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RESEARCH UPDATES

Comparison of Clopidogrel Monotherapy After One to Two Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients with Acute Coronary Syndrome The STOPDAPT-2 ACS Randomized Clinical Trial¹

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Background: Due to increasing concerns with bleeding events associated with prolonged dual antiplatelet therapy (DAPT), there is speculation over the idea of decreasing the duration of dual therapy. Specifically, this study was looking at acute coronary syndrome (ACS) patients for this extended therapy regimen. With limited recent comprehensive studies, this is an area to re-evaluate for safety and efficacy of extended treatment.

Purpose: This non-inferiority study looked at the safety and efficacy of DAPT for one to two months followed by clopidogrel as monotherapy versus 12 months of DAPT in patients with ACS.

Study Design: This multicenter study was completed in 96 centers around Japan between December 2015 through June 2020. Patients were randomly assigned to one of two open label treatment arms after receiving percutaneous coronary intervention (PCI): DAPT for one year or DAPT for one to two months with clopidogrel monotherapy continued for one year. Patients were assigned in a one-to-one stratified fashion. Assessing a hazard ratio margin of 50% for cardiovascular events pertaining to cardiovascular death, myocardial infarction (MI), any stroke, or definite stent thrombosis or bleeding (major or minor) events at 12 months was the primary endpoint. The secondary endpoints assessed were cardiovascular and bleeding components related to the primary end point. Inclusion criteria was identical to the STOPDAPT-2 trial inclusion criteria with the addition of the following exclusion criteria: continued use of oral anticoagulants and previous history of hemorrhagic stroke. Stratification was done by the center before discharge from the hospital. Study group assignments were blinded to everyone: statisticians, members of the independent clinical event committee, steering committee, and Abbott Medical (the sponsor).

Results: Patients who were enrolled were noted to be younger with fewer comorbidities than patients who were not enrolled. A total of 4136 completed the study with an average age of 66.8 (11.9) years old and 856 (21%) were women. Patients were on clopidogrel (52%) or prasugrel (47%). At the one year clinical follow-up, the shorter duration of DAPT failed to prove non-inferiority criteria when compared to those who completed a year of DAPT. Shorter duration of DAPT was associated with a reduction in major bleeding events. There was not a difference between these two arms when it came to primary and major secondary cardiovascular and bleeding end points. One to two months of DAPT was found to be inferior to a year of DAPT relating to the primary end point (absolute difference, 0.37% [95% CI -0.68% to 1.42%]; HR, 1.14 [95% CI 0.80-1.62]; P for non-inferiority = .06).

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Conclusion: Shortened duration (one to two months) of DAPT failed to show non-inferiority when compared to the standard 12 month of DAPT for ACS patients post PCI. For now, there is not enough evidence to fully support using a shortened duration of DAPT for ACS patients and further clinical trials are needed.

Key Points/Clinical Impact:

- One-to-two-months of DAPT did not demonstrate noninferiority to 12 months of DAPT for composite cardiovascular or bleeding events.
- Shortened DAPT was associated with a reduction in major bleeding events but increased cardiovascular events.

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction - The PACMAN-AMI Trial²

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Background: The risk of recurrent atherothrombotic events remains particularly high in patients with acute myocardial infarction, which is largely attributed to frequent coexistence of multiple non-obstructive lesions in the non-infarct-related arteries. Previous trials have demonstrated the benefits of statin therapy and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors on reduction in low-density lipoprotein cholesterol (LDL-C) levels and a reduction of ischemic cardiovascular events. Currently, there is limited evidence concerning the effect of PCSK9 inhibition on coronary plaque burden, composition, and phenotype. This trial utilized three different intracoronary imaging modalities to assess plaque composition, plaque lipid content, and fibrous cap thickness within non-infarct-related arteries to study the effectiveness of early initiation (within 24-hours after randomization) of alirocumab on coronary atherosclerosis in patients with acute myocardial infarction at baseline and after 52-weeks of therapy.

Objective: The objective of this trial was to determine the effects of alirocumab on coronary atherosclerosis using three different modes of intracoronary imaging in patients with acute myocardial infarction, both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), in addition to high-intensity statin therapy.

Study Design: A total of 300 patients were randomized between May 2017 to October 2020, to receive treatment with alirocumab (n=148) or placebo (n=152) in addition to high-intensity statin. The trial was designed as an investigator-initiated, multicenter, randomized, double-blind clinical trial. Patients 18 years or older who underwent percutaneous coronary intervention of the culprit lesion for urgent STEMI or NSTEMI were eligible if they were considered suitable for intracoronary imaging with evidence of coronary atherosclerosis, but without significant obstructive disease (greater than 20% blockage but less than 50% by visual estimate) in the proximal portion of two non-infarct-related arteries. For enrollment, patients were also required to have an LDL-C level of at least 125 mg/dL if they had not been receiving a stable statin dose for at least four weeks or an LDL-C level of at least 70 mg/dL if they had been receiving a stable statin dose for at least four weeks prior to acute coronary infarction and randomization. Patients were excluded from enrollment if they had left main or three-vessel coronary artery disease, history of coronary artery bypass grafting, severe kidney dysfunction, liver disease, or known statin intolerance. Once enrolled, patients were randomly allocated in a 1:1 fashion to receive either 150 mg alirocumab or placebo, administered biweekly via subcutaneous injection for 52-weeks, in addition to rosuvastatin 20 mg once daily. Lab values and intracoronary imaging with three different modalities were used at baseline and at 52-weeks to assess disease state progression or regression in non-infarct-related arteries.

