register. Girls and women were considered vaccinated if they had at least one dose of the HPV vaccination series. Those who were vaccinated were then compared to unvaccinated comparators over the same time period. Poisson regression models were used to estimate the incidence rate ratios which compared the incidence rate of those who were vaccinated with their unvaccinated counterparts.

Results: A total of 1,672,983 girls and women were included in the study. Baseline characteristics were similar in both groups. The majority of participants did not have a maternal history of cervical cancer or non-cervical cancer. Of those enrolled, 527,871 had received at least one dose of the HPV vaccine. Invasive cervical cancer was diagnosed in 19 vaccinated women and 538 unvaccinated women. After adjustment for age at follow-up, calendar year, residential and parenteral characteristics, the incidence rate ratio was 0.12 [95% confidence interval (CI), 0.00 to 0.34] in those vaccinated before 17 years of age and 0.47 [95% CI, 0.27 to 0.75] in those vaccinated between 17 to 30 years of age.

Conclusions: Administration of the quadrivalent HPV vaccine was associated with a significantly lower risk of invasive cervical cancer. The risk was lower with vaccination at a younger age. Additionally, lifestyle and health factors were not assessed in this study, such as smoking status, sexual activity, oral contraceptive use, and obesity, and other potential confounders.

Key Point: Girls and women between the ages of 10 and 30 years old receiving the HPV vaccination was associated with lower incidence of developing invasive cervical cancer.

Colchicine in Patients with Chronic Coronary Disease
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Background: Inflammation plays a key role in the progression of coronary disease, particularly in individuals who are at high risk for acute cardiovascular events. In the 2019 Colchicine Cardiovascular Outcomes Trial (COLCOT), patients who had a myocardial infarction (MI) within 30 days before enrollment and received 0.5 mg of colchicine daily were less likely to have the composite end point of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization than those who received placebo. However, it is unknown if colchicine has potential cardiovascular benefits in chronic coronary disease, not just in individuals who have had a past medical history of an MI.
Objective: To determine if colchicine can lower the risk of cardiovascular events in chronic coronary disease.

Study Design: Investigators performed a randomized, controlled, double-blind, intention-to-treat trial. The primary endpoints included a composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary endpoint was similar to the primary outcome but did not include the ischemia-driven coronary revascularization. Inclusion criteria included adults between the ages of 35-82 years with established coronary artery disease who had been clinically stable for at least 6 months. Exclusion criteria included moderate to severe renal impairment, severe heart failure, severe valvular heart disease, and known side effects from colchicine. The eligible subjects entered an open-label, run-in phase for one month in which they received 0.5 mg of colchicine daily. The patients who were stable without adverse effects, adhered to the open-label colchicine regimen, and remained willing to continue participation were randomly assigned in a 1:1 ratio to receive 0.5 mg of colchicine daily or matching placebo. 5,522 individuals underwent randomization in the study, 2,762 of whom were assigned to the colchicine arm and 2,760 to the placebo arm. The median duration of follow-up was 28.6 months.

Results: A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; HR 0.69 [95% CI 0.57-0.83, P<0.001]. The key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group (incidence, 1.5 vs. 2.1 events per 100 person-years; HR 0.72 [95% CI 0.57-0.92], P = 0.007). In addition to colchicine, most patients were taking appropriate secondary prevention therapies for chronic coronary disease. In these patients, colchicine led to a 31% lower relative risk of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization compared to placebo. However, colchicine did not result in a lower incidence of death from any cause (73 vs. 60 fatalities; incidence, 0.9 vs. 0.8 events, respectively, per 100 person-years; 1.21 [95% CI 0.86-1.71]). The incidence of death from non-cardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; 1.51 [95% CI 0.99-2.31]). The risk of non-cardiovascular death, hospitalization for a GI cause, and myalgia were higher with colchicine, but were not statistically significant.

Conclusions: The primary and key secondary endpoints had a lower incidence rate in the colchicine arm compared to placebo. Colchicine 0.5 mg daily resulted in a 31 percent lower relative risk of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization. In addition, the incidence rates of various other secondary singular and composite endpoints (spontaneous MI or ischemia-driven coronary revascularization, cardiovascular death or spontaneous MI, ischemia-driven coronary revascularization, and spontaneous myocardial infarction) were all significantly lower with colchicine than with placebo. Based on this study, the effects of colchicine seem to be consistent across each component of the primary end point and many secondary endpoints. However, the study did also show a non-significant trend in higher rates of non-cardiovascular death among patients receiving colchicine.

