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Research Updates

Rivaroxaban vs Aspirin for extended VTE treatment¹

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Background: Patients undergoing anticoagulation for venous thromboembolism (VTE), which includes either deep vein thrombosis or pulmonary embolism, may have up to a 10% risk of recurrence if treatment is stopped within the first year. The initial treatment duration varies between 3-12 months depending on the balance of risks of bleeding or recurrence of VTE. Beyond this initial treatment window, there is concern that the risk of bleeding may outweigh the benefit of continued anticoagulation. The use of aspirin or a reduced dose of rivaroxaban are two approaches examined in this study to minimize the risk of bleeding with extended treatment.

Purpose: The Reduced-dosed rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism (EINSTEIN CHOICE) study compared the safety and efficacy of aspirin, full-dose rivaroxaban, and reduced-dose rivaroxaban as options for continued treatment of VTE past the initial treatment duration for patients in equipoise for continued anticoagulation.

Study Design: This was a randomized, double blind study in which 3365 patients were followed for a median duration of 351 days. The study design excluded patients with a contraindication to continued anticoagulant therapy, with a requirement for continued therapy, creatinine clearance <30 ml/min, or hepatic disease associated with coagulopathy.

Participants were randomized to receive rivaroxaban 20mg, rivaroxaban 10mg, or aspirin 100mg daily. The primary efficacy outcome was a composite of symptomatic recurrent fatal or nonfatal VTE and unexplained death for which pulmonary embolism could not be ruled out as a cause. Secondary efficacy outcomes included myocardial infarction, ischemic stroke, systemic embolism, venous thrombosis outside deep veins, and death from any cause. The primary safety outcome was major bleeding (associated with decrease in hemoglobin of 2g/dl or more, leading to transfusion of 2 or more units of red blood cells, occurring in a critical site, or contributing to death).

Results: The primary efficacy outcome occurred in 4.4% of participants receiving aspirin, 1.5% receiving 20mg rivaroxaban (HR 0.34 compared to aspirin, [95% CI 0.20-0.59]), and 1.2% receiving 10mg rivaroxaban (HR 0.26 compared to aspirin, [95% CI 0.14-0.47]). The hazard ratio for rivaroxaban 20mg compared to 10mg was 1.34, [95% CI 0.65-2.75]. The composite of secondary efficacy outcomes occurred in 5% of the aspirin group, 1.7% of the 20mg rivaroxaban group (HR 0.34 compared to aspirin, [95% CI 0.20-0.57]), and 1.6% in the 10mg rivaroxaban group (HR 0.32 compared to aspirin, [95% CI 0.19-0.54]). No significant differences were identified for any of the safety outcomes related to bleeding, or in adverse event rates.

Conclusions: The main conclusion of the study was that rivaroxaban at both 10 and 20mg doses was superior to aspirin 100mg daily for the efficacy of extended treatment of VTE, without identifiable differences in safety endpoints. The authors acknowledge that one limitation is the duration of the study, 12 months of extended treatment past the initial treatment time period, which leaves the utility of even longer treatment unknown. Also, while the comparison between each of the rivaroxaban doses and aspirin were powered for superiority, the comparison between the 10 and 20mg rivaroxaban doses was not. Since it did not include a placebo arm, there remains a lack of direct comparison between initial treatment and extended treatment. In other words, this study does not offer information to guide the choice of whether it is better to extend treatment or not.

Key Point: When a decision is made to extend VTE treatment, rivaroxaban 20mg or 10mg daily are reasonable choices over aspirin.

Bariatric Surgery versus Intensive Medical Therapy for Diabetes – Five-year Outcomes²

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Background: Bariatric surgery, when used specifically to treat diabetes, has been shown to improve glycemic control and reduce cardiovascular risk factors. In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, at one year and three years after randomization, both gastric bypass and sleeve gastrectomy were superior to intensive medical therapy alone in achieving excellent glycemic control (A1c \leq 6.0%), reducing cardiovascular risk, improving quality of life, and decreasing medication use. This article shows the results from the five-year follow-up analyses of the trial.

Objective: To analyze the relative long-term efficacy and safety of bariatric surgery and its effects on diabetes-related end-organ disease.