Results: For the primary endpoint, change in mean percent atheroma volume (PAV) from baseline with intravascular ultrasound, showed significantly greater reduction in the alirocumab group compared with placebo (-2.13% [95% CI -2.53% to -1.73%] vs -0.92% [95% CI -1.28% to -0.56%]; and a between group difference of -1.21% [95% CI -1.78% to -0.65%]; P<0.001). For secondary clinical outcomes, the number of centrally adjudicated clinical events in the alirocumab vs the placebo group were found to be 2 (1.4%) vs 1 (0.7%) for all cause mortality, 2 (1.4%) vs 0 for cardiac death, 2 (1.4%) vs 3 (2.0%) for myocardial infarction, and 12 (8.2%) vs 28 (18.5%) for ischemia-driven coronary revascularization. Additionally, the biochemical analysis showed a significant reduction in LDL-C from baseline and 52-weeks between the two as-treated groups. Upon enrollment, the mean (SD) LDL-C level was 152.8 (33.8) mg/dL (n=258). After 52-weeks, the mean (SD) LDL-C level was 74.4 (30.5) mg/dL in the placebo group (n=132) and 23.6 (23.8) mg/dL in the alirocumab group (n=126) (P<0.001), which represents a 76.5 (95% CI -83.2 to -69.8) mg/dL reduction in the placebo group and a 131.2 (95% CI -137.0 to -125.4) mg/dL reduction in the alirocumab group

(providing a between group difference of -54.7 mg/dL [95% CI -63.5 to -45.9]; $P < 0.001$). Of note, patients assigned to the alirocumab treatment group also demonstrated significantly greater reductions in triglycerides, lipoprotein(a), and apolipoprotein B.

Conclusion: Trial results indicated that among patients with acute myocardial infarction, the addition of alirocumab, compared with placebo, to high-intensity statin therapy, resulted in greater coronary plaque regression in non-infarct-related arteries after 52-weeks. Limitations to consider with this trial compared to previous intravascular ultrasound based studies include lower enrollment and patient retention. Strengths include investigating two non-infarct related arteries per patient to achieve power for the primary and secondary endpoints. Authors also noted that additional research is needed to understand if alirocumab improves clinical outcomes in patients with acute myocardial infarction.

Key Point: The early initiation of alirocumab, in addition to high-intensity statin therapy, may result in greater coronary plaque regression in non-infarct-related arteries after 52-weeks among patients with acute myocardial infarction, both STEMI and NSTEMI. Alirocumab, in addition to high-intensity statin, may be a viable treatment option for secondary prevention of acute coronary syndrome and to further reduce the risk of disease state progression.

Safety of Novel Asundexian Compared to Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF Trial)³

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Background: Oral anticoagulant therapy, preferably with direct-acting oral anticoagulants (DOACs), is recommended for patients with atrial fibrillation to reduce risk of stroke due to atrial thrombi. However, these DOAC medications increase the risk of bleeding which poses a serious safety risk to patients. Asundexian, a novel oral small molecule activated coagulation factor XIa (FXIa) inhibitor, may reduce cardioembolic stroke risk while causing only minimal increased risk of bleeding.

Purpose: This trial aimed to determine the optimal dose of asundexian and assess if lower incidence of bleeding was demonstrated in patients with atrial fibrillation taking asundexian compared to those taking apixaban.

Study Design: This study was an international, multicenter, randomized, double-blind, double-dummy phase 2 trial comparing asundexian and apixaban. Included participants had atrial fibrillation documented by electrocardiography within the previous 12 months, a CHA₂DS₂-VASc score of two or higher (males) or three or higher (females), an indication for treatment with an oral anticoagulant but not currently treated with any oral

anticoagulant or treated with a DOAC, with at least one bleeding risk feature (history of previous bleeding requiring medical attention within 12 months, estimated glomerular filtration rate (eGFR) of 30-50 mL/min, or current indication for aspirin). Exclusion criteria included stroke within the last 30 days of screening, uncontrolled hypertension (>160/100 mmHg), known bleeding disorders, eGFR < 30 mL/min, and known significant liver disease. Participants were randomly assigned in a 1:1:1 ratio to 20 mg asundexian daily, 50 mg asundexian daily, or standard dosing of apixaban (5 mg twice daily with dose reduction to 2.5 mg twice daily when clinically indicated) treatment groups. Participants were supplied with active medication based on randomized group assignment and the matching placebo of the medication (asundexian or apixaban) for the medication the participant was not selected to take. Participants took active medication for 12 weeks and completed a safety follow-up visit 14-21 days after the end of the treatment period. Use of non-steroidal anti-inflammatory drugs (NSAIDs) was strongly discouraged during the treatment period, however aspirin under 100 mg daily was permitted. The primary outcome was the composite of major bleeding or clinically relevant non-major bleeding per International Society on Thrombosis and Haemostasis (ISTH) criteria. Secondary safety outcomes were all bleeding, ISTH major bleeding, ISTH clinically relevant non-major bleeding, and ISTH minor bleeding. Ischemic stroke, systemic embolism, myocardial infarction, and cardiovascular death were analyzed in an exploratory manner.

