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## RESEARCH UPDATES

### Apixaban, is it a One-Size-Fits-All Anticoagulant? Using Apixaban to Treat VTE in Individuals of Higher Body Weight[1]

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Background: Historically, guidelines from the American Heart Association advised using caution when selecting direct oral anticoagulants (DOACs) in populations with low or high body weight due to lack of evidence. New evidence from a multi-center retrospective study comparing apixaban versus warfarin supports the safety and efficacy of apixaban for treatment of venous thromboembolism (VTE) in patients with severe obesity.

**Purpose**: The comparison trial of apixaban versus warfarin aimed to evaluate the efficacy and safety of the two agents to treat VTE in individuals with a BMI >40 kg/m2 or weight >120 kg. The primary efficacy and safety outcomes were time to recurrence of VTE and time to major bleeding at 12 months, respectively.

**Study Design**: This retrospective, cohort, multi-center trial involved 26 hospitals across six different states. Data was pulled from inpatient admissions between January 1, 2012 and December 31, 2019 as a subset from a larger multi-study research group. The information obtained from a patient's first admission was used to determine trial enrollment for patients with multiple admissions linked with a VTE diagnosis code. Inclusion criteria consisted of patients ≥18 years of age, have a BMI >40 kg/m2, actual body weight >120 kg, have at least one dose of apixaban or warfarin during hospitalization, and anticoagulation treatment was continued at discharge. Exclusion criteria included any history of mechanical valve replacement, severe liver disease (hepatic encephalopathy or esophageal varices), pregnancy, or taking a medication contraindicated for concurrent use with DOAC or warfarin therapy (i.e. itraconazole, ketoconazole, ritonavir, rifampin, carbamazepine, phenytoin, and St. John's wort).

**Results**: Of 1099 patients enrolled in the study, there were 314 patients in the apixaban group and 785 patients in the warfarin cohort. The baseline characteristics were similar between the two cohorts and included an average age of 58 years, average BMI of 44-47 kg/m2, and 60-70% White and 24-30% Black patients. Through manual chart review, common clot risk factors of the enrolled patients included diabetes mellitus (DM), history of VTE, active smoker, and chronic kidney disease. The results were adjusted for these confounding variables and noted the warfarin cohort having a greater percentage of patients with DM and/or history of VTE than the apixaban cohort. The study observed better outcomes for the apixaban cohort before and after adjusting for confounding variables.

Without adjustment, apixaban demonstrated better results compared to warfarin at 12 months for time to recurrent VTE (P= 0.018), incidence of recurrent VTE (4.5% versus



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8.7%, P= 0.02) and had significantly fewer hospital encounters (2.92 + 4.3 versus 6.5 + 9.2, P< 0.01). With adjustment, apixaban still showed a reduced incidence of recurrent VTE compared to warfarin (HR 0.54, 95% CI 0.29-0.97, P= 0.04). In terms of safety, there was no significant difference between the apixaban and warfarin groups in time to major bleeding (P= 0.665) or major bleeding events in 12 months (3.8% versus 3.3% , P= 0.715).
To further eliminate the influence of confounding variables, the study completed a propensity match analysis of baseline characteristics and paired 297 patients of each arm. They found no significant differences in recurrent VTE (HR 0.515, 95% CI 0.26-1.04, P=0.057) or major bleeding in 12 months (HR 1.25, 95% CI 0.5-3.18, P=0.632). There was also a reduced risk of clinically relevant non-major bleeding (CRNMB) (HR 0.27, 95% CI 0.08-0.98, P= 0.031) and lower total number of hospital encounters within 12 months in the apixaban group compared to warfarin (2.9 + 4.4 apixaban versus 6.7 + 9.1 warfarin, P< 0.01).

Lastly, a subgroup analysis included 428 patients with BMI >50 kg/m2 and/or weight >140 kg. This included 93 patients on apixaban and 335 patients on warfarin. There was no significant difference in VTE recurrence (3.2% versus 9.9%, P= 0.06), major bleeding (4.3% versus 3.0%, P= 0.52), CRNMB (1.1% versus 2.7%, P= 0.7) and all-cause mortality (4.3% versus 2.4%, P= 0.30) between apixaban and warfarin respectively.

**Conclusions**: Historically, warfarin has been preferred in situations where there was insufficient evidence to support the use of DOACs, including patients with increased body weight. This study found that apixaban is safe and effective at treating and preventing recurrence of VTE while not increasing risk of major bleeding for patients with a BMI >40 kg/m2 and/or actual body weight >120 kg. The subgroup analysis suggests that apixaban may even be effective for treatment of VTE of BMI >50 kg/m2 and/or weight >140 kg. Limitations of this study include the warfarin cohort had an overall greater BMI and higher frequency of VTE history, both of which are underlying risk factors for clots. As a retrospective study, it did not assess for adherence, duration of anticoagulation therapy or events that occurred in the outpatient setting after discharge. Nonetheless, the study acknowledges that these limitations would still display apixaban as a non-inferior alternative to warfarin in patients with increased body weight.