Key Point: The results of the trial demonstrate that in patients with chronic coronary disease, the majority of whom were already taking appropriate secondary prevention therapies, there is a significantly lower occurrence of cardiovascular events while receiving colchicine 0.5 mg daily compared with placebo.

THERAPEUTIC THOUGHT

First-line Pharmacotherapy for Smoking Cessation with Comorbid Psychiatric Conditions

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Background: According to the National Survey on Drug Use and Health (NSDUH) performed by Substance Abuse and Mental Health Services Administrations (SAMSHA), approximately one in four adults in the U.S. has some form of behavioral health condition, and these adults consume almost 40% of all cigarettes smoked by adults. There are several therapeutic options for smoking cessation including five nicotine replacement therapy (NRT) products, bupropion sustained release (SR), varenicline, or combination therapy. Previous concerns with possible neuro-psychiatric effects of varenicline and black box warnings, led physicians and patients to be reluctant to use this medication. The 2018 American College of Cardiology (ACC) Expert Consensus on Tobacco Cessation Treatment recommends varenicline or combination NRT for first-line therapy over single NRT or bupropion, with only brief mention of considerations in psychiatric disease. Furthermore, the 2020 American Thoracic Society (ATS) Clinical Practice Guideline for tobacco dependence strongly recommends the use of varenicline over NRT or bupropion SR in patients with or without a comorbid psychiatric condition.

Evidence and Discussion: The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was one of the largest trials assessing neuropsychiatric safety and efficacy of varenicline,
bupropion, and NRT in smokers with and without psychiatric disorders. In this randomized, double-blind, triple-dummy, placebo-controlled and active-controlled trial, participants were randomized 1:1:1:1 to receive either varenicline, bupropion, nicotine patch, or placebo and divided into non-psychiatric or psychiatric cohorts.

Of the participants (n=3984) in the non-psychiatric cohort, the difference in risk (RD) of the primary composite neuropsychiatric between the varenicline-placebo, varenicline-bupropion, and varenicline-nicotine patch for moderate and severe neuropsychiatric adverse events were -1.28 [95% CI -2.40 to -0.15], -1.19 [95% CI -2.30 to -0.09], and -1.07 [-2.21 to 0.08], respectively.

In the psychiatric cohort (n=4074), the RD between the varenicline-placebo, varenicline-bupropion, and varenicline-nicotine patch for moderate and severe neuropsychiatric adverse events were 1.59 [95% CI -0.42 to 3.59], -0.20 [95% CI -2.34 to 1.95], and 1.22 [95% CI -0.81 to 3.25], respectively.

This large multinational trial did not show a significant increase in rates of moderate-to-severe neuropsychiatric adverse events with either varenicline or bupropion relative to nicotine patch or placebo in those with or without psychiatric disorders. In addition, varenicline showed significantly higher abstinence rates compared to all other treatment regimens (P<0.001). The results of this trial did not support the concerns about psychiatric side effects previously voiced by the FDA in 2009, leading to the removal of the black box warning in 2016.

The updated 2020 ATS guidelines for smoking cessation further addressed whether or not patients with a history of mental health or substance use disorders should start with the optimal controller medication identified for patients without psychiatric conditions or use NRT. A systematic review was performed identifying two randomized clinical trials that directly compared varenicline with NRT patch. Both trials concluded that varenicline may result in a large benefit for abstinence and would likely result in little to no difference in serious adverse events (SAEs) in patients with substance use or psychiatric disorders. The systematic review suggested a slight yet trivial decrease in risk of SAEs with varenicline compared to a NRT patch (RR, 0.95 [95% CI 0.54 – 1.67]). The results from this systematic review drove the ATS guidelines to recommend using varenicline over a nicotine patch for tobacco-dependent adults with comorbid conditions, including substance use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom treatment is being initiated.

Clinical Impact: ACC and ATS guidelines address limitations and misconceptions around treating vulnerable patients with behavioral health disorders for smoking cessation. With the evidence presented in both the ACC and ATS guidelines, it allows providers to be more confident in choosing the most appropriate and affordable therapy for smoking cessation.