Results: A total of 251 participants were assigned to receive asundexian 20 mg, 254 participants were assigned to receive asundexian 50 mg, and 250 participants were assigned to receive apixaban. The average age of participants was 73.7 years, with 46% being older than 75 years. Participants frequently had other comorbidities including heart failure (44%), hypertension (89%), and diabetes (32%). Asundexian 20 mg resulted in an 81% reduction in baseline FXIa at trough concentrations and 90% reduction at peak. Asundexian 50 mg resulted in a 92% reduction in FXIa at trough concentrations and 94% reduction at peak. ISTH major or clinically relevant non-major bleeding occurred three times in the asundexian 20 mg group, one time in the asundexian 50 mg group, and six times in the apixaban group. The ratio of incidence proportions for all bleeding events in asundexian (pooled 20 mg and 50 mg daily data) versus apixaban was 0.42 [95% CI 0.26 - 0.67].

Conclusions: Asundexian at both 20 mg and 50 mg daily had lower observed rates of bleeding compared to apixaban. Both doses of asundexian also led to similar suppression of FXIa with once-daily dosing. This study provides additional evidence that asundexian can be an effective DOAC while minimizing bleeding risk.

Key Point: This study shows the potential benefits of a novel anticoagulant and warrants a phase 3 trial to continue assessing efficacy and safety of this medication.

Growing Pains: Controversies of Levothyroxine^{4,7}

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Background: For decades, leading organizations for thyroid-related conditions have warned against switching between levothyroxine formulations, from brand to generic or even between different generic formulations. In 2004, the American Thyroid Association, Endocrine Society, and the American Association of Clinical Endocrinologists issued a joint statement decrying the Food and Drug Administration's (FDA) decision to label certain levothyroxine preparations as therapeutic equivalents. Their concerns stem from levothyroxine's narrow therapeutic window, their recommendations for small dose adjustments (typically 12.5-25 mcg every 6 weeks), and from the FDA's definition of bioequivalence. Bioequivalence is met when a new drug's C_{max} and AUC is within 80-125% of the reference drug's $\geq 90\%$ of the time. With this definition of bioequivalence, a 100 mcg tablet of levothyroxine could contain 80-125 mcg of active ingredient, a range that spans 4 tablet strengths.

Evidence: Despite the concerns of professional organizations, several studies have documented that the large bioequivalence window has minimal clinical relevance. The first of these studies, published in 1997 by Dong et al., showed both the bioequivalence and therapeutic equivalence of Synthroid®, Levoxyl®, and two generic formulations of levothyroxine. This 4-way cross-over study was conducted in 22 women with hypothyroidism; each woman took each levothyroxine formulation for 6 weeks with no washout period. There was no difference in reported symptoms between formulations, and all formulations met FDA bioequivalence standards with each other.

A recent retrospective study of 2780 patients published by Brito et al. in JAMA Int Med studied the implications of switching between generic levothyroxine products based on information obtained from a national database of commercially insured or Medicare Advantage patients. Patients were included if they continued to receive the same stable dose of levothyroxine for three months prior to and at least six weeks after switching manufacturers, they had at least one thyroid stimulating hormone (TSH) value in normal range (defined as 0.3-4.4 mIU/L) prior to the switch, and TSH was recorded six weeks to 12 months after the switch. These patients were compared to a matched cohort of patients who were maintained on the same levothyroxine generic. There was no significant difference in patients who maintained normal TSH values between those who were maintained on the same manufacturer of levothyroxine and those who switched (82.7% vs 84.5%, P=0.07). A subgroup analysis of patients on ≥ 100 mcg/day of levothyroxine showed similar rates of normal TSH levels between those who did and did not switch (70.9% vs. 76.6%, P=0.08).

Discussion & Clinical Impact: Controversy of levothyroxine

product interchangeability has existed for decades. According to King's 1996 article, Dong et al.'s paper was originally pulled from publication due to the study sponsor threatening legal action if it was published. The sponsor, then-maker of Synthroid®, had selected Dong as lead investigator since she had previously published articles on the lack of bioequivalence between levothyroxine products. The results of the study defied expectations, and multiple studies have since indicated bioequivalence between multiple levothyroxine products. Although guidelines are slow to change, prescribers and dispensers of levothyroxine can reassure their patients that a change in manufacturer is unlikely to warrant close monitoring of thyroid levels.

Treatment of Chronic Hypertension during Pregnancy: Is it time to be more aggressive?⁸⁻¹⁴

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Background: Chronic hypertension during pregnancy, defined by the American College of Gynecology (ACOG) as hypertension diagnosed before pregnancy or during pregnancy before 20 weeks of gestation, is associated with many maternal and fetal risks. Per a 2019 American Heart Association (AHA) study, as many as 1.5% of pregnancies in the United States are affected by this condition and that percentage continues to rise. Maternal hypertension during pregnancy presents risk for cerebrovascular accidents, gestational diabetes, postpartum hemorrhage, maternal mortality, low birth weight, preterm births, and congenital anomalies independent of subsequent additional risk for progression to preeclampsia. However, recommendations for when to initiate treatment and how aggressive to be varies widely across international guidelines due to lack of studies in this population, concern for low-birth weight due to reduced placental perfusion caused by antihypertensives, and potential fetal risk due to in-utero exposure to these medications.