**Key Point**: Growing evidence supports the use of DOACs, like apixaban, in a larger range of patients due to their demonstration of unfaltered efficacy and safety in patients with higher BMI and actual body weight.

**Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction[2]**

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**Background**: Sacubitril-valsartan has been shown to reduce the risk of hospitalization and death from cardiovascular causes more effectively than angiotensin-converting enzyme inhibitors (ACE-I) in patients experiencing symptomatic heart failure. However, there is a lack of information regarding the effects of these medications in patients experiencing acute myocardial infarctions (MI).

**Purpose**: The objective of this trial was to evaluate the superiority of sacubitril-valsartan versus ACE-I in reducing heart failure events after myocardial infarctions.

**Study Design**: The study was an international, multicenter, randomized, double-blind, active-comparator trial. All eligible patients were assigned in a 1:1 ratio to receive sacubitril-valsartan 97-103 mg or ramipril 5 mg and were followed for a total of 22 months. Patients included were adults without a history of heart failure, and had a spontaneous myocardial infarction within one-half to seven days before presentation with a reduced left ventricular ejection fraction (LVEF) ≤40%, pulmonary congestion requiring intravenous treatment, or both conditions. Patients also needed to have at least one of eight predetermined risk-augmenting factors (age ≥70 years, diabetes mellitus, previous MI, an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2 of body surface area, atrial fibrillation, LVEF <30%, Killip class III or IV, or ST-segment elevation MI without reperfusion within 24 hours after presentation). Patients were excluded if they were clinically unstable (defined as receiving IV diuretics, vasodilators, vasopressors, or inotropes) within 24 hours before randomization, an eGFR <30 mL/min/1.73m2 , serum potassium >5.2 mmol/L, history of angioedema, or were unable to take an ACE-I or angiotensin receptor blocker (ARB). The use of other ACE-I or ARBs were discontinued at randomization. The primary outcome was death from cardiovascular causes or incidental heart failure, whichever occurred first. Secondary outcomes included hospitalization for heart failure or outpatient episodes of symptomatic heart failure, non-fatal MI, and non-fatal stroke.

**Results**: A total of 2,830 patients were assigned to receive sacubitril-valsartan and 2,831 patients were assigned to receive ramipril. The average age of both groups of patients were 64 years, roughly 23% of patients were female, and nearly 75% of patients were identified as white. A total of 338 primary outcome events occurred in patients receiving sacubitril-valsartan whereas a total of 373 primary outcome events occurred in patients receiving ramipril (HR 0.90, [95% CI 0.78-1.04]). Patients receiving sacubitril-valsartan were also more likely to experience hypotensive events (28.3% and 21.9% respectively, P<0.001) but were less likely to experience cough-related side effects (9% and 13.1% respectively, P<0.001) Other adverse events such as elevated serum creatinine and potassium were similar in both trial arms. Serum creatinine ≥ 2.0 mg/dL were 5.7% in the sacubitril-valsartan group and 6.0% in the ramipril group (P 0.60). The percentage of elevated serum

potassium levels > 5.5 mmol/L in the sacubitril-valsartan group were 14.2% and 12.8% in the ramipril group (P=0.10).

**Conclusion/Key Point**: Overall, the treatment with sacubitril-valsartan did not show statistically significant results compared to ramipril in reducing heart failure events post-MI. Secondary outcomes such as hospitalization for heart failure or outpatient episodes of symptomatic heart failure, death from cardiovascular causes, non-fatal MI, and non-fatal stroke were also not statistically significant when comparing both treatment options.

**Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease[3]**

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**Background**: Thiazide diuretics are a first line pharmacologic treatment for hypertension, but limited studies exist to demonstrate the efficacy and safety of thiazide diuretics in patients with advanced chronic kidney disease (CKD). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends the use of thiazide diuretics in CKD Stages 1-3, but there is limited evidence that the medications remain effective below an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m2.

**Purpose**: The Chlorthalidone in Chronic Kidney Disease (CLICK) Trial looked to evaluate the antihypertensive efficacy of chlorthalidone in patients with stage 4 CKD, along with evaluating safety and renoprotective properties of the drug.