Cardiovascular Risk Reduction in Type 2 Diabetes10-13
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Background: The Center for Disease Control estimates that over 34 million Americans have diabetes, with 90-95% of those patients managing type 2 diabetes. The number one cause of morbidity and mortality in individuals with type 2 diabetes is cardiovascular (CV) disease. As such, it is very important for healthcare providers across disciplines to collaboratively manage diabetes and related comorbidities. The American College of Cardiology (ACC) recently released their 2020 Expert Consensus Decision Pathway (ECDP) on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes (T2D) to summarize recent studies showing the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide receptor agonists (GLP-1RAs) in reducing cardiovascular risk in patients with type 2 diabetes.

Evidence and Discussion: The 2020 American Diabetes Association Standards of Medical Care in Diabetes recommends using SGLT2 inhibitors and GLP-1RAs for patients with either established or a high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD). Following the first-line recommendation of metformin and lifestyle management for anyone with type 2 diabetes, it is recommended to consider the use of agents to lower the risk of ASCVD, CKD, or heart failure regardless of the patient’s hemoglobin A1c.

An SGLT2 inhibitor, provided the patient has sufficient kidney function, or GLP-1RA with cardiovascular benefit is preferred for patients with established ASCVD or risk factors for ASCVD, including those at least 55 years old with over 50 percent stenosis of a coronary, carotid, or lower extremity artery, or left ventricular hypertrophy. The GLP-1RA agents with proven CV benefit include dulaglutide, liraglutide, and semaglutide. The SGLT2 inhibitors include canagliflozin, empagliflozin, and dapagliflozin. For patients with heart failure, specifically those with an ejection fraction less than 45 percent, or chronic kidney disease (defined as an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m2 or urine albumin-to-creatinine ratio greater than 30 mg/g) an SGLT2 inhibitor is preferred, given sufficient kidney function. A GLP-1RA with CV benefit is recommended if the SGLT2 inhibitor is contraindicated or intolerable.

The 2020 ACC Expert Consensus Decision Pathway provides updates to the 2018 ECDP, highlighting the use of SGLT2 inhibitors and GLP-1RAs in specific comorbidities. The 2018 pathway included patients with type 2 diabetes and clinical ASCVD. This update has expanded to adults with type 2 diabetes and established ASCVD, heart failure, diabetic kidney disease (DKD), and/or a high risk of ASCVD, which includes those with end organ damage or several risk factors. In the 2018 ECDP, it is...
recommended to follow guideline recommendations for comprehensive CV risk reduction, while simultaneously considering the initiation of an SGLT2 inhibitor or GLP-1RA. While the 2020 ECDP contains a similar recommendation regarding comprehensive risk reduction, the recommendation for SGLT2 inhibitors or GLP-1RAs has been strengthened to recommend an agent from one of these classes with cardiovascular benefit. Since publication of the 2018 ECDP, there are now additional agents to use within each class of medication and the indications for use of these medications have been expanded.

The SGLT2 inhibitors act on the sodium-glucose cotransporter in the kidney, which prevents glucose reabsorption and causes excretion of excess glucose in the urine. They can also assist in weight loss and blood pressure control for patients. Data from multiple large, randomized controlled trials were evaluated and compiled in the ECDP to support the cardiovascular and renal benefits of these agents. Canagliflozin was shown by these trials to reduce the risk of major adverse cardiovascular events (MACE), a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death, in patients with type 2 diabetes and cardiovascular disease. Dapagliflozin was shown to reduce the risk of HF hospitalization in patients with type 2 diabetes and CV disease or with several risk factors for CV disease. Empagliflozin reduces the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease.

GLP-1RAs cause an increase in concentration of GLP-1, a hormone released in response to intake of food. This hormone promotes glucose-dependent insulin secretion, slows gastric emptying, and reduces glucagon secretion. These agents are also beneficial for weight loss, blood pressure, and triglyceride management, and may provide renal benefits. A number of large, randomized controlled trials looking at the cardiovascular effects of these medications were compiled in the ECDP. Only dulaglutide, lixisenatide, and subcutaneous semaglutide were shown to reduce MACE in patients with type 2 diabetes and cardiovascular disease, indicating heterogeneity within the pharmacological class. Dulaglutide is also indicated to reduce MACE in those without established ASCVD. Oral semaglutide and exenatide showed positive outcomes for MACE reduction; however, they were not statistically significant.