Evidence: Current treatment recommendations are focused primarily on preventing progression to severe hypertension. A 2014 Cochrane Review of 49 trials demonstrated that treatment of mild to moderate hypertension during pregnancy did result in reduced risk of progression to severe hypertension, but showed no confirmed benefit to fetal/maternal outcomes or impact on development of preeclampsia. The 2015 Control of Hypertension in Pregnancy Study, which compared tight hypertension control during pregnancy (diastolic blood pressure target of <85 mm Hg) to less tight control (diastolic blood pressure target of <100 mm Hg), found a similar lack of evidence for benefits to fetal and maternal outcomes. An ACOG 2019 practice bulletin recommended initiation of antihypertensive treatment for persistent systolic blood pressures >160 mm Hg and/or diastolic blood pressures >110 mm Hg. However, other international

organizations, including the International Society for the Study of Hypertension in Pregnancy, recommend initiation of treatment for persistent systolic blood pressures >140 mm Hg and/or diastolic blood pressures >90 mm Hg.

New evidence suggests that tighter blood pressure control in pregnancy is more beneficial than what has previously been shown. The Chronic Hypertension and Pregnancy (CHAP) study, a large, multi-center, randomized control trial, sought to clarify when to initiate antihypertensives in pregnant women. This study enrolled 2,408 participants with a singleton pregnancy and a known or confirmed diagnosis of hypertension before 23 weeks of gestation (as defined by a systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg measured twice at least four hours apart). Exclusion criteria included severe hypertension (as defined by a systolic blood pressure >160 mm Hg and/or diastolic blood pressure >105 mm Hg measured twice at least four hours apart), requirement of more than one antihypertensive medication at initiation, multiple fetuses, contraindications to nifedipine or labetalol, and other concurrent conditions that increased fetal or maternal risk.

Participants were randomized to a target blood pressure of $<140/90$ mm Hg with antihypertensive medications or a standard treatment where antihypertensive medications were only initiated at a blood pressure of $>160/105$ mm Hg. First line treatment involved nifedipine extended-release and/or labetalol, although amlodipine or methyldopa was also used per patient preference. Tighter blood pressure control showed statistically significant decreases in development of preeclampsia (RR 0.79 [95% CI 0.69 - 0.89]), preterm births (RR 0.87 [95% CI 0.77-0.99]), and development of maternal severe hypertension (RR 0.82 [95% CI 0.74 - 0.90]), as well as statistically significant increases in birth weight (RR 0.83 [95% CI 0.71-0.97]). However, no statistically significant differences were seen in other safety endpoints including maternal death, cesarean deliveries, or maternal blood transfusions.

Discussion & Clinical Impact: Healthcare providers should recognize that hypertensive risk in pregnancy lies outside just the risk for development of preeclampsia. Chronic hypertension during pregnancy is also associated with progression of Atherosclerotic Cardiovascular Disease (ASCVD) later in life, in addition to adverse peripartum maternal and fetal outcomes. The CHAP trial lends support to organizational recommendations that advocate for stricter blood pressure control in pregnant women given the evidence that blood pressure management improves maternal and pregnancy outcomes, while preventing development of preeclampsia and severe hypertension. Further studies are needed to delineate this role in improving maternal and fetal ASCVD outcomes as well as determining optimal, ideal, and effective antihypertensive treatment strategies for this condition.

Social Determinants of Health: How is Your CMM Practice Screening for Them?¹⁵⁻¹⁷

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Background: Social determinants of health (SDoH) are factors from a person's surroundings that impact health and quality of life. These social determinants that stem from systemic, structural, and environmental factors often impact patient healthcare outcomes. SDoH are categorized into five categories: economic stability, health care access and quality, education access and quality, neighborhood and built environment, and social and community context. Over the past decade, numerous studies have shown that SDoH have a more significant impact on health outcomes than healthcare alone, specifically in chronic conditions such as asthma, diabetes, and cardiovascular health. SDoH impact on health outcomes has been estimated to be as high as 80%.

Comprehensive medication management (CMM) encompasses a whole-person approach which seeks to focus on the patient's clinical and personal goals of therapy. The comprehensive, holistic service goes beyond optimizing a single medication or focusing on one medical condition. Pharmacists providing CMM assess all conditions and medications to better understand a patient's motivations and struggles toward health which often includes multiple aspects of SDoH. Therefore, CMM must continue to be promoted as an important pharmacy service which should include SDoH screening.

Evidence: The Pharmaceutical Care Process is part of CMM and starts with identifying a philosophy of practice. This is described by Cipolle, Strand, and Morely as "The philosophy of practice specific to pharmaceutical care describes a purpose for the practice that is to meet the social need to manage drug-related morbidity and mortality, with an explicit objective to care for a patient's drug-related needs by making it the practitioner's responsibility to ensure that all of a patient's drug therapy is appropriate, the most effective available, the safest possible, and is taken as indicated." This includes a patient-centered and whole-person approach which considers more than just a medication list. In order to identify barriers to health and wellbeing, SDoH screening must be worked into a pharmacist's patient care process. Since SDoH play such a critical role in patient wellbeing, pharmacists need to push to develop and provide CMM services for their patients. Additionally, those practicing CMM should include screening and identifying SDoH with patients to help drive meaningful interventions, which may not always be in the form of a prescription medication.