**Study Design**: This was a double-blind, randomized, placebo-controlled trial with patients recruited from three different hospitals in Indiana. Eligible patients were those with stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m2 of body surface area) and uncontrolled hypertension. Uncontrolled hypertension was defined as patients taking at least one antihypertensive drug with a mean 24-hour ambulatory blood pressure (BP) >130/80 mmHg over a 2-week period. Patients were excluded from the trial if their mean 24-hour ambulatory BP over the 2-week period was greater than 160/100 mmHg. Additionally, patients were excluded if they had a history of stroke or myocardial infarction, used high-dose loop diuretics (>100 mg torsemide daily or >200 mg furosemide daily), or if in the 12 weeks prior to randomization they used a thiazide or thiazide-like diuretic or were hospitalized for heart failure. Nine prespecified follow up visits occurred prior to, throughout, and after the study. During each follow up, labs and vitals were monitored to evaluate electrolyte levels, glucose, renin, aldosterone, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and renal function. Additionally, patients were instructed to limit sodium intake and were standardized to receive a preferred drug within each drug class based on the patient's current hypertension regimen (angiotensin-converting-enzyme inhibitors changed to lisinopril 20-40 mg daily; angiotensin-receptor blockers changed to losartan 50-100 mg daily; dihydropyridine calcium-channel blockers changed to amlodipine 10 mg daily; beta-blockers changed to atenolol 25-100 mg daily; loop diuretics changed to torsemide 10-20 mg daily). Randomization occurred in a 1:1 ratio for patients to receive chlorthalidone or placebo and was stratified based on use of a loop diuretic. Chlorthalidone doses were increased throughout the study based on BP measurements to a maximum dose of 50 mg once daily. The primary outcome was change in 24-hour ambulatory systolic BP from baseline to 12 weeks. The secondary outcomes were the change in urinary albumin-to-creatinine ratio (UACR), NT-proBNP level, plasma renin and aldosterone levels, and total body volume from baseline to 12 weeks.

**Results**: A total of 160 patients underwent randomization with 140 patients completing the full 12-week trial. 81 patients received chlorthalidone and 79 patients received placebo. The mean dose of chlorthalidone used in the treatment arm was 11.5 mg at 4 weeks, 18.3 mg at 8 weeks, and 23.1 mg at 12 weeks. For the primary outcome, baseline BP readings from the 24-hour ambulatory monitor for chlorthalidone were 142.6 ± 8.1 mmHg systolic and 74.6 ± 10.1 mmHg diastolic. For placebo, baseline readings were 140.1 ± 8.1 mmHg systolic and 72.8 ± 9.3 mmHg diastolic. After the 12-week trial, ambulatory systolic blood pressures were reduced by 11.0 mmHg in the chlorthalidone group and 0.5 mmHg in the placebo group (mean difference =10.5 mmHg [95% CI -14.6 – -6.4]). Diastolic blood pressures were reduced by 4.9 mmHg in the treatment group versus 1.0 in the placebo group (mean difference =3.9 mmHg [95% CI -6.3 – -1.5]). For secondary outcomes, the percent reduction in the UACR was 52% for chlorthalidone and 4% for placebo after 12 weeks. However, some of the reductions in UACR were lost following discontinuation of chlorthalidone (change from baseline [38% for chlorthalidone and 6% for placebo]). The percent decrease in NT-proBNP level was 30% for chlorthalidone and 11% for placebo after 12 weeks. Changes in plasma renin and aldosterone levels, along with changes in body volume, decreased during the treatment period and increased when chlorthalidone was discontinued. Adverse events were reported in 91% of patients receiving chlorthalidone and 86% receiving placebo, which included hypokalemia, hypomagnesemia, hyponatremia, hyperglycemia, hyperuricemia, increased serum creatinine, and dizziness. Increases in serum creatinine greater than 25% of baseline were observed in 45% of chlorthalidone patients and 13% of placebo patients.

**Conclusion**: Chlorthalidone was shown to improve BP control in patients with stage 4 CKD disease after twelve weeks of treatment when compared to placebo. The degree of albuminuria was reduced in patients receiving chlorthalidone but did increase slightly two weeks after discontinuation of treatment, suggesting that chlorthalidone may provide both cardiovascular and renal

protection. There was a high number of adverse events and electrolyte level changes in the chlorthalidone group, which the study concluded to be similar adverse events to those reported in other chlorthalidone trials in patients without CKD. Phase 3 trials are recommended to further support using chlorthalidone in advanced chronic kidney disease patients. The key point is that the use of chlorthalidone in patients with an eGFR<30 mL/min/1.73 m2 improved blood pressure control. Close monitoring is recommended to evaluate for electrolyte and renal function changes.

# THERAPEUTIC THOUGHT

### Pregnancy and Medication Safety[4-7]

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**Background**: Medication use, both prescription and over-the-counter, is quite common in pregnancy with studies estimating that 95-97% of women use at least one medication during their pregnancy. However, the data behind the safety of medication use in pregnancy is limited. Questions surrounding the state of the United States Food and Drug Administration's (FDA) pregnancy and lactation labeling have become more frequent lately, especially with the shift away from letter drug categories and the 2015 implementation of the Pregnancy and Lactation Labeling Rule (PLLR). There are concerns among researchers and clinicians regarding the number of new and pre-existing FDA drug labels that have not yet transitioned to the new PLLR format, which leads to uncertainty around the quality of data that exists for pregnancy, lactation, and reproductive impacts. Moreover, further studies are needed to assess the safety of common medications used before, during, and after pregnancy.