Clinical Impact: The newly published ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes provides strong support for the use of SGLT2 inhibitors and GLP1 receptor agonists to reduce the risk of cardiovascular morbidity and mortality. Individuals with type 2 diabetes and heart failure, particularly those with an ejection fraction less than or equal to 40 percent, are recommended to initiate an SGLT2 inhibitor. These agents are also recommended for individuals with either established or risk factors for ASCVD, DKD, or heart failure and type 2 diabetes. GLP1-RAs are recommended in patients with a history of ASCVD or a high risk of developing ASCVD. Of course, before the initiation of any medication, potential adverse effects, pertinent medical history, and patient preferences should be taken into consideration.

FROM THE PHARMACY PRESS

Risk Factors for Genitourinary Infections with SGLT-2 Inhibitors

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Background: Patients with diabetes are at an increased risk of genitourinary infections (GUI), such as urinary tract infections and genital mycotic infections. The infections have also been described as common side effects of sodium-glucose cotransporter-2 (SGLT2) inhibitor medications. Premarketing clinical trials for SGLT2 inhibitors have suggested a combined absolute risk of 13.9-20.7% for these infections. There is minimal evidence on whether certain patient characteristics could be defined as risk factors for developing GUI.

Purpose: The primary objective of this analysis by Benjamin and Schumacher was to evaluate if hemoglobin A1c at initiation of therapy was a predictor for increased risk of developing a GUI in patients with type 2 diabetes. The secondary objective was to evaluate whether additional factors, such as age, body mass index (BMI), eGFR, fasting plasma glucose, serum sodium, serum potassium or serum creatinine, impacted the risk of developing a GUI with concurrent use of an SGLT2 inhibitor.

Study Design: This study was a retrospective, multicenter cohort analysis that utilized ambulatory care patient data from a total of 42 different clinics in the south and southeastern suburbs of Chicago. Inclusion criteria consisted of patients who were 18 years or older with a diagnosis of type 2 diabetes treated with an SGLT2 inhibitor for at least seven days during a prespecified five year window. Exclusion criteria included those patients who had no laboratory values recorded, a history of GUI in the past year, or a contraindication to SGLT2 inhibitor therapy (pregnancy, eGFR <30mL/min/1.73 m2, and end stage renal disease). A history of GUI was defined as a single instance of GUI confirmed by urinalysis, urinary culture, history of antibiotic or antifungal prescriptions with corresponding physician documentation or appropriate diagnosis code.

Results: The researchers included data from 584 patient charts
in their retrospective analysis. Of those, there were 30 (5.14%) patients who developed a GUI after initiating an SGLT2 inhibitor. Baseline A1c was not found to have a significant impact on the incidence of GUI in these patients on SGLT2 inhibitors. The only prespecified secondary outcome that showed statistically significant increased risk of GUI was a lower eGFR [79.28 vs. 73.37 mL/min/1.73 m², P=0.0361]. BMI, fasting glucose, potassium, sodium, and serum creatinine were not statistically significant indicators, nor was increased risk associated with any one particular SGLT2 inhibitor. Male sex was found to have a lower incidence of GUI [7 vs. 23, P=0.0019], which was expected due to previously documented risk for GUI being higher in females on SGLT2 inhibitors at baseline. A post-hoc analysis that included the 30 patients who were initially excluded due to a history of GUIs within one year of SGLT2 therapy found that 13 (43.3%) of these patients experienced a GUI subsequent to SGLT2 inhibitor initiation, making prior history of GUI within one year the largest risk factor in this analysis. Of the 43 total patients diagnosed with a GUI in the post-hoc analysis, 23 (55%) were diagnosed with a fungal infection, 19 (45%) as presumed bacterial infection, and one of these was presumed to have both a fungal and bacterial GUI. The average time to GUI was 336 days [SD 232 days, median 247 days, range 5-1190 days].

**Conclusions:** The results of this retrospective, multicenter cohort study demonstrated that baseline A1c had no effect on the risk of developing a GUI on SGLT2 inhibitor therapy. A lower eGFR was the only secondary outcome that showed a statistically significant increased risk for a GUI while taking an SGLT2 inhibitor. Based on the post-hoc analysis, the largest risk factor to take into account for GUI on SGLT2 inhibitors is a prior history of GUI.