How do pharmacists work this screening for SDoH into their practice? The first step is to consider where within a pharmacist's workflow may be best suited to collect this information. The initial visit with a patient allows for an introduction to CMM services

provided by a pharmacist and may be a good place to start. This introduction in which a pharmacist inquires about social and environmental factors creates a relationship with a patient helping them to realize that the care team understands that wellbeing involves more than pharmaceuticals. Some SDOH such as education level or community structure do not change rapidly and follow-up visits may not cover as extensive of a list, so a brief screening evaluating safety, food status, financial status and transportation may be sufficient.

Screening tools for SDOH can be integrated into some electronic health records (EHR) and can be built into a patient care process which includes questions to assess family life, housing, education, employment, health insurance, financial status, safety, legal issues, transportation, and basic needs like food and utilities. To help design these questions or if paper screening tools are preferred, there are resources provided by Association of American Medical College, Kaiser Permanente, National Association of Community Health Centers, American Academy of Family Physicians, Center for Medicare and Medicaid, and Health

Leads, all of which may be modified to fit a CMM practice. Once these needs have been identified, pharmacists providing CMM can help navigate healthcare programs and resources on the care team to aid patients in achieving better healthcare outcomes. These needs can be documented and shared amongst the care team using ICD-10 codes and/or integrated health records to form a multi-layered approach to tracking and addressing these barriers.

Discussion & Clinical Impact: Medications cannot work if a patient is not able to take them due to affordability, access to a pharmacy or transportation, or low health literacy to name a few. Similarly, pharmacists providing CMM often recommend lifestyle interventions, such as increasing physical activity, and if patients live in a community where they do not feel safe, this may be a challenge. By knowing the SDOH that impact a patient's life, pharmacists can provide more patient-centered care and can help connect them with resources to improve their health outcomes -- which may be separate from prescribing the medication itself. Thus, pharmacists must work to provide patient-centered CMM services by including SDOH screening to improve patients' health.

FROM THE PHARMACY PRESS

Do PPIs Increase the Risk of Community-Acquired Pneumonia? Findings from an Updated Meta-Analysis¹⁸

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Background: Emerging evidence has explored the potential harms of utilization of proton pump inhibitors (PPIs). PPIs are commonly prescribed to treat dyspepsia, peptic ulcers, and gastroesophageal reflux disease (GERD). Numerous small-scale studies have examined a potential increased risk of community-acquired pneumonia (CAP). However, this correlation has not been assessed on a large-scale--warranting the assessment via a meta-analysis.

Objective: The objective of this meta-analysis was to systematically assess the correlation between PPI utilization and CAP in adults.

Study Design: Studies between January 1, 2004 and February 1, 2021, examining the incidence of CAP with PPI use, were pulled from the literature. Inclusion criteria included clinical studies with a clear presentation of the incidence of CAP in both placebo and treatment arms. Studies examining *H. pylori*, those not written in English, or those with insufficient data for estimation of odds ratios (OR) and 95% confidence interval (CI) were excluded from the meta-analysis. Seven case-control, four cohort, and two observational studies were included in this meta-analysis, encompassing over 700,000 PPI users and 1.3 million nonusers. The primary outcome was the incidence of CAP overall. The secondary outcome specified PPI duration, examining the

incidence of CAP for patients prescribed PPIs for less than 30 days.

Results: After a random effect model was applied due to significant heterogeneity between the studies, the OR of developing CAP in patients who used PPIs was 1.37 (95% CI 1.22 - 1.53) when compared to non-PPI users. Therefore, utilization of PPIs could significantly increase the occurrence of CAP compared to non-PPI users. Four of the 13 studies (N = 6,684) specifically examined the relationship of PPI use for less than 30 days. The OR of contracting CAP in patients prescribed PPIs for less than 30 days was 1.49 (95% CI 1.34 - 1.66) compared to non-PPI users. This demonstrates that even PPI use for less than 30 days can significantly increase the incidence of CAP compared with non-PPI use.

Conclusion: Utilization of PPIs could increase the likelihood of CAP when compared to not using PPIs. Given this meta-analysis included studies with lower quality study designs, more research is warranted to confirm the relationship between PPI use and CAP. However, given the availability of the literature, these results may help with risk-benefit conversations with patients when evaluating if prescribing PPIs is appropriate.