**Evidence**: A recent cross-sectional study completed by Byrne et al. reviewed the labeling data for 290 newly approved FDA therapeutic products between 2010 and 2019. Within the 10 years of the study, researchers found that a significant amount of FDA drug labels were in compliance with the new PLLR format, especially ones that were submitted for approval after 2015 (P<0.001); however, 32.6% of drug labels submitted between 2010 and 2015 were not in compliance with the new PLLR format by June 2019. Upon review, there were only 31 drugs with data from human studies, whereas most of the approved drugs only have data from animal studies. In a prospective cohort study conducted by Haas et al., medication use was documented throughout the length of pregnancy for the cohort of women. Medications were categorized based on classification and reason for use. The data from this cohort study found that 97% of women took at least one medication during pregnancy and 30.5% of women took five or more medications during pregnancy, meeting the study's definition for polypharmacy. Findings in this study were congruent with previous studies that indicated the high rates of medication use in pregnancy. Despite this finding, researchers failed to classify medication data by either the FDA's PLLR system or the previous pregnancy category letter system.

**Clinical Impact and Discussion**: As the pregnant population in the United States continues to grow in medical complexity, there is an increasing need for evidence-based medicine and research. While studies have shown that most new therapeutic products are compliant with the new PLLR rules, more than one-third of labels are not compliant, and human data on pregnancy and lactation is unavailable for more than 20% of new drug labels. Clinicians who care for pregnant patients should be familiar with available resources such as Drugs in Pregnancy and Lactation, TERIS (Teratogen Information System), LactMed, and Mother's Milk to help guide clinical and shared decision making throughout pregnancy.

### Addressing High Elder Suicide Rates: A Call to Action[8-12]

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**Background**: Suicide is a serious public health issue that has increased in prevalence throughout the last decade. There have been many initiatives focused on reducing the suicide rate among teens and young adults. However, suicidal ideation among the elderly is often overlooked, as highlighted in a recent article from the Senior Care Pharmacist. points out.Suicide rates are particularly high among older men. According to the National Institute of Health, men 65 years of age and older had a suicide rate higher than any age group in 2017 (31/100,000 persons), which is significantly higher than the overall national rate (22.4/100,000 persons) and much higher than the rate for older women (5/100,000 persons). The suicide rate for men increases with age and is highest for men 85 years of age and older (39.2/100,000 persons). The COVID-19 pandemic has exacerbated known risk factors for suicidal ideation, including isolation, and it is expected to worsen this already alarming problem. With effective training, pharmacists can play an active role in identifying suicidal ideation among older adults. However, suicide prevention training varies widely among pharmacy professionals.

**Evidence and Discussion**: Pharmacists are well-positioned to be gatekeepers for suicide prevention. This is especially true for individuals that work in senior care or community pharmacies. A study of 680,000 Medicare beneficiaries by Berenbrok et. al found that beneficiaries visited community pharmacies approximately

twice as frequently as they visited primary care offices. Studies have also shown that pharmacy personnel frequently interact with patients who display warning signs of suicidal ideation. A study of over 500 community pharmacy staff in North Carolina by Carpenter et. al found that 21.6% had been asked about lethal medication doses by patients or encountered patients requesting a lethal dose of medication. Additionally, the authors noted that one out of three student pharmacists report that they have experienced concerning statements related to suicide while at work. Due to these concerns, more suicide prevention (SP) training programs for pharmacy employees have been developed. A scoping review by [authors] of SP training programs for pharmacists and student pharmacists published online in the American Journal of Pharmaceutical Education (AJPE) found evidence of growing interest in SP training in the pharmacy profession. A previous review in 2018 identified 16 training programs, four of which targeted student pharmacists. Between January 2018 and December 2020, seven additional programs were identified; five of which were geared towards student pharmacists. The authors of the review recommend that SP training for pharmacy professionals address the following areas: 1) identify warning signs for suicide; 2) communicate with individuals to assess risk of suicide; 3) refer patients to appropriate resources; and 4) counsel about which medications may increase the risk of suicidal ideation.

**Clinical Impact**: High rates of suicidal ideation, particularly among older adults, is an alarming public health trend. Due to the accessibility of and knowledge regarding the role of medication in causing and managing suicidal ideation, pharmacists are uniquely positioned to help address this crisis. Pharmacy educators and employers should implement SP training experiences that are specific to the profession and address all four recommended competencies as supported by [authors] in APJE. This training will help empower more pharmacy personnel to intervene when concerns for suicidal ideation arise.

### Young Women with Premature ASCVD are at Risk for Worse Outcomes[13-16]

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**Background**: New evidence suggests that sex-based healthcare disparities exist among patients with premature atherosclerotic cardiovascular disease (ASCVD), defined as having an initial ASCVD event at age <55 years for men and <65 years for women. Women tend to bear a higher risk burden and mortality rate of ASCVD due to multiple factors including socioeconomic barriers, inferior secondary preventative care, and an underestimation of cardiovascular risk factors. According to a 2019 study by Vikulova et al, over the last two decades a decline in cardiovascular events and mortality rate did not occur for young women despite a decline in the general population. This worrisome finding indicates that more work and education is needed to reverse this disparity. Dismantling sex-based health disparities requires multidisciplinary and patient-centered interventions. This article aims to increase awareness among the medical community and provide recommendations to narrow the gap.

**Evidence**: Three recent articles highlight the existence of sex-based healthcare disparities in patients with premature ASCVD.