**Key Point:** Baseline A1c has no significant effect on GUI risk in patients on SGLT2 inhibitors. However, patients with a decreased eGFR and prior history of GUI may be at higher risk for these infections if started on an SGLT2 inhibitor and should be educated on their risk and risk reduction strategies when initiating these medications.

A Call to Action- Pharmacists’ role and responsibility regarding systemic racism
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The recent increase in recognition of the systemic racism that has plagued the United States and the world for centuries has culminated in declarations of racism as a public health crisis. This has highlighted the need for many, including pharmacists, to better understand their role within this system and what can be done to dismantle it. A recent article in the Journal of the American Pharmacists Association by Arya et al sought to help address this issue within pharmacy by illustrating the shortcomings that currently exist and providing actionable recommendations for how to improve. As pharmacists, especially white pharmacists who hold privilege in these spaces, we owe it to our patients and the communities we serve, as well as our colleagues, current and future pharmacy students, and society as a whole to use our knowledge and unique accessibility to do our part in addressing structural racism and its consequences.

Despite inclusion of cultural competency training in pharmacy school curricula, identifying the role systemic racism plays in social determinants of health is not often explicitly taught, and as a result the connection is not always understood by students and healthcare professionals. Pharmacists who identify as Black, Indigenous, and Persons of Color (BIPOC) often face the expectation to lead diversity initiatives and be ambassadors for diverse groups within their often predominantly white organizations while also facing racism in both their personal and professional worlds. Furthermore, our BIPOC colleagues may also be dealing with past trauma resulting from the horrific treatment of these communities that has been going on for centuries. It is an understatement to say that significant work must be done to address these failings, and Arya et al. outline areas in which we can begin to make an impact and where white pharmacists must take the lead.

The scope of the implications and pervasiveness of systemic racism can make it feel difficult to identify where to begin in the fight for justice and equity. However, the first action item in the article centers around taking personal responsibility for increasing one’s understanding of where and how systemic racism impacts different communities.

On an institutional level, organizations should review policies and procedures to ensure they are equitable, support advocacy efforts regarding diversity and equity, and focus on creating opportunities for BIPOC individuals in leadership positions. These organizations should also consider creating antiracism task forces and/or committees, designing a position such as a Chief Diversity Officer, and to support these initiatives with adequate resources to truly have an impact. Furthermore, professional organizations should also review policies and consider strengthening their positions regarding equity and diversity. From an academic perspective, pharmacy schools and colleges need to better incorporate teachings on implicit bias and antiracism training. Additionally, the recruitment efforts of these schools must place an increased emphasis on recruiting students more representative of the communities we serve, as well as our colleagues, current and future pharmacy students and society as a whole can work toward minimizing and eventually eliminating...
systemic racism will be essential. Equally important will be engaging patients and the community by soliciting input and engaging in shared decision-making, while avoiding making assumptions around the needs of the community. As the pharmacy community joins in the fight against systemic racism, it’s easy to see that the time is now for white pharmacists, institutions, and others with the power to dismantle oppressive systems to start investing time and resources to that end, but it is also important to understand that really the time for action was decades ago. As the authors conclude, pharmacists, especially white pharmacists, must critically review their role in dismantling structural racism such that they can truly uphold the tenets of the Oath of the Pharmacist: to consider the welfare of humanity and relief of human suffering— for all patients.

Implementation of Primary Care Clinical Pharmacy Services for Adults Experiencing Homelessness\*\*
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Background: Homeless individuals experience proportionately higher rates of mental illness, substance abuse, diabetes, hypertension, and HIV than the general population. By the same token, several barriers stand in their way to access care, including food scarcity and limited healthcare resources. Additionally, they may have lower health literacy and competing health concerns. If they are able to gain access to care, these patients can experience social stigma, uncompassionate healthcare, and misconceptions about their homelessness that decrease their quality of care. These negative experiences can decrease their willingness to seek medical care in the future. The addition of a pharmacist on interdisciplinary teams taking care of these patients can improve access, provide more opportunities for patient education, and potentially improve health outcomes. This article set out to bridge the gap in literature regarding pharmacist-led clinical services for the homeless population.