Retrospective Cohort Review of Pharmacists' Impact on Disparities in Care in the Management of Type 2 Diabetes with Glucagon-Like peptide -1 Agonists and Sodium-Glucose Co-transporter 2 Inhibitors¹⁹⁻²¹

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Background: According to the Look AHEAD trial, obesity, cardiovascular disease, and chronic kidney disease disproportionately affect Black patients. Therefore, guideline-directed prescribing practices would indicate that more Glucagon-Like Peptide-1 (GLP-1) agonists and Sodium-Glucose Co-transporter 2 (SGLT-2) inhibitors should be prescribed in this patient population. However, secondary analyses of the trial reported that GLP-1 agonists and SGLT-2 inhibitors were prescribed at a significantly lower rate during treatment initiation in Black patients than in White patients. Pharmacists' knowledge of patient saving programs, copay cards, discounts, and medication formularies could provide a unique opportunity to lower racial disparities in prescribing GLP-1 agonists and SGLT-2 inhibitors.

Objective: This study assessed if there was a disparity in prescribing of GLP-1 agonists and SGLT-2 inhibitors between White patients and Black patients in a primary care setting.

Study Design: This study was a single-center, retrospective chart review cohort study that enrolled patients seen between June 1, 2018 and May 30, 2020 for the diagnosis of type 2 diabetes in a primary care setting. The study included a pharmacist comanaged group and a provider managed group. The patients in the pharmacist comanaged group completed at least one visit with a provider and one visit with a pharmacist during the study period. The primary outcome was the difference in prescribing rates of GLP-1 agonists and SGLT-2 inhibitors between White and Black patients. The secondary outcomes were prescribing rate differences for both groups based on insurance status, serious mental illness, and the overall impact of these variables on prescribing rates in both groups combined. The overall impact assessed if pharmacist involvement made a difference in prescribing the two classes of medications.

Results: No significant difference was seen for the study's primary outcome between the races within the pharmacist comanaged groups (White 64%, Black 62%, Hispanic 58%, and other races 64% (P=0.77)). In the provider managed group, the prescribing rates of the diabetic agents between the races were: White 14%, Black 11%, Hispanic 15%, and other races 32%. Insurance status was significantly associated with prescribing a GLP-1 agonist or SGLT-2 inhibitor in the pharmacist managed group.

Sixty-four patients (43%) who did not have insurance were prescribed a GLP-1 agonist compared with 384 patients (56%) with insurance (P=0.005). Seventy-eight patients (52%) who did not have insurance were prescribed either a GLP-1 agonist or SGLT-2 inhibitor compared with 442 patients (64%) with insurance (P=0.007). The study found no statistical significance in prescribing in the provider managed group based on insurance status.

In the pharmacist comanaged group, GLP-1 agonists were

prescribed at a higher rate (n=111, 61%) in patients with serious mental illness compared to those without (n=337, 51%; P=0.019). Moreover, more than two-thirds of those with serious mental illness (n=125, 69%) were prescribed either of the two agents compared with those without a mental illness (n=395, 60%). No statistical difference was shown in prescribing rates in patients with serious mental illness in the provider managed group.

Overall, when only a provider was involved in diabetes care, it was a predictor of not being prescribed either a GLP-1 agonist or SGLT-2 inhibitor (odds ratio (OR)=0.096; P<0.001). Having insurance was also a predictor of being prescribed either agent (OR=1.592; P=0.006). Race and serious mental illness did not reach significance for the prescribing of either agent (OR=1.14; P=0.128 and OR=1.209; P=0.07, respectively).

Conclusion: The limitations of the study include selection and recall bias due to the study being retrospective, weak external validity due to being a single-centered study, and confounding variables that were not identified and accounted for. Race did not contribute to the prescribing rate differences of GLP-1 agonists and SGLT-2 inhibitors in both groups. Involving pharmacists in diabetes care and having insurance positively affected the prescribing of the two agents.

Key points: GLP-1 agonists and SGLT-2 inhibitors are drugs of choice in patients with diabetes, obesity, cardiovascular disease, and chronic kidney disease. Involving pharmacists in the care of patients with diabetes and having insurance coverage can help increase prescribing rates of GLP-1 agonists and SGLT-2 inhibitors in Black patients when indicated.

Effects of Pharmacist Interventions on Pain Intensity: Systematic Review and Meta-Analysis of Randomized Controlled Trials²²⁻²³

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Background: Pain plays a significant role in the lives of many individuals. It is associated with a high rate of disability and disease burden and can also have a substantial impact on quality of life. Patients experiencing chronic pain may not only notice physical limitations but may also see an impact on several areas of daily life such as poor sleep quality, inability to accomplish daily tasks, and mental health challenges. Over 100 million adults in the United States have chronic pain, which contributes to staggering costs up to 635 billion dollars per year to the US healthcare system. Pharmacists continue to be one of the most accessible health care professionals. As a result, pharmacists providing clinical services not only increase access to care but may also contribute to improved outcomes in overall functioning and reduction in pain.

Prior to this review, comprehensive assessment of pharmacist interventions on pain intensity was limited.

Purpose: The aim of this systematic review and meta-analysis was to assess current literature on the effect of any type of pharmacist intervention, whether led by a pharmacist or in a supportive role, on pain intensity over time in patients with any type of pain.

Study Design: Electronic databases including MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched from inception until May 2021. Several search terms were pharmacy, pain, and randomized controlled trial. Randomized controlled trials (RCTs) and clinical trials were screened by two reviewers independently. Each trial required a control group who received usual care. Pain types, pharmacist intervention types, settings, and pain assessment tools varied. The outcome of interest was a reduction in pain intensity. Data was pooled using a random-effects model. Results were presented as standardized mean differences (SMD) and their 95% confidence interval (CI). Subgroup analyses were performed based on pain etiology.

Results: Upon reviewing 1478 records through the database search, 12 studies were eligible for inclusion. Within the 12 studies, a total of 1710 participants were identified, over 60% of whom were female. Study locations were across the world, including the United States (n= 2), and most were based in a community pharmacy setting (n=4). Other settings included community clinics (n= 3), hospitals (n=3) or specialized outpatient settings such as pain clinics (n=3). Pain etiologies included originating from the

musculoskeletal and neurologic systems, cancer-related pain, postoperative pain, and chronic pain. Pharmacist interventions ranged from medication reviews, patient education (e.g. counseling), dosage adjustments, and nonprescription medication recommendations. Results of the pooled estimates of the studies revealed a statistically significant reduction in pain intensity compared with controls (SMD -0.22 [95% CI -0.31 to -0.12]). Educational interventions alone were not found to be statistically significant in reduction in pain intensity. Subgroup analyses based on pain type showed pharmacist intervention was effective in reducing pain intensity for patients with chronic pain (SMD -0.26 [95% CI -0.37 to -0.14]) but no reduction in pain intensity for patients with acute pain (SMD -0.14 [95% CI -0.40 to 0.12]). Subgroup analyses showed that pharmacist interventions at outpatient clinics and hospitals were effective, but not in community pharmacy settings.

Conclusion: While there were several limitations, including small sample size and variability in pharmacist interventions and settings, findings from this systematic review and meta-analysis showed that pharmacists in both community clinic and hospital settings may play an important role in reducing pain intensity in patients with pain of different etiologies. However, further high-quality studies are needed to determine clinical significance.

Key Point: Pharmacists are well-positioned within the healthcare team to provide education and patient care for patients with pain from various etiologies. These interventions have the potential to reduce pain and improve patient outcomes and quality of life.

MISCELLANEOUS NEWS

Shots, Shots, Shots! Updates for Hepatitis B, Pneumonia, and the Zoster Vaccines.²⁴⁻²⁷

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In a recent update from the Center for Disease Control and Prevention (CDC), new vaccination protocols and recommendations are being provided for the shingles and hepatitis B vaccinations. Previously, the CDC recommended the shingles recombinant zoster vaccine (RZV) to all adults aged 50 and older. However, in July 2021, the Food and Drug Administration (FDA) expanded the recommendation to include adults 19-49 years old who are or will be at increased risk of infection because of high level immunosuppression from drug therapy or diseases. Both the CDC and the Advisory Committee on Immunization Practices (ACIP) recommended two doses of the vaccine to prevent shingles in adults aged 19 and older. The schedule and timing of the doses remain the same as previous recommendations. After receiving one dose of the RZV, the second dose should be administered within two to six months. For

patients who are or expect to be immunodeficient or immunocompromised, it is reasonable to administer the second dose at least four weeks after receiving the first dose.

Previous guidance by the CDC and ACIP for hepatitis B vaccinations were recommended for adults with diseases such as chronic liver disease or HIV. Moving forward, it is now recommended that all adult patients aged 19 through 59 receive the vaccination if they previously were unvaccinated. The CDC reports increasing rates of hepatitis B infection despite vaccinations following childbirth. The rationale of this recommendation is to reduce the rate of hepatitis B infections and mortality by providing universal injections to all age groups. Patients who were previously unvaccinated or have received Pneumovax 23 (PPSV23) without Prevnar 13 (PCV13) are recommended to receive either Prevnar 20 (PCV20) or Vaxneuvance (PCV15). Conversely, patients who received PCV13 without PPSV23, or have received both, should follow the usual schedule for PPSV23 if they have not previously received PPSV23 or are due for the next dose.

Male Birth Control Update²⁸⁻³⁰

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A medication for male hormonal contraception has been talked about for many years. Yet, a male birth control pill has not joined the market despite research in this area since the 1970s. Researchers have looked at various formulations such as hormonal pills, injections, gel formulations, and nonsurgical vasectomies. All of these still require extensive studies and trials conducted in humans. In the past, research was conducted investigating testosterone as a form of contraception which was found to be highly effective at decreasing sperm levels, but only in high doses. This was promising until unfavorable side effects were reported which included weight gain, mood swings, and acne. At this time, there are only two forms of approved male birth control available: vasectomies and male condoms.

A recent animal study conducted by the University of Minnesota evaluated a non-hormonal male contraceptive (YCT529) that substantially reduced sperm counts in male mice. During the four week study period, it was 99% effective in preventing pregnancy and no apparent side effects were seen. They found after discontinuation of the contraceptive that mice could impregnate a female mouse four to six weeks later. The researchers looked to develop a non-hormonal contraceptive because most male birth control compounds previously studied targeted testosterone. The most recent trials utilizing testosterone have used a combination of physiological testosterone doses and progestin which demonstrates suppression of gonadotropins and sperm concentration. This has been shown to be safer and much more tolerable compared to previous studies that used supraphysiological doses of testosterone. The side effects of the hormones still remain to be one of the biggest challenges that hinders progress in this field.