Jain V et al. looked at 748,090 patients aged 18-55 years enrolled in the US Behavioral Risk Factor Surveillance System (BRFSS) survey. The authors conducted a retrospective analysis to evaluate sex-based difference in physical and mental health and health access in adults with premature ASCVD. The primary outcomes and measures of the study were self-reported physical and mental health, healthcare access, and medical adherence. Self-reported ASCVD was defined as having a history of coronary artery disease, myocardial infarction (MI), or stroke. Out of the enrolled patients, 28,522 had self-reported premature ASCVD, and about 47% were women. The study reported that women were significantly more likely to report poor physical health (OR 1.39 [95% CI 1.09-1.78]), clinical depression (OR 1.73 [95% CI 1.41-2.14]), medical nonadherence (OR 1.42 [95% CI 1.11-1.82]), and inability to access a physician (OR 4.52 [95% CI 2.24-9.13]) due to cost barriers. These disparities were observed despite women having a higher rate of health care coverage and established primary care physicians than men. The study's strengths include having a large sample size with high representation of women and measuring multiple outcomes to assess the impact of disparities. The study's weaknesses include low internal validity as a retrospective cohort study, risk of response and recall bias in utilizing self-reported outcomes, and selection bias in gathering data from a voluntary survey. Moreover, the authors failed to determine if worsening physical and mental health outcomes occurred before or after the ASCVD diagnosis.

Another study by Michelle T. Lee et al. examined sex-based differences in cardiovascular care in premature ASCVD. The study enrolled 147,600 veterans with premature ASCVD identified from the VITAL (Veterans with Premature Atherosclerosis) nationwide Veterans Affairs (VA) healthcare registry. Enrolled patients had at least one primary care visit at the VA from October 2014 to October 2015. Out of all the subjects, 7.1% were women with premature ASCVD. The researchers found that women with premature ASCVD were less adherent to statin therapy (β coefficient −0.01; [95% CI 0.02 to −0.01]) than men and less likely to receive antiplatelets (OR 0.59 [95% CI 0.56-0.61]), statins (OR 0.66 [95% CI 0.63-0.69]), and high-intensity statin therapy (OR 0.64 [95% CI 0.60-0.67]). Authors also observed other disparities in this cohort based on race with a higher incidence of women with premature ASCVD were Black than White or Asian. However, the study failed to report why these differences may exist.

The VIRGO study was a prospective observational study designed to examine sex differences in the presentation, treatment, and outcomes of young patients with acute MI. The study enrolled 3,501 patients aged 18-55 years. The researchers found that women were less likely than men to be informed that they were at risk of cardiovascular disease (1039/2349 [45.1%] versus 554/1152 [49.2%) and have a physician discuss risk modification before an MI. Per patients' reports, providers correctly identified more heart problems in men than women (87% versus 76%, p<0.01), and more men considered themselves at risk of heart disease compared to women (642/1152 [55%] versus 1221/2349 [52.2%].

**Clinical Impact and Discussion**: Current data suggests that age and gender biases have contributed to young women having worse cardiovascular disease outcomes compared to any other age and sex-based group. Multidisciplinary and patient-centered interventions are needed to improve these outcomes. Since women of childbearing age were previously excluded from medication trials, representation of young women in ASCVD clinical trials should be increased. Creating a nationwide or individual state-based campaigns aimed to improve ASCVD risk awareness, especially in Latinx and Black communities, would draw attention to these groups who are often underrepresented. Policy-level interventions to address prohibitive out-of-pocket costs would also improve young women's access to physicians and other beneficial health services aimed at reducing their cardiovascular risks. Lastly, treatment guidelines must be updated to incorporate age- and sex-based distinctions and risks. The implementation of the above recommendations would help foster equitable care and assist with reducing sex-based healthcare disparities.

# FROM THE PHARMACY PRESS

**Medical Pedagogy Beyond the Boundaries of a Textbook: Teaching Intellectual Humility**[17-19]

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**Background**: Whether pharmacists practice within a large hospital system, an outpatient clinic, or a community pharmacy, effective collaboration with other healthcare professionals is crucial to providing quality patient care. In 2011, the Interprofessional Education Collaborative identified four core competency domains to teach widely across disciplines in healthcare: values and ethics, roles and responsibilities, communication, and team and teamwork. The communication competency includes an aspect of emotional intelligence. Emotional intelligence is defined as the ability to understand and manage one's emotions in a way that enables others to effectively work together toward common goals. The concept has been recognized as an essential skill for future pharmacists and has made its way into pharmacy curricula, as illustrated in an article published in the American Journal of Pharmaceutical Education by Lust and Moore in 2006. More recently, intellectual humility, defined as the awareness that one's ideas or opinions might be incorrect, has surfaced as another vital piece within communication to cultivate interprofessional collaboration.

**Evidence & Discussion**: In a 2021 commentary published in the American Journal of Pharmaceutical Education, Pena and Koch believe that teaching intellectual humility must go beyond the typical class work. Core dimensions of intellectual humility include open-mindedness, intellectual modesty, engagement, and corrigibility - all concepts falling outside of traditional pharmacotherapy textbooks. Initially, an elective course was proposed by the authors to address this area within pharmacy learners, however the authors felt that intellectual humility would be best received through the Interprofessional Education (IPE) curriculum that includes students in a variety of healthcare programs.