Study Design: The trial was a three-group, randomized, controlled, non-blinded, single-center study involving 150 patients. Patients were randomly assigned in a 1:1:1 ratio to one of the three groups: intensive medical therapy (IMT) alone, IMT plus gastric bypass, or IMT plus sleeve gastrectomy. Patients were eligible with the following criteria met: age 20-60 years, A1c $>$ 7.0%, and BMI 27-43 kg/m². The primary outcome was A1c \leq 6.0%. Secondary outcomes included measures of glycemic control, weight loss, blood pressure, lipid levels, renal function, ophthalmologic outcomes, medication use, adverse events, and quality of life. The strategy for all three groups was the adjustment of IMT (every 3 months

for 2 years and every 6 months thereafter) with the goal of achieving A1c \leq 6%, without unacceptable side effects. Patients in the surgical groups were instructed to take daily supplemental vitamins: vitamin B12, vitamin D, calcium, and iron.

Results: Overall, 134 of the 150 randomized patients were included in the five-year assessment. For the 134 patients, 66% were women, mean age was 49 \pm 8 years, mean BMI was 37 \pm 3.5 kg/m², mean A1C was 9.2 \pm 1.5%, mean duration of diabetes was 8.4 \pm 5.2 years, and 44% of patients required insulin at baseline. For the primary endpoint, A1c of \leq 6% was achieved in 2 of 38 patients (5%) in the IMT alone group, compared with 14 of 49 patients (29%) in the gastric bypass plus IMT group (P=0.01) and 11 of 47 patients (23%) in the sleeve gastrectomy plus IMT group (P=0.03). Intention-to-treat analysis was performed with all 150 patients and the P values changed to 0.08 and 0.17, respectively. A duration of diabetes of less than 8 years and random assignment to either gastric bypass surgery group were the only significant predictors of achieving A1c \leq 6% (P=0.007 and P=0.03, respectively). For the secondary endpoints at five years, changes from baseline observed in the gastric bypass plus IMT and sleeve gastrectomy plus IMT groups were superior to the changes seen in the IMT alone group with respect to body weight (-23%, -19%, and -5% in the gastric bypass plus IMT, sleeve gastrectomy plus IMT, and IMT alone groups, respectively), triglyceride level (-40%, -29%, and -8%), HDL level (32%, 30%, and 7%), use of insulin (-35%, -34%, and -13%), and quality-of-life measures (general health score increases of 17, 16, and 0.3; scores on the RAND 36-item Health Survey ranged from 0 to 100, with higher scores indicating better health). All secondary endpoints showed p $<$ 0.05 for all comparisons.

Conclusions: The results of the five-year follow-up analysis showed that gastric bypass plus IMT or sleeve gastrectomy plus IMT were superior to IMT alone in terms of glycemic control, weight reduction, medication reduction, improvement in lipid levels, and quality of life. Patients who underwent bariatric surgery were significantly more likely to achieve and maintain A1c \leq 6%, with or without medications, than those who received IMT alone.

Key Point: Five-year outcome data from the STAMPEDE trail showed that, among patients with type 2 diabetes and BMI $>$ 27 kg/m², bariatric surgery (either gastric bypass or sleeve gastrectomy) plus IMT was more effective than IMT alone in improving diabetes control.

No Increase in Fractures After Stopping Hormone Therapy: Results from the Women's Health Initiative³

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Background: The Women's Health Initiative (WHI) studied hormone therapy in postmenopausal women in two trials where participants were randomly assigned to receive either appropriate hormone therapy based on having or not having an intact uterus, or placebo. WHI trials were discontinued prematurely due to safety concerns of the observed increased risk of stroke in the study population. There were additional concerns that the study population was at an increased risk for hip fractures in the immediate 12 months after discontinuing hormone therapy (HT).

Objective: The objective of this study was to compare fracture rate in the 5 years following the end of the WHI trials in study participants who had received HT to those who had received placebo.

Study Design: Women were included in this study if they had been enrolled in the conjugated equine estrogen (CEE) vs placebo WHI trial or conjugated equine estrogen plus medroxyprogesterone acetate (CEE+MPA) vs placebo WHI trial, had not stopped their study drug early, and did not take any HT in the post-intervention phase. Data collection was done through semiannual questionnaire of the study participants. The

researchers evaluated the rates of total fracture during the five-year post-intervention phase and the rates of hip fracture early in the post-intervention phase.