Objective: To evaluate the type and frequency of the interventions made by the pharmacist at a clinic caring for patients experiencing homelessness, to describe the patients receiving the novel service, and assess the clinical outcomes related to primary care disease states, such as diabetes, hypertension, obesity and tobacco use disorder.

Practice Description: This was a pilot service provided by a postgraduate year 2 (PGY-2) ambulatory care resident pharmacist located at Pedigo Clinic within Eskenazi Health in Marion County, IN. Pedigo Clinic was established to provide care to patients experiencing homelessness and a clinical pharmacist had not previously been a member of the interdisciplinary care team. Prior to the study, pharmacists in this health system had an existing collaborative practice agreement (CPA) for cardiovascular risk reduction (CVRR) clinics to manage diabetes, hypertension, dyslipidemia, smoking cessation and vaccines. During the pilot period, the PGY-2 ambulatory care resident pharmacist attended the Pedigo Clinic one half-day each week to provide CVRR service under a CPA through referrals by the physician to patients noted to be experiencing homelessness. Additionally, the resident pharmacist consulted with the clinic staff regarding specific patients.

Practice Innovations: The pharmacist was able to address several aspects of patient care within the Pedigo Clinic. They helped patients with insurance coverage issues, provided bus passes to and from the clinic, monthly medication refills, and provided medication vouchers for copayments backed by health system funding. They helped store patient-specific medications for those unable to store refrigerated medications or where the patient possessing their medications posed a safety risk. They subsequently administered patient-specific medications at the clinic or dispensed smaller quantities to avoid any safety issues. Additionally, they tried to coordinate care on the same day as other visits.

Results: The service was piloted for 6 months, from September 2019 to March 2020. The resident pharmacist documented patient encounters in the electronic medical record and then retrospectively reviewed this convenience sample to collect data. Review included any patient with an appointment or consultation the pharmacist participated in. Twenty-eight patient encounters were completed for fourteen unique patients with a total of one hundred and twenty-four interventions. Eighty-six percent of the patients were men, with ages ranging from 33 to 64 years old. Comprehensive medication review comprised 82.1% of the interventions, followed by patient education (75%), medication regimen optimization (64.3%), tobacco cessation (64.3%), coverage/cost inquiry (39.3%), and vaccination screening (28.6%). Evaluation of clinical outcomes at baseline and each subsequent visit happened for six patients that were seen more than one time. There were no statistically significant changes in clinical outcomes, given that this was a small convenience sample over a limited time period and therefore may not have been adequately powered to detect any meaningful differences in clinical outcomes.

Clinical Impact: The researchers found that pharmacists can have a positive impact on patient care for the homeless population. The pharmacist spent the most time optimizing patients’ medication regimens, as well as educating patients about disease states, goals of care, medication use, and adherence. Through extrapolation from previous data, they found a potential cost savings of an average of $160.58 per patient encounter translating to an approximate savings of nearly $323,000 annually.
FDA Updates on Black Box Warnings

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The FDA has updated black box warnings on several medications seen in primary care in recent months. Invokana® (canagliflozin) has had a warning removed, while there are new warnings to be aware of for benzodiazepines and non-steroidal inflammatory drug (NSAID) use in pregnancy.

The sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin (Invokana®, Invokamet®, and Invokamet XR®) reduces renal glucose reabsorption through the blockage of SGLT2 receptors in the kidney, therefore lowering blood sugars through an increased excretion of glucose through the urine. In 2017, a black box warning was assigned to canagliflozin regarding increased risk of leg and foot amputations. The FDA has removed this boxed warning after new data has emerged. They found that while the risk of amputation remains with use of Invokana, the magnitude of the risk has been determined to be lower than previously described. Additionally, heart and kidney related benefits that have been studied since the introduction of Invokana are now thought to outweigh the relatively small risk of amputation. Specifically, 2018 the CANVAS study released data to show Invokana reduced the risk of heart attack, stroke, and death in patients with type 2 diabetes with concomitant heart disease. In 2019 the CREDENCE study showed additional benefit via a reduction in risk of end-stage kidney disease, worsening of kidney function, hospitalization for heart failure, and cardiovascular death. Continue to encourage preventative foot care and monitoring of instances of new pain, tenderness, soreness, or ulcers in the feet.