In preparation for formal IPE sessions, interprofessional students could self-assess their degree of intellectual humility, be introduced to the core dimensions, learn employment strategies, and evaluate biases and stereotypes within a variety of healthcare professions. During the IPE sessions, students could be given a patient case that requires effective communication, sharing and appreciating various perspectives, acknowledging personal limitations, and respectfully responding to feedback. After the IPE session, reflective writing can be used as a self-assessment tool to identify areas in the sessions where students felt intellectual humility was necessary to gain progress in the case and what challenges they experienced.

Alternative strategies for teaching intellectual humility include intentional instruction by preceptors during introductory and advanced pharmacy practice experiences. In these settings, role modeling of intellectual humility by pharmacy educators and preceptors can be a successful technique if done consistently and intentionally. Examples of role modeling include sharing personal stories and experiences, verbalizing one's own knowledge gaps, and becoming more involved in overall interprofessional collaboration.

**Clinical Impact**: Successful incorporation of intellectual humility and other core competencies of interprofessional collaboration in pharmacy education can prepare future pharmacists to work collaboratively on interdisciplinary teams in a variety of different settings.

**Medical Pedagogy Beyond the Boundaries of a Textbook: Teaching Intellectual Humility[20]**

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**Background**: Polypharmacy has been associated with many harmful patient outcomes, such as adverse effects, falls, and hospitalizations. Deprescribing, defined as the process of tapering, discontinuing, or consolidating inappropriate medications, is used to combat polypharmacy and reduce unfavorable outcomes. Comprehensive medication reviews (CMRs) may aid in identifying medications no longer indicated or appropriate for patients. Currently, there are tools to help identify potentially inappropriate medications (PIMs), such as the American Geriatric Society Beers Criteria, Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) Criteria, and Medication Appropriateness Index. Although helpful for identifying many PIMs, other medications may still be inappropriate for patients due to indication, comorbidities, or individualized patient goals. The Veterans Health Administration (VHA) developed and implemented a deprescribing tool in 2016 called VIONE, which stands for Vital, Important, Optional, Not indicated, and Every medication has a specific indication or diagnosis (Table 1). The VIONE tool was initially utilized for veterans enrolled in Geriatric and Extended Care Programs and the goal was to expand use to those receiving care through primary care Patient Aligned Care Teams (PACT).

**Purpose**: To pilot the VIONE methodology to assist with deprescribing in a single Veteran Affairs (VA) primary care PACT.

**Study Design**: This was a quality improvement project conducted at a VA primary care clinic in Lexington, Kentucky. The VIONE Risk Scorecard (Table 2) was used to identify the primary care PACT with the greatest number of veterans at high risk for polypharmacy within the investigators' institution. Veterans within the pilot PACT that were deemed "high-risk" (having 15 or more active medications) were included in the study population. Patients with upcoming primary care appointments during the six-month study period were offered a CMR appointment with a Clinical Pharmacy Specialist (CPS). CMRs were completed via telephone or face-to-face prior to the primary care provider's (PCP) appointment. Recommendations for deprescribing, utilizing the VIONE methodology, were documented for the PCP to review. After the PCP discussed recommendations with the CPS and patient, changes were implemented at the PCP appointment, including documentation of the VIONE medication discontinuation reasons. Data was electronically stored in a national dashboard. The sum-annualized cost avoidance by deprescribing medications was estimated using the following calculation:

$$\frac{(Price/unit) * (Quantity\ dispensed)}{(Days\ supply)} * (Days\ of\ medication\ avoided; \max 365\ days$$

**Results**: Between September 1st, 2019 and March 1st, 2020, 231 veterans were identified as high-risk for polypharmacy-related adverse events. Of the 231 veterans, 99 (42.9%) were contacted by PCP with or without CPS, resulting in 136 medications discontinued. On average, 1.37 medications were discontinued per veteran, leading to an annualized estimated cost avoidance of $21,904.80. During this six-month period, 20 CMRs were performed by a CPS with 90 recommendations identified for deprescribing and 38 recommendations implemented (42.2%). The most common reason for medication discontinuation was "not indicated/treatment complete," and the most common medications discontinued were ranitidine, cyanocobalamin, cholecalciferol, and aspirin.

**Conclusion**: VIONE methodology was successfully implemented in the primary care PACT setting. The use of this tool resulted in over one-third of veterans identified as high risk for polypharmacy decreasing their pill intake by at least one medication.

**Key Point**: Deprescribing tools, such as the VIONE risk scorecard and methodology, may be utilized to assist healthcare providers in identifying patients at high risk for polypharmacy and determining which medications would be most appropriate to modify or discontinue.