The new compound, YCT529, targets a protein in the body called retinoic acid receptor alpha (RAR- α) which is part of the receptor that binds retinoic acid. Retinoic acid plays a key role in embryonic development and sperm formation. With the removal of RAR- α , mice became sterile. Although these results are promising, it is important to keep in mind that there are many differences between human and mice reproductive systems. The hope is for clinical trials to begin by the end of 2022 to determine efficacy in humans. The researchers at the University of Minnesota are hopeful that even if trials for this compound are unsuccessful, there is now a starting compound to investigate other male contraceptive options in the future.

Although there has been success in mice in this study, a male birth control pill likely will not come to market for another 10 years. With that said, scientists at the University of Minnesota appear to be playing a key role in advancing reproductive health medicine.

Improving Statin Therapy Adherence: New Recommendations³¹⁻³³

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If you are a pharmacist working in a clinical setting, it is likely a frequent occurrence that you have a discussion of statin-induced myalgias with your patients. While a recent meta-analysis showed the prevalence of statin intolerance is less than 10%, approximately one-half of patients stop taking statins, reduce the dose, or take them irregularly due to fears of adverse effects (or AEs). The International Lipid Expert Panel (ILEP) recently published new recommendations that could help practitioners better identify patients with true statin-intolerances, manage statin-intolerances, and prevent the development of AEs with statin use.

ILEP recommendations, as published in *Journal of Cachexia, Sarcopenia and Muscle*, discuss the “nocebo/drucebo” effect. “Nocebo” (NO drug + plaCEBO) describes the AEs a patient may experience when given an inert tablet (no active ingredient), whereas “drucebo” (DRUG + plaCEBO) refers to the difference in AEs experienced when an active ingredient-containing tablet is taken, whether it is known or blinded that it is a statin. The ILEP discusses how to diagnose statin intolerance and exclude nocebo/drucebo effect, which should include: 1) intolerance in at least two different statins, even at their lowest doses; 2) laboratory confirmed abnormalities with statin use such as elevated creatine kinase; 3) symptoms either resolve or improve upon statin discontinuation; and 4) diagnostic exclusion of other possible etiologies (e.g. drug interactions, thyroid disorder, vitamin D deficiency, neuromuscular disorders, etc.).

The ILEP recommends creating a Personalized Lipid Intervention Plan (PLIP) for each patient. The PLIP is a one-page document which helps patients understand the risks and benefits of statin treatment, how to manage AEs if they do occur, and what non-pharmacological options are available to decrease the risk of heart attacks and strokes. Patients should be informed of their 10-year atherosclerotic cardiovascular disease (ASCVD) risk with and without statin therapy. In addition, routine follow-ups should be performed to check safety, efficacy, and adherence to statin therapy. If statin associated muscle pain does occur, the ILEP recommends utilizing the “MEDS” principle as follows: Minimizing disruption to therapy; Educating the patient regarding the benefits of statin therapy, using Diet and nutraceuticals to complement pharmaceutical lipid-lowering, and monitoring Symptoms and biomarkers.

As pharmacists, helping patients to make fully informed decisions about initiating/discontinuing any medications, statins included, is vital to promoting a feeling of empowerment for patients in their health and improving adherence to prescribed therapies.

Switching to Over-the-Counter Availability of Rescue Inhalers for Asthma³⁴⁻³⁶

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As it stands, epinephrine inhalation aerosol (Primatene Mist®) is the only over-the-counter (OTC) inhaler approved to manage asthma symptoms. Currently, there are no clinical guidelines that recommend inhaled epinephrine to manage and treat asthma. Guideline-recommended rescue inhalers are only available with a prescription and prices of these inhalers can make accessibility an issue for many patients with asthma. Historically, inhaled albuterol has been recommended as rescue therapy for patients with asthma. More recently, however, the Global Initiative for Asthma recommends low-dose inhaled corticosteroid - long-acting beta agonist (ICS-LABA) for rescue therapy which marks a change in clinical prescribing. Recently, the Food and Drug Administration approved the first generic of budesonide/formoterol (Symbicort®), ICS/LABA, in March 2022, and there are generic versions of albuterol inhalers on the market currently. Because of these generics, prescription-to-OTC switches can have up to three years of OTC exclusivity which provides another revenue option for manufacturers. In addition, legislation passed in 2020 offers a new path for prescription-to-OTC switches which avoids the new drug

application while still maintaining product exclusivity.

Another avenue for this change could come from the FDA itself in initiating this switch. There has only been one instance of this happening. In 1982, another nonselective β -agonist was made OTC but was switched back to prescription status following negative feedback from physician groups. If manufacturers do not plan on pursuing OTC status for these inhalers, it would behoove the FDA to exercise this authority again in order for patients to have an affordable and efficacious option to help manage their asthma.

With these changes and an increasing need for accessible asthma management, manufacturers and the FDA have a plethora of options to make the switch from prescription to OTC for these rescue inhalers. One argument against making these inhalers OTC could stem from the potential for inappropriate and inaccurate use without proper counseling. However, with any medication, OTC or prescription, proper education can assuage these doubts. As mentioned, these changes can occur either directly from the FDA, from the manufacturer, or from pressure from the FDA. Either way, healthcare professionals should advocate for this change to not only help get their patients the medications they need but a safer and more effective option.

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