Results: The demographics of the women included in this study, including fracture risk, were similar to the demographics of the initial WHI study, except the women in the CEE alone trial were on average an additional 6 years removed from menopause. Women who had received CEE alone, women who had received CEE+MPA, and women who had received placebo had no difference in hip fracture risk in the five-year post-intervention phase (an average of approximately 2.5 fractures per 1000 patient-years). Women who had received CEE alone did have a lower frequency of overall fractures compared to placebo at every time point, but this was not a statistically significant trend. No difference was found in evaluating risk of fracture between the two treatment groups when adjusting for years since menopause.

Conclusions: Although this study found a loss of benefit in lowering hip fracture risk after HT was stopped, it also found that there was no rebound increase in fracture risk after discontinuation of HT. Future studies should further evaluate if CEE-alone HT users have residual benefit in reducing total fracture risk.

Key Point: There was no increase in fracture risk after discontinuation of HT used in the WHI.

Therapeutic Thoughts

GOLD 2017: Updated Recommendations for the Treatment of COPD⁴⁻⁷

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Background: The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report includes updated recommendations for the diagnosis and management of chronic obstructive pulmonary disease (COPD). The GOLD Report provides clinicians with a non-biased review of the current evidence available for the management of COPD patients.

The classification of treatment groups as determined by disease severity and patient-reported outcomes introduced in the 2011 GOLD update was a major advancement from the simple spirometric grading system of earlier versions of GOLD. However, this grading tool presented limitations in mortality prediction. Moreover, practicing clinicians found it confusing because spirometry and exacerbation history were considered together.

In 2017, this tool was refined to separate spirometric grades from symptoms and exacerbation history. Patients are now classified as GOLD grades 1–4 on the basis of percent predicted forced expiratory volume in 1 second (FEV₁) for disease severity and then further classified by groups A–D on the basis of exacerbation history, assessment of symptoms, and risks of future exacerbations (e.g., GOLD grade 4, group B vs. GOLD D in the prior classification system). Drug therapy selection is now based on group and not spirometric value.

Non-pharmacologic treatment strategies (i.e., smoking cessation, physical activity, pulmonary rehabilitation programs, self-management education, nutritional support, oxygen therapy, interventional bronchoscopic, and surgical treatments) are also emphasized in great detail within the updated guidelines in their importance toward disease management.

Evidence: The revised GOLD guideline includes a pharmacologic treatment algorithm for maintenance therapy based on groups A–D. Patients in group A (few

symptoms and exacerbations) can be given a bronchodilator such as a short-acting beta-agonist (SABA), a short-acting muscarinic antagonist (SAMA), or long-acting agents if needed to improve symptoms. For those in group B (increased symptoms with ≤ 1 exacerbation/year), a long-acting beta agonist (LABA) or a long-acting muscarinic antagonist (LAMA) should be given, and if symptoms persist, a combination of these two agents is recommended. For patients in group C (few symptoms, ≥ 2 exacerbations/year), a LAMA should be started and stepped up to a LAMA and LABA combination, but consideration can also be given to a LABA and inhaled corticosteroid (ICS) combination. Recommended treatments for patients in group D (increased symptoms, > 2 exacerbations per year) focus on initiation with combination or LAMA/LABA with addition of a ICS if further control is needed.

The substantial guideline change highlighting combination LAMA/LABA therapy over LABA/ICS or LAMA/LABA/ICS was supported in two recent studies.

A retrospective, observational study compared real-world COPD exacerbation rates among patients treated with LAMA/LABA versus LABA/ICS. Although the crude annualized exacerbation rates were higher in the LAMA/LABA cohort, after adjustment with appropriate effect modifiers and confounders, these differences no longer remained. No difference in exacerbation rates were seen among the LAMA/LABA and LABA/ICS cohorts among patients younger than 65 years of age (1.04 [95% CI 0.99-1.10] vs. 0.95 [95% CI 0.91-1.01]). A slightly lower rate of exacerbations was seen in the LAMA/LABA cohort among patients 65 years and older (0.96 [95% CI 0.92-0.99]). Although this difference is statistically significant, it is unclear whether it is clinically significant.