Benzodiazepines are a widely used class of medications used for generalized anxiety disorder, insomnia, seizures, social phobia, panic disorder, and other anxiolytic uses. Although commonly used, benzodiazepines are often abused and misused. This may be especially dangerous when combined with opioid pain relievers, alcohol, social drugs, or other prescribed medications, such as antihistamines and sleep medications. Additionally, physical dependence on benzodiazepines can occur after several days to weeks, leading to withdrawal symptoms if abruptly discontinued. Due to these concerns, the FDA has added a black box warning to include the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions to the labeling in order to help guide prescribers and patients to use the medications safely. This added labeling is a part of the FDA’s ongoing effort towards improving public health by minimizing risks of controlled substances. Prescribers should continue to use benzodiazepines with caution to minimize these risks.

New labeling has been added to NSAIDs regarding use in pregnancy. Medications classified as NSAIDs include ibuprofen, naproxen, diclofenac, meloxicam, and celecoxib. NSAIDs are used both over the counter (OTC) and as prescription medications to treat pain, fever, and inflammation. The FDA warns that using NSAIDs after 20 weeks of pregnancy may cause kidney problems in the fetus, which can lead to low levels of amniotic fluid. This condition has shown to be resolved after discontinuation of NSAID use. This has been a known risk, but is a risk that the FDA has decided should be more widely known to avoid complications in pregnancy. Warnings to avoid NSAIDs after 28 weeks are already established due to the risk of premature closing of the ductus arteriosus in the fetus. It is recommended that NSAID use be limited after 20 weeks gestation and if required, should be limited to the lowest dose and shortest duration possible. This updated warning will also be reflected in the Drug Facts labels on OTC NSAID products.

Comprehensive Medication Review: New Poll Indicates Interest but Low Receipt Among Older Adults

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M Health Fairview

Over time, the use of prescription medications by Medicare patients has increased, leading to an increased potential for drug interactions, adverse effects, use of medications no longer needed, incorrect doses, nonadherence, and elevated costs. A way to address and prevent these problems is through a comprehensive medication review (CMR) as a part of Medication Therapy Management (MTM). Medicare Part D plans require an annual CMR to help resolve drug therapy problems and prevent medication-related adverse events. A study conducted by the University of Michigan surveyed 2,048 adults between the ages of 50-80 years old and found many would benefit from a CMR due to self-reported polypharmacy. Despite this potential benefit, only one in four adults aged 65 to 80 years old enrolled in a Medicare Part D plan had received a CMR. Among adults aged 50-80 years old, 86% were not aware that a CMR was an included insurance benefit and 36% were interested in completing a CMR. CMRs have been a benefit of Medicare Part D plans for almost 15 years, but there is a continued lack of awareness about CMRs among older adults. Overall, these results showed that few older adults received a CMR, most were unaware of this service, and over a third were interested in receiving the service.

Flu, Pneumonia Vaccinations Tied to Lower Risk of Alzheimer’s Dementia

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A new study has shown that influenza and pneumonia vaccinations
are associated with a reduced risk of Alzheimer’s disease. Prior studies have suggested the vaccination may protect against cognitive decline but were too limited in size for a definitive recommendation. The Medical School at the University of Texas looked at 9,066 patients retrospectively via a health record database and found receiving one flu vaccine was associated with a lower prevalence of Alzheimer’s (p<0.0001). It was found to be even lower in those who consistently received their flu vaccine (p=0.0342). In those 75-84 years old who consistently received their annual flu vaccine, there was almost a 6% absolute risk reduction of Alzheimer’s disease. The protective benefit was also stronger in those who received their first vaccine at a younger age.

Researchers at Duke University investigated the association between pneumococcal vaccination, with and without the flu vaccine, and accounted for those with a genetic risk for Alzheimer’s. After looking at 5,146 participants, it was found that pneumococcal vaccination between 65-75 years old reduced the risk of developing Alzheimer’s by 25-30%, with the largest benefit being in those who were non-carriers of the Alzheimer’s risk gene. A study conducted by the University of Copenhagen in Denmark found that infections in those with dementia lead to increased mortality. All of these studies support the need for further investigation into the role of vaccination and infection on the development of Alzheimer’s.

REFERENCES


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