**Table 1. VIONE Methodology for Deprescribing Practices**

| | Description | Suggested Action |
|---|---|---|
| **V** | Vital: Life-sustaining medications | Continue but monitor dosage, frequency, and adjust accordingly |
| **I** | Important: Important for quality of life, though not life sustaining cost-effective | Continue but use medication with least side effects and most cost effective |
| **O** | Optional: Consolidate medications | Seriously consider reducing or stopping |
| **N** | Not Indicated: Discontinue medications no longer appropriate for the patient given age and current health status | Stop and monitor the outcome after stopping the medication |
| **E** | Every Medication has a Specific Indication or Diagnosis: Why is the patient being prescribing this drug? If you don't know, then you must find out | Stop, reduce, or change it. Always document changes |

**Table 2. VIONE Risk Scorecard**

| Criteria | Points |
|---|---|
| ≥ 15 Active medications* | 1 |
| ≥ 65 Years of age | 1 |
| Optional: Consolidate medications | 1 |
| Care Assessment Need score ≥ 90 Percentile | 1 |
| ≥ 2 Emergency department visits in the last year | 1 |
| Fall documentation in the last year | 1 |

*Baseline Inclusion Criteria

**A Scoping Review Evaluating the Effect of SGLT-2 Inhibitors on Insulin Dose Requirements in Insulin-Dependent Patients With Type 2 Diabetes**[21]

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**Background**: Sodium-glucose cotransporter-2 inhibitors (SGLT2-I) are commonly used as an adjunct medication for patients with type 2 diabetes. Currently, there are four SGLT2-Is on the market in the US: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. These medications have been proven to lower blood glucose levels, reduce cardiovascular risk, reduce progression of chronic kidney disease, and improve outcomes in heart failure with both preserved and reduced ejection fraction. To date, there have not been any large randomized controlled trials assessing SGLT2-Is and total daily insulin (TDI) requirements, though there are various smaller studies that have looked at these endpoints.

**Objective**: The objective of this scoping review was to assess evidence on the effect of SGLT2-Is on TDI requirements in patients with type 2 diabetes who are insulin dependent.

**Study Design**: This scoping review examined studies from January 1, 2005, to April 12, 2021, assessing insulin dose requirements with concurrent use of an SGLT2-I. There were 16 studies included in the scoping review based on inclusion criteria of patients with type 2 diabetes, concurrent use of insulin and SGLT2-I, a study design of 12 weeks or longer, and a description of changes in insulin dose. Three studies were prospective open-label trials, one trial used a retrospective design, and the other 12 studies were prospective, randomized, double-blind, placebo-controlled trials. All studies evaluated insulin doses at baseline and follow-up. Ten studies included dapagliflozin as the SGLT2-I.

**Results**: Three studies found a statistically significant decrease in mean insulin dose from baseline to follow-up, with decreases of 2.8 units at 16 weeks, 6.6 units at 24 weeks, and 18.4 units at 12 weeks. In Pujante et al, there was a statistically significant decrease in TDI for patients with an A1c <7.5%, but no statistically significant decrease for the patients with an A1c of >7.5%. In the 13 remaining studies, baseline TDI ranged from 27 units to 93 units. The mean insulin dose change from baseline to follow-up in the SGLT2-I groups ranged from an increase of 4.7 units to a decrease of 2.33 units. Changes in total daily rapid insulin versus total daily basal insulin individually were not found to be significant. Two studies found a reduction in TDI of >10% that was significant.

Of 12 studies, eight reported a significant decrease in TDI requirements. The difference in TDI requirements between insulin with placebo versus insulin with SGLT2-I ranged from -0.72 units to -19.2 units. Across all studies, hypoglycemic events varied, but adverse events were minimal.

**Conclusion**: SGLT2-Is, in addition to insulin in uncontrolled insulin-dependent type 2 diabetes patients, significantly reduced TDI requirements in the majority of studies and across all study designs in this review. Larger randomized controlled trials are needed to assess the effect on insulin dosing, including assessing for differences in the reduction of basal insulin versus bolus insulin when adding an SGLT2-I.

**Key Point**: SGLT2-Is, in addition to insulin therapy in type 2 diabetes patients above their A1c goal, may reduce TDI requirements in addition to the known cardiovascular and renal benefits.

# MISCELLANEOUS NEWS

**Social Determinants of Health - New Resources in 2022**[22-27]

*Ann Nagle, PharmD, MPH*
*M Health Fairview - Entira Family Clinics*

Affordability of medications is often a reason for referral to Medication Therapy Management (MTM) services. What may be uncovered in these MTM visits is that multiple social determinants of health (SDOH) are often impacting patient access to medications and contributing to complex healthy lifestyle choices. For some patients, balancing pharmacy copays with grocery budgets and housing payments is a difficult reality. In addition to housing and food access, other areas of SDOH impacting access to medications include transportation, education, job opportunities, discrimination, pollution, language, literacy, and neighborhood safety. While some patients qualify for Patient Assistance Programs or coupon cards for expensive brand name medications, the process may be challenging to navigate and time-consuming. Two new programs in the new year aim to help patients with both food access (FarmboxRx) and reduced-cost medications (Mark Cuban Cost Plus Drug Company).

FarmboxRx is a grocery delivery benefit that is being rolled out by HealthPartners Minnesota Senior Health Options (MSHO) plans in 2022. It is one HealthPartners insurance benefit aimed at Minnesota Seniors adding to other food insecurity partnerships including PowerUp, SuperShelf, and Hunger Solutions. Starting February 2022 and running through December 2022, HealthPartners MSHO patients who would like to opt-in to receive fresh produce and nutritional education materials sent to their home must simply call FarmboxRx at 1-888-416-3589. FarmboxRx will verify the benefit with the patient's name and insurance information. Once their eligibility has been determined, patients

may opt to receive one or two boxes of produce per month delivered on the 2nd and/or 4th weeks of each month.

Mark Cuban (Yes, THAT Mark Cuban of Shark Tank and Dallas Mavericks fame) has partnered with a generic drug startup to provide reduced-cost medications to patients across the United States. Mark Cuban Cost Plus Drug Company has been established as a medication wholesaler which purchases medications and sells them directly to patients at 15% of the wholesale price. Prescriptions may be sent via electronic medical record, phone, fax, or mail. Currently, the pharmacy does not bill through insurance and requires patients to pay out of pocket for medications before being shipped to their home. Though there are some notable medications such as Zetia, Plavix, Prograf, Gleevec and Epzicom that are offered at lower price points, the formulary is limited. For example, diabetes medications are restricted to metformin, glipizide, and glimepiride. As for asthma and COPD, only albuterol inhalers are available. There are forms for patients to request expansion of the formulary, so as this pharmacy grows, there is potential for more of these medications to be included.

**In the Fine Print - Safety First![28-29]**
*Sonal Parmar, PharmD*
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The Institute of Medicine and the World Health Organization undertook initiatives to improve current patient safety standards. This was largely geared towards health systems to avoid the assumption that medication safety is the sole responsibility of patients. Pharmacists, as medication experts, pride themselves on ensuring every medication has an indication for which it is effective and can be safely and conveniently dispensed.

As medication use becomes more accessible and inclusive of various disease states, its safety net lapses. An article by *The New York Times* has revealed gaps in medication safety after cannabis was legalized in eighteen states. The unintentional child exposure to THC products has risen significantly despite some states requiring adequate labeling and child-resistant packaging. Cannabis edibles in the form of lollipops, cookies, gummies, and candy have become increasingly popular yet risky amongst all age groups for overdose. Since its legalization, many people assume that cannabis products are harmless and disregard their potential addictive properties. Parents and guardians should lock away any/all medications rather than assume it's out of reach of children.

Another safety warning, released by the Food and Drug Administration (FDA), revealed new risks associated with the use of oral disintegrating buprenorphine in the form of sublingual tablets and buccal films. They have been found to cause significant dental issues in patients with or without a history of dental problems such as tooth decay, cavities, oral infections, and loss of teeth. Despite the risk, FDA recommends against discontinuation given its benefit in opioid use disorder and pain. They advise patients to rinse their mouth with water after the medication has completely dissolved then swallow and wait out an hour before brushing their teeth. Healthcare workers should also counsel patients to have a dental visit soon after starting this medication so a tooth-decay preventative plan can be customized.

The occurrence of any adverse events should be reported to the MedWatch Safety Information and Adverse Event Reporting Program. Medication safety requires a team-based approach to recognize, understand and develop a patient-centered plan to ensure safety is practiced beyond the patient's appointment time.

**Virtual Reality for Chronic Pain[30-32]**
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Chronic low back pain is one of the most common chronic pain conditions in the United States and has been associated with smoking, depression, sleep disturbances, and other medical comorbidities according to the National Health and Nutrition Examination Survey from 2009–2010. Additionally, patients with chronic low back pain reportedly have less formal education, lower income levels, and more frequent healthcare visits.

A new treatment device, granted Breakthrough Device designation by the U.S. Food and Drug Administration, has been introduced for patients who are at least 18 years old with chronic low back pain. EaseVRx™ is a virtual reality experience delivered by a device worn over the face. It integrates cognitive behavioral therapy into virtual reality, while also utilizing deep breathing exercises with a breathing amplifier, to help patients manage aspects of chronic pain that are not treated with medication therapy.

EaseVRx™ includes 2-16 minute treatments completed daily for 8 weeks. Skills practiced include deep relaxation, attention-shifting, interoceptive awareness, perspective taking, distraction, immersive enjoyment, self-compassion, healthy movement, acceptance, visualization, knowledge of pain, and rehabilitation. The device cost and addition of traditional pharmacologic or physical therapies that the patients used in the study are unknown. Chronic pain diagnoses in the study were self-reported and not verified with medical records. Results showed greater reductions in the EaseVRx™ group compared to the control group for average pain intensity and pain-related interference with activity, along with improved mood, stress, and sleep. Although some supportive evidence is present, more research is needed to determine the potential clinical impact of virtual reality treatment for chronic pain. Specifically, understanding full treatment plans of patients prior to EaseVRx™ use, and significance of EaseVRx™ on outcomes, will be essential going forward.

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