In a double-blind, parallel-group, randomized controlled trial, treatment with “fixed triple therapy” of extrafine beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) was compared with tiotropium alone and an “open triple therapy” of BDP/FF plus tiotropium in patients with moderate-to-severe COPD. The primary endpoint of moderate-to-severe COPD exacerbations was 0.46 [95% CI 0.41-0.51] per patient per year for fixed triple therapy, 0.57 [95% CI 0.52-0.63] for tiotropium, and 0.45 [95% CI 0.39-0.52] for open triple therapy. Fixed triple therapy was superior to tiotropium, with an adjusted rate ratio of 0.8 [95% CI 0.69-0.92; $p=0.0025$]. The rates of moderate-to-severe exacerbations were similar with fixed triple and open triple therapies.

Discussion: The GOLD 2017 Report is a valuable source of information to guide therapy and will be used

throughout the world to inform management guidelines. The Report’s revised ABCD assessment tool helps clinicians tailor therapy towards a patient’s symptoms with the greater goal of reducing symptoms and hospital readmissions. The document highlights the need for more research and additional clinical studies, as well as the need to find therapies that reduce disease progression and mortality.

Clinical Impact: The 2017 GOLD guideline provides robust recommendations on management of patients with COPD. Pharmacists can play a key role in prevention and treatment of the disease, as many of the interventions listed in the guideline are well suited for pharmacist-led management. Pharmacists are well equipped to lead smoking cessation interventions and educate patients on proper use of prescribed therapies, including inhaler technique and potential adverse drug effects. LAMA/LABA combinations are now preferred over LABA/ICS combinations in COPD without concurrent asthma.

Biosimilars: A Review of Their Approval Process and Clinical Considerations⁸⁻¹¹

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Background: Generic versions of large, protein-based drugs are called biosimilars. These biosimilar medications are distinct from generic versions of small molecule drugs in their production, approval process, and clinical considerations. While mechanistically similar, differences in manufacturing of biosimilar medications can result in varying degrees of efficacy, safety, and immunogenicity when compared to the reference product. A reference product is also described as the original branded product.

Evidence: The indications of biologic medications vary widely, and the high degree of complexity in their amino acid sequence, molecular weight, target binding, and higher order structures can result in significant variation in effect on clinical efficacy, safety, and immunogenicity. Variations between these characteristics are usually related to differences in manufacturing processes compared to the reference product. Manufacturing differences can result in posttranscriptional changes to the product such as glycosylation that can change the drug’s clinical effects.^{1,3}

In order to measure, define, and track the differences in attributes of biosimilar medications, the FDA developed a pathway to enable the approval of these biosimilar products. This pathway does not require a pass through a Phase III clinical trial, which largely evaluates clinical safety and efficacy. The biosimilar approval pathway instead requires demonstration that a biosimilar product

is considered “highly similar” to the reference product. Components related to similarity are determined and evaluated in the approval pathway.

Depending on the reference product in question, various characteristics that have significant impact on clinical safety and efficacy of the drug are identified by the FDA. These characteristics are stratified and categorized by “criticality.” For example, Zarxio®, one of the first biosimilar products to be approved by the FDA, is a biosimilar to the reference drug Neupogen®. For approval of Zarxio®, primary amino acid structure, potency, target binding, and protein concentration were four benchmarks categorized as “very high” criticality that would need to have clear demonstration of little variability from the reference product.³ Overall, the goal of this process is to determine the interchangeability of the biosimilar to the reference product. A biosimilar that is considered interchangeable is one that “can be expected to produce the same clinical result as the reference product for any given patient.”^{2,4}

Discussion: While it is understood that the approval pathway for these biosimilar medications is tightly regulated, the important takeaway is that a biosimilar can have significant differences from reference products. The demand for these biosimilar products is largely driven by very high costs associated with their reference product. The decision making process for healthcare providers when determining whether or not to use a biosimilar requires further evaluation when compared to generic substitution with small molecule drugs.

Clinical Impact: While few are available now, biosimilar products will continue to populate the drug market. A crucial component of clinical decision making is assessment of cost, which biosimilar drugs aim to lower. Clinicians must be keen to evaluate data surrounding other factors such as safety, efficacy, and other quality related factors such as cost effectiveness when deciding to use biosimilar drugs. It is possible that long-term outcomes may vary with post-marketing studies due to these nuanced differences between biosimilar drugs and their reference products. Ultimately, the true degree of difference between biosimilars and their reference products will be realized as they are increasingly used.

PCSK9 Inhibitors: How do they fit into practice?¹²⁻¹⁷

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Background: Under normal physiologic conditions, proprotein convertase subtilisin kexin type 9 (PCSK9) binds to LDL receptors. This binding promotes low density lipoprotein receptor (LDLR) degradation; the function of LDLR is to decrease levels of circulating LDL-C. By preventing LDLR degradation, PCSK9 inhibitors are able to lower levels of LDL-C. Recent studies have

investigated the lipid-lowering effects of PCSK9 inhibitors, and have found they may reduce LDL-C by an additional 40 to 70% when added to statin therapy.¹

Evidence: Three different PCSK9 inhibitors have been developed. Alirocumab and evolocumab are fully human monoclonal antibodies, whereas bococizumab is a humanized monoclonal antibody.² Bococizumab is not fully human and as a result was found to be more likely to induce the development of antidrug antibodies.²

Only two of the three PCSK9 inhibitors are FDA approved. Alirocumab is approved for treatment of heterozygous familial hypercholesterolemia or clinical ASCVD when additional lowering of LDL-C is needed. Evolocumab is FDA-approved for both heterozygous and homozygous familial hypercholesterolemia, as well as clinical ASCVD.

Results from the ODYSSEY LONG TERM trial, a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study, showed that LDL-C was reduced at 78 weeks when patients were taking alirocumab added to other cholesterol lowering agents. Average follow-up for this group was 70 weeks. This study included patients who had heterozygous familial hypercholesterolemia or who had established coronary heart disease or a disease risk equivalent, and an LDL-C ≥ 70 mg/dL. Results showed a percentage change from baseline LDL-C at 78 weeks of -52.4 ± 0.9 in the alirocumab group vs. 3.6 ± 1.3 in the placebo group.¹

The FOURIER Trial was a randomized, double-blind, placebo-controlled, multinational clinical trial that investigated reduction of major cardiovascular events using evolocumab added to moderate-intensity or high-intensity statin therapy. In the treatment group, 9.8% of patients experienced the primary composite outcome of cardiovascular events compared with 11.3% in the placebo group (HR 0.85 [95% CI 0.79 to 0.92]). Average duration of follow-up was 2.2 years.³

Bococizumab is the third PCSK9 inhibitor. In the SPIRE trial, the development of antidrug antibodies with bococizumab was shown to decrease the lipid-lowering effects when antidrug antibody titers were in the top third.² As a result, the SPIRE-2 trial was ended prematurely and the manufacturer ceased production.

Alirocumab is \$672 per 150mg dose, which is injected every 2 weeks (or 300mg every 4 weeks). The cash cost is \$17,472 per year. Evolocumab is \$670 per 140mg dose, which is injected every 2 weeks. The alternative is 420mg once per month, which costs \$1452 per dose. The cash cost is \$17,423 per year.

Discussion: When providers are prescribing medications, FDA approvals, documented efficacy, treatment guidelines, and cost to the patient should all be taken into consideration. Although PCSK9 inhibitors reduce LDL-C, the effect on cardiovascular morbidity and mortality has not been established. The American College of Cardiology/American Heart Association (ACC/AHA) 2013 guideline has moved away from treating to LDL goals, and instead statin medications are chosen based on ASCVD risk to target statin intensity.⁵ The SHARP trial showed that when used in combination with statin therapy, ezetimibe further reduced risk of cardiovascular events.⁵ Other than ezetimibe in combination with a statin, there was no evidence of decreased cardiovascular morbidity or mortality for non-statin agents, such as niacin and fibrate derivatives. The ACC released an update in 2016 that identified PCSK9 inhibitors may be considered in addition to statin therapy once statin therapy is maximized, but this recommendation is typically after ezetimibe add-on therapy.⁶ Bile-acid sequestrants may be used if patients cannot tolerate ezetimibe. Additionally, PCSK9 inhibitors were recommended if patients are on the maximum tolerated dose of a statin with concomitant clinical

ASCVD, or without ASCVD and a baseline LDL-C above 190mg/dL.

Clinical Impact: With the updated guideline and recent studies, statin medications remain the mainstay of therapy when treating clinical ASCVD and hypercholesterolemia. Ezetimibe may be considered if a maximum dose of statin is not tolerated and providers believe additional lowering of LDL-C is necessary. Additional agents aside from ezetimibe, such as niacin or fibrate derivatives are no longer recommended. The newer PCSK9 inhibitors offer evidence of additional LDL-C lowering; however, these agents were added to statin medications in trials. PCSK9 inhibitors may hold a place in therapy for patients who are unable to tolerate statins, but this should be evaluated on a case by case basis.

From the Pharmacy Press

American College of Clinical Pharmacy (ACCP) Guideline: Template for Evaluating a Clinical Pharmacist¹⁸

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Background: Part of the American College of Clinical Pharmacy (ACCP)'s mission is to ensure the competency of clinical pharmacists "to deliver comprehensive medication management in team-based, direct patient care" settings. To this end, the first "Template for Evaluation of a Clinical Pharmacist" was created in 1993. It created a standard for which clinical pharmacy services are provided, evaluated, and expanded.

Objective: The 2016 ACCP Clinical Practice Affairs Committee (CPAC) aimed to update the template to reflect "essential tasks of today's clinical pharmacists" and assess performance of the clinical pharmacists.

Study Design: The CPAC reviewed literature and professional pharmacy and other health professional organization websites for guidance and policies on the "roles, responsibilities, and expected competencies of clinical pharmacists." The CPAC's members also appraised performance evaluation templates from their respective institutions and other health systems. This input was incorporated into the Board of Pharmacy

Specialties' "Pharmacotherapy Specialist Certification Content Outline" and aligned with six competency domains for medical residents per the Accreditation Council for Graduate Medical Education (ACGME). The CPAC completed several rounds of refining so that in each domain, the template 1) contained concise, relevant criteria, 2) was easy to complete, 3) identified objective measures for evaluation, and 4) defined possible benchmarks for success of the clinical pharmacist.

Results: The six competency domains identified for evaluating a clinical pharmacist are: 1) direct patient care, 2) pharmacotherapy knowledge, 3) systems-based care and population health, 4) communication, 5) professionalism, and 6) continuing professional development. Each domain has associated tasks, suggested performance measures, and potential criteria for success. Three optional tasks (research, teaching, and leadership) are also included.

Example Template for Evaluating a Clinical Pharmacist for Domain 1: Direct Patient Care		
Task	Example performance evaluation	Example criteria to define success
Documents accurate, complete list of medications, discrepancies between prescribed and actual use of medications, allergies, and prior adverse drug reactions in accordance with institution-specific medication reconciliation processes	Review and evaluate pharmacy progress notes and/or patient records with accepted standards and practice- or institution-specific policies	Complete information is documented in an audit of random sampling of five pharmacy progress notes (written or in an electronic health record) by a peer review committee

Conclusions: The template developed by the 2016 ACCP CPAC updates the competencies for the clinical pharmacist. Supervisors, peers, and other healthcare professionals can use the template, which offers flexibility to modify evaluation and success criteria based on department, institution, and scope of services provided.

Key Point: ACCP has developed a customizable, practical template for evaluating a clinical pharmacist, including six competency domains with sample tasks, performance evaluation, and criteria to define success.

Adherence Reminders¹⁹⁻²⁰
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Background: Medication adherence is defined as the extent to which patients are able to follow instructions for their medication regimen.¹ Studies have found that adherence rates to maintenance medications in chronic disease states average 50% in developed countries.² As a result, medication non-adherence can result in up to 50% of treatment failures and 125,000 deaths annually.¹ Multiple investigators have studied the effects of telephone reminders, mailed reminders, electronic medication-reminder caps, patient counseling, simplification of dosing regimens, and so on. However, with the current widespread use of modern technologies

across the population, creative investigators have begun to consider the utility of a smartphone as an aide in improving medication adherence rates.

Objective: To assess the efficacy and safety of different medication adherence tools – smartphone dose reminder messages with the use of sensor-enabled medicines and smartphone-activated quick-response (QR) barcoded low health literacy education flashcards and videos – at increasing medication adherence and disease state understanding, as well as risk for overdose.

Results: In a prospective, matched, quasi-experimental design based on pharmacist-run intervention in Dallas, Yeung et al found that study participants receiving smartphone-activated QR barcoded low health literacy education flashcards and videos had higher proportion of days covered (PDCs) of medications filled at 180 days after intervention compared with the controlled group match on the basis of comorbid conditions, targeted medications, and medication class. (71% vs 44%; P=0.0069). In this study, 91.2% of participants scored a high possibility of limited health literacy on the Newest Vital Sign (NVS), a validated health literacy tool at baseline.

In the post-hoc analysis of a Proteus Digital Health funded study, the use of Digital Health (DH) device reminder messages with the use of sensor-enabled medicines were associated with a 16±16% increase in medication taking, if not taken before dose reminder. The mean overall adherence for all subjects was 86±12%; the mean on-time adherence was 69.7±19.7%. Subjects with lower adherence benefited more from seeing DH reminder messages. In the safety study, no events of overdoses related to DH medication dose reminders occurred.

Conclusions: The use of flashcards and QR-coded prescription bottles for medication and disease-state education is an innovative way of improving adherence to maintenance therapy for chronic disease states such as diabetes, hypertension, and heart failure in a low-health literacy patient population.¹ In the Proteus Digital Health study, DH medication dose reminders demonstrated improved medication adherence, especially in patients with initially lower adherence rates. In addition to that, the study found that the dose reminders appear to be safe, resulting in no overdose cases.

Key Point: With the widespread use of modern technologies across the socioeconomic strata,

innovative methods to improve medication adherence have been studied and demonstrated increased adherence rates. Further large-scale studies can contribute further evidence regarding the use of innovative technologies to improve medication

adherence in chronic disease states, especially for those patients with lower health literacy.

Miscellaneous News

Integrating Pharmacists in Primary Care-Based Accountable Care Organizations²¹

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Value-based care is a core component of accountable care organizations (ACO) which strive to improve the health care delivery model. Medication management, a large contributor to health care costs, continues to be suboptimal due to the underutilization of pharmacists. Pharmacist integration in a primary care provider team, within an ACO can help achieve quality improvement benchmark requirements established by the Centers for Medicare & Medicaid Services (CMS) and reduce provider workload.

Review of current literature yields few results regarding pharmacist-pioneered services within an ACO to optimize drug therapy management. To resolve this issue, the Accountable Care Organization Research Network, Services, and Education (ACORN SEED) founded by pharmacy practice faculty at the Nova Southeastern University College of Pharmacy collaborated with regional ACOs in South Florida. According to the article, pharmacists have the unique opportunity to provide services focused on patient safety (medication management/reconciliation), preventative health (screenings, immunizations) and work with at-risk populations (patient education, adherence assessment). Based on their professional experiences, the authors discuss the benefits and obstacles when integrating the pharmacist in an ACO setting for medication therapy management, annual wellness visits, chronic disease state management, chronic care management, and transitions of care services.

The authors state that while there are plenty of opportunities for pharmacist clinicians, several challenges and barriers continue to impede full integration into interdisciplinary provider teams in health systems/ACOs. These include provider perception/knowledge of a pharmacist's role in primary care, compensation for pharmacist services as providers, access to medical records, and laws and regulations regarding collaborative practice models via

clinic protocols and pharmacy practice. They also acknowledge a cost-benefit analysis of pharmacist-interventions may further support pharmacist impact to reduce costs to the overall healthcare system.

Pharmacist caring for transgender persons²²⁻²⁴

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The overall health and health-related needs of the transgender community are not well understood due to lack of research and discrimination, both inside and outside the healthcare system. Sexual stigma with transgender is associated with high tobacco use, increased risk of HIV infection, depression and increased suicide attempts compared to the general population. Alternative care models involving pharmacists may be a venue for engaging transgender patients in primary care. As transgender persons are less likely to have health insurance causing disengagement in care, pharmacists can play a vital role in complex prior-authorization processes, learning the diagnosis codes to facilitate medication coverage, and referring patients to compounding pharmacies to obtain hormone therapy at lower costs. By becoming familiar with transgender medicine and drug therapies, pharmacists can effectively care for patients going through the process of medical transition. Pharmacy practitioners should be also trained in cultural competency to improve their interactions with transgender patients.

There has been an increased use of illegal sex-steroids among this population due to lack of health insurance. By becoming more aware of challenges faced by transgender patients within the healthcare system, pharmacists can assist in improving access to medications and can potentially link these patients to culturally sensitive providers in order to decrease the use of illegal sex-steroids. This is a great opportunity for the pharmacy profession to serve as an educational resource and encourage pharmacy-based smoking cessation to potentially reduce cardiovascular risk in this community. By increasing awareness towards safe syringe use, pharmacy-based HIV testing programs and preexposure prophylaxis medications, pharmacists can

have an impact in preventing HIV infections within transgender population. Steroids use by transgender community often interact with HIV medications. The need to use these medications together offers the opportunity for pharmacists to do

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

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