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Updates in Pharmacotherapy

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Research Updates

Liraglutide and Cardiovascular Outcomes in Diabetes Mellitus Type II (the LEADER trial)[1-2]

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Background: Liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, is FDA-approved for treatment of type 2 diabetes mellitus (T2DM). Patients with T2DM are at a higher risk for cardiovascular disease. There is controversy related to cardiovascular benefit versus risk with various antihyperglycemic agents. To date, the cardiovascular effect of liraglutide in patients with T2DM is unknown.

Purpose: To determine the cardiovascular effect of liraglutide compared to placebo, when added to standard care, in patients with T2DM at high risk for cardiovascular disease.

Study Design: In this large, multicenter, double-blind, placebo-controlled trial, patients were randomized in a 1:1 ratio to subcutaneously receive liraglutide 1.8mg (or highest tolerable dose) or matching placebo daily in addition to usual care as determined by the investigators. The randomization was stratified according to estimated glomerular filtration rate (eGFR, calculated by Modification of Diet in Renal Disease equation) at screening <30 or ≥30mL/min/1.73m2. The study population consisted of patients with T2DM (HbA1c ≥7% at time of randomization) at high risk for cardiovascular disease, defined by age ≥50 years with at least one co-existing cardiovascular condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease (CKD) of stage 3 or greater, or chronic heart failure NYHA class II of III), or age ≥60 years with at least one cardiovascular risk factor as determined by the investigators. Exclusion criteria included use of GLP-1 analogues, dipeptidyl peptidase 4 inhibitors, pramlintide, and rapid-acting insulin (these agents were excluded as add-on therapies throughout the trial). Personal or familial history of medullary thyroid cancer or history of multiple endocrine neoplasia type II was also excluded. The planned follow-up was 42 months with a maximum of 60 months of treatment. Patients received follow-up visits at months one, three, and six and then every six months thereafter. The trial was an intention-to-treat, time-to-event noninferiority analysis with the primary composite outcome being first occurrence of death from a cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke. The investigators planned to complete superiority testing only if noninferiority was established (upper bound of 95% CI <1.3). Superiority would be established if the upper bound of the 95% CI is <1; their closed-testing procedure required no adjustment in significance level. Secondary outcomes included an expanded composite cardiovascular outcome, a composite renal and retinal microvascular outcome, death from any cause, and incidence of neoplasms and pancreatitis.

Results: The trial included 9340 patients, with 4668 receiving liraglutide and 4672 receiving placebo for a median of 3.5 years. At baseline, patients had T2DM for a mean duration of 12.8 years and average HbA1c of 8.7%. Demographics were similar between groups, with a majority of patients having established cardiovascular disease (72.4%), CKD (24.7%) or both (15.8%). The primary composite outcome occurred in fewer patients in the liraglutide group (608 of 4668 patients; 13.0%) compared to placebo (694 of 4672; 14.9%) (HR 0.87; [95% CI 0.78 - 0.97]; P<0.001 for noninferiority; P=0.01 for superiority). Additionally, a statistically significant effect was demonstrated during the subgroup analysis favoring liraglutide treatment in patients with established cardiovascular disease or eGFR <60mL/min/1.73m^2. Secondary outcomes including death from cardiovascular cause, the rate of death from any cause, and microvascular outcomes (renal and retinal) were significantly lower in the treatment group compared to placebo (HR 0.84; [95% CI, 0.73 - 0.97]; P=0.02). There was no significant difference in the incidence of pancreatitis and neoplasm. The number of adverse drug events were similar between groups (62.3% vs. 60.8%; P=0.12). For serious adverse events, acute gallstone disease was significantly higher in the liraglutide group than placebo (3.1% vs. 1.9%; P<0.001). Gastrointestinal side effects leading to discontinuation including abdominal pain, nausea, vomiting, and diarrhea were significantly more common with liraglutide treatment compared to placebo.

Conclusions: Patients receiving liraglutide had a lower risk of the primary composite cardiovascular outcome and lower risk of cardiovascular death, death from any cause, and mircovascular events compared to placebo. Based on the analysis of the primary composite outcome, 66 patients over three years would need to be treated to prevent one event (or 98 patients in the analysis of all cause mortality). The subgroup analysis suggests patients with eGFR <60mL/min/1.73m^2 or established cardiovascular disease saw a greater benefit from liraglutide treatment.

Key Point: In patients with T2DMI at high risk for cardiovascular disease, those treated with liraglutide, in addition to standard therapy, had lower rates of cardiovascular events and death compared to placebo.

The Effectiveness of Pharmacist Interventions on Cardiovascular Risk: The Multicenter Randomized Controller RxEACH Trial[3]

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Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Most risk factors for CVD are modifiable and include smoking, hypertension, hyperlipidemia, diabetes, and obesity. It is estimated that over 50% of patients in the community setting are not meeting blood pressure, diabetes, or cholesterol goals. In Alberta, Canada, pharmacists in certain settings are able to both prescribe medications and order lab tests independently. These pharmacists are in a unique position to monitor these risk factors due to their knowledge of medications and frequent contact with patients. Studies have proven the benefit of pharmacists in reduction of individual risk factors, but not multiple risk factors and overall cardiac risk as this study aims to do.

Purpose: To evaluate the impact of a pharmacist-initiated, community-based, cardiovascular risk reduction program on patients at high risk for CVD.

Design: This study was a multicenter, randomized controlled trial that took place in 56 community pharmacies in Alberta, Canada. The study population included adults over the age of 18 with diabetes, chronic kidney disease (CKD), atherosclerotic vascular disease, prior stroke or transient ischemic attack, coronary artery disease, peripheral vascular disease, or patients with multiple risk factors and a Framingham risk score over 20%. Patients also needed an additional uncontrolled risk factor including blood pressure >140/90 mmHg or >130/80 mmHg if they have diabetes, HbA1c >7%, LDL >2 mmol/L or current smoker. Exclusion criteria included those unwilling to provide written informed consent, those unwilling or unable to follow-up, and those who were pregnant. The care provided for the treatment group included blood pressure monitoring, HbA1c testing, fasting glucose checks, eGFR monitoring, CVD risk calculation, and education. Treatment for glycemic control, lipids, and blood pressure was in accordance with most recent guidelines. The treatment group received communication from their primary care provider after each interaction and had follow-up every three to four weeks for three months. The other group received usual care; normal pharmacist and physician interaction for three months. Outcomes were assessed on an intention-to-treat basis using analysis of covariance. The primary outcome of this study was change in CVD risk and the secondary outcome was change in individual risk factors including blood pressure, LDL, HbA1c, and smoking cessation.

Results: Baseline cardiovascular risk was assessed and 723 individuals were randomized into the two treatment groups. Estimated cardiovascular risk changed over three months from 26.6 ± 19.3% to 25.9 ± 19.6% in the usual care group and 25.6 ± 17.8% to 20.5 ± 15.9% in the intervention group. This correlated to an absolute risk reduction of 5.37% [95% CI 4.17 - 6.56]; p<0.01. For

secondary endpoints at three months, patient blood pressures in the intervention improved with a 9.37 mmHg [95% CI 7.67 – 11.07]; p<0.01, reduction in systolic blood pressure, and 2.92 mmHg [95% CI 1.62 – 4.21]; p<0.01, reduction in diastolic blood pressure. Other secondary measures in the treatment group improved with patient LDL values decreasing by 0.2 mmol/L [95% CI 0.08 – 0.31]; p<0.01, and HbA1c lowering by 0.92 [95% CI 0.72 – 1.12]; p<0.01. The treatment group also saw a 20.2% [95% CI 9.9 – 30.4] decrease in number of smokers. During the screening process, 290 participants in the study were noted to have CKD, 40% of whom had previously unrecognized kidney dysfunction.

Conclusion: Pharmacists are able to meaningfully reduce patients' overall cardiovascular risk, as well as all CVD risk factors, measured in a short amount of time. Though it was not an outcome of the study, the large number of patients identified by pharmacists to have CKD shows the important role pharmacists can play in the identification of progressive disease in patients. The results of this study likely understate the impact that these pharmacist interventions have on cardiovascular risk factors such as HbA1c and lipid values, since patients were only followed for three months.

Key Point: This trial suggests that clinical pharmacists are able to significantly reduce patients' risk of CVD through lab monitoring, patient cardiovascular disease assessment and education, and monthly follow-up over a three month period.

Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicenter, randomized, double-blind, double-dummy, strategy trial[4-8]

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Background: Current recommendations for the treatment of rheumatoid arthritis (RA) recommend promptly initiating treatment with methotrexate, a synthetic disease modifying anti-rheumatic drug (DMARD) after diagnosis.[2,3] Published data supports immediate initiation of treatment to achieve remission and prevent disability. Remission is measured using assessment tools such as the Disease Activity Score (DAS28) to assess RA disease activity and response to therapy. European League Against Rheumatism (EULAR) recommends adding a biologic DMARD such as a tumor necrosis factor (TNF) inhibitor only if a synthetic DMARD fails.[3] One-third of patients continue on TNF inhibitor monotherapy due to methotrexate intolerance. However, TNF inhibitor monotherapy has demonstrated reduced efficacy compared to TNF inhibitor plus methotrexate.[4-6]

Purpose or Objective: To study patients newly diagnosed with RA (within the last year) who had not yet started DMARD therapy assessing the efficacy and safety of treat-to-target strategies comparing the current standard of therapy to a tocilizumab regimen. The treatment comparison was between those following the current recommendation of the synthetic DMARD, methotrexate, to those who initiated the interleukin-6 receptor blocking biologic DMARD, tocilizumab +/- methotrexate. The primary endpoint was sustained remission (defined as DAS28 <2.6) with a swollen joint count $\leq$4, persisting for 24 weeks.

Study Design: Over two years, 317 patients meeting inclusion criteria were randomized (1:1:1) across 21 rheumatology clinics in the Netherlands to start an initial regimen of one of the following:

- Tocilizumab plus methotrexate
- Tocilizumab plus placebo methotrexate, or
- Methotrexate plus placebo tocilizumab
-

All aspects of the study were blinded including: placebos similar in appearance to active drug; patients; study physicians; pharmacists; monitors; and assessors. Exclusion criteria included use of a glucocorticoid within six weeks before baseline. A noted post-hoc endpoint was duration of sustained drug-free remission. A power calculation was included and the sample size of 100 patients was met in each arm.

Results: From January 2010 to July 2012, 317 eligible patients were recruited into the study. All patients received at least one dose of the assigned study medication and were all included in the safety and intention-to-treat analysis. Study completion was achieved by 75% of patients, and there were no significant completion proportion differences between groups. Sustained remission on the initial treatment regimen was achieved by 86% of patients in the tocilizumab plus methotrexate arm, 84% in the tocilizumab arm, and 44% in the methotrexate arm. Relative risk 2.00 [95% CI 1.59 - 2.51] for the tocilizumab plus methotrexate arm vs. the methotrexate arm and 1.86 [95% CI 1.48 - 2.32] for the tocilizumab arm vs. the methotrexate arm, both p<0.0001. The most common adverse event in all three treatment arms was nasopharyngitis. The occurrence of serious adverse events was not statistically different between the three groups. Patients in both tocilizumab arms had a higher proportion of patients achieving sustained drug-free remission compared with the methotrexate arm.

Conclusions: In patients with early RA, tocilizumab or tocilizumab plus methotrexate show promise to achieve sustained remission compared to methotrexate alone. In addition, tocilizumab and methotrexate have a similar safety profile. One distinct finding was a significantly higher number of patients having sustained drug-free remission in the tocilizumab +/- methotrexate arms after both methotrexate and tocilizumab were withdrawn ($p<0.0001$ and $p<0.0037$, respectively).

Key Point: The data show promise for patients to achieve remission from RA symptoms and possible drug-free sustained remission with tocilizumab. Results from a current three-year observational extension of this study may answer questions regarding the possibility of superior long-term outcomes. Considering cost and unknown long-term outcomes, this study may not change the course of initial RA treatment. However, this study is useful to show tocilizumab provides an option to achieve remission for those unable to tolerate methotrexate.

The FLAME Trial: A Long-Acting Beta-Agonist (LABA) plus a Long-Acting Muscarinic Antagonist (LAMA) compared to a LABA plus an inhaled corticosteroid (ICS) in COPD[9]

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Background: Chronic obstructive pulmonary disease (COPD) exacerbations negatively impact patients and their health in many ways including reduced quality of life, mortality, and increased health care costs. For patients at risk of exacerbations, current COPD guidelines recommend first-line therapy should be either a long-acting beta agonist/inhaled corticosteroid (LABA/ICS) combination or a long-acting muscarinic antagonist (LAMA) as monotherapy. These therapies have been shown to control symptoms and also prevent COPD exacerbations. Inhaled corticosteroids can reduce the frequency of exacerbations when in combination with a LABA but carry the increased risk of pneumonia along with other adverse effects. Therefore, the dual bronchodilator combination (LABA/LAMA) has been proposed as an alternative to the LABA/ICS combination.

Currently in the United States, there are four approved LABA/LAMA combinations including Anoro Ellipta™ (umeclidinium/vilanterol), Stiolto Respimat™ (tiotropium/olodaterol), Bevespi Aerosphere™ (glycopyrronium/formoterol), and Utibron Neohaler™ (indacaterol/glycopyrronium). The Utibron Neohaler™ is the combination that was used in the FLAME trial.

Objective: The FLAME trial compared COPD treatment combination of LAMA/LABA to the combination of a LABA/ICS for non-inferiority with regard to the annual rate of COPD exacerbations of all severities.

Study Design: This was a multicenter, randomized, double-blind, double-dummy, parallel-group, non-inferiority trial. Patients were started with a four-week run-in period in which all patients were treated with inhaled tiotropium, a LAMA, once daily. Pre-existing LABA, LAMA, ICS, and LABA/ICS therapies were discontinued prior to the run-in phase. After this phase, tiotropium was discontinued and the patients were randomly assigned in a 1:1 ratio to receive either indacaterol 110 µg plus glycopyrronium 50 µg once daily or salmeterol 50 µg plus fluticasone 500 µg twice daily for 52 weeks. Open-label salbutamol 100 µg was provided as a rescue medication.

Patients were included in the trial if they were 40 years of age or older and had COPD with a grade of two or higher on the modified Medical Research Council scale (ranges from 0 – 4 with higher grades indicating more severe COPD). Patients were also required to have a documented history of at least one COPD exacerbation within the past year for which they received treatment including systemic glucocorticoids, antibiotics, or both.

The primary outcome was the annual rate of COPD exacerbations of all severities. Secondary outcomes included the time to first COPD exacerbation of any severity, time to first moderate or severe exacerbation, the annual rates of moderate or severe exacerbations, and the use of rescue medication. The safety of both of these regimens was also analyzed.

A total of 1680 patients were assigned to receive the indacaterol/glycopyrronium group and 1682 patients were assigned to the salmeterol/fluticasone group.

The non-inferiority margin of 15% was set and was based off of a previous study. A per-protocol analysis was done for the primary outcome along with a supportive analysis of the modified intention-to-treat population. All other outcomes were analyzed using the modified intention-to-treat population.

Results: In the per-protocol population with the intervention treatment, the annual rate of all COPD exacerbations was 3.59 [95% CI 3.28 – 3.94] and for the intervention treatment group, the rate was 4.03 [95% CI 3.68 – 4.41], (rate ratio: 0.89 [95% CI 0.83 – 0.96] which represents an 11% lower rate, P=0.003). Since the upper limit of the 95% CI for the rate ratio (0.96) was less than the non-inferiority margin of 1.15, the intervention (LABA/LAMA) demonstrated non-inferiority to the standard of care (LABA/ICS) with regard to exacerbations of any severity. Non-inferiority was also

demonstrated in the modified intention-to-treat population with the rate ratio of 0.88 [95% CI 0.82 – 0.94], P<0.001).

Additionally, superiority was demonstrated for the intervention (LABA/LAMA) group compared to the standard of care (LABA/ICS) group in both the per-protocol and modified intention-to-treat analyses in reducing the annual rate of all COPD exacerbations.

The majority of adverse effect rates were similar between the two treatment groups with the exception of the incidence of pneumonia which was 3.2% in the intervention group (LABA/LAMA) and 8% in the standard of care (LABA/ICS) group (P=0.02).

Conclusions: The LABA/LAMA combination of indacaterol-glycopyrronium not only demonstrated non-inferiority to the LABA/ICS combination of salmeterol/fluticasone but also showed superiority in reducing the annual rate of COPD exacerbations of any severity. The LABA/LAMA patients also had a longer time to first exacerbation for all severities. Another benefit of LABA/LAMA was the lower incidence of pneumonia.

Key Point: The treatment combination with two long-acting bronchodilators demonstrates the synergistic role those two classes of medications play in the treatment of COPD. While there is still a place for steroids in the treatment of some patients with COPD, it is encouraging to have a treatment option that is effective without the unwanted consequences of inhaled corticosteroids.

Therapeutic Thoughts

Comparative Recurrence Rates Between Clostridium difficile Colitis Treatments[10-18]

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Background: Clostridium difficile accounts for up to 25% of the antibiotic-associated diarrhea in the United States,[5] commonly referred to as C. diff colitis. Recurrence rates of C. diff colitis are generally 12-20% after the initial episode and as high as 65% after two or more episodes.[4] In recent years, many states have reported increased incidence and severity of these infections, and an increase in C. diff related mortality.[5] Recurrence (alternatively, sustained cure rate) is measured for only those who have been deemed as "clinically cured" via a successful treatment. Selecting treatments that have shown reduced recurrence could help reduce overall incidence and mortality associated with C. diff.

Evidence: According to the IDSA, oral metronidazole is the drug of choice for initial occurrences of C. diff that are mild-to-moderate and oral vancomycin is the drug of choice for initial occurrences that are severe.[1] Vancomycin orally (and rectally if ileum is present) with or without intravenous metronidazole is considered the treatment of choice for severe completed infections.[1] Metronidazole and vancomycin have been shown to have similar sustained cure rates for both mild and severe infections.[2] However, metronidazole is inferior to vancomycin for severe infections because it has a lower cure rate.[2] Cure rates for mild infections are similar.[2]

While IDSA represents a gold standard of infection disease control, the 2010 guideline regarding C. diff infections does not address treatment with fidaxomicin. Fidaxomicin (Dificid®) is a narrow-spectrum macrolide antibiotic that was approved in 2011 for the treatment of diarrhea due to Clostridium difficile.[3] In two separate phase III clinical trials, fidaxomicin was found to have 30% and 28% recurrence rates at 25 days post-treatment.[3] In comparison, vancomycin was found to have 43% recurrence in both clinical trials.[3] Two larger Canadian trials published together in 2016 supported the finding that fidaxomicin is non-inferior to vancomycin in cure rate and superior to vancomycin in sustained cure rate for C. diff colitis.[6]

It is expected that FDA approval for a new treatment targeting C. diff colitis will be evaluated on October 23, 2016. On June 9th, the FDA Antimicrobial Drug Advisory Committee recommended that bezlotoxumab (Zinplava®), an FDA Qualified Infectious Disease Product, be approved for the treatment of C. diff colitis.[8] Bezlotoxumab is a novel fully-humanized monoclonal antibody that targets C. diff toxin B.[9] Phase III clinical trials showed that a one-time infusion of bezlotoxumab after completion of standard therapy decreased recurrence from 26-28% for standard therapy alone to 16-17% when also given bezlotoxumab.[9] The approval of bezlotoxumab was already reviewed by the FDA on July 23, 2016 and was determined to need additional supporting data before approval would be granted.
Discussion: Since the publication of the most recent IDSA guidelines on C. diff colitis, new treatments have emerged that have the potential to improve long-term outcomes for patients. Fidaxomicin and bezlotoxumab

are new and upcoming treatments for C. diff with improved recurrences rates over vancomycin, but it is unknown if they will become a mainstay of treatment. Potential high costs of these treatments may be a barrier to patient care. New drug development is heavily focused on superior sustained cure rates over vancomycin. When considering treatments for C. diff in upcoming years also watch for cadazolid, a novel fluoroquinolone-oxazolidinone from Actelion,[7] which is another FDA Qualified Infectious Disease Product that may be a future treatment option.

Clinical Impact: When treating initial infections and first recurrences of C. diff colitis, choose standard of care treatments of metronidazole or vancomycin. For patients who have continued recurrences, consider treatment with fidaxomicin for subsequent infections. If a patient has had numerous recurrences or a long standing history with C. diff colitis, consider a novel treatment like bezlotoxumab.

Obesity Pharmacotherapy[19-21]

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Background: Obesity (BMI >30 kg/m^2) is a growing epidemic worldwide. Among American adults, the prevalence of obesity from 2013 to 2014 is estimated to be roughly 38% with a slightly higher prevalence in women 40.5% [95% CI 37.6-43.4] than in men 35.2% [95% CI 33.0-37.4] when adjusted for age.[1] Obesity has been linked to numerous comorbidities, including type 2 diabetes mellitus, hypertension, dyslipidemia, stroke, and coronary heart disease as well as being associated with an increased risk of mortality from cardiovascular disease.[2] With the prevalence of obesity increasing, the prevalence of these comorbidities is likely to increase as well. Sustained weight loss of 5% from baseline is considered to be clinically meaningful.[2] Thus, weight loss and obesity management is extremely pertinent.

Currently, there are five weight loss therapies approved by the FDA for long-term use (greater than twelve weeks) as adjuncts to lifestyle interventions in patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in the presence of comorbidities associated with obesity, including: type 2 diabetes mellitus, hypertension, and dyslipidemia.[2,3] Medications include: orlistat (Xenical®), phentermine-topiramate ER (Qsymia®), liraglutide (Saxenda®), lorcaserin (Belviq®), and naltrexone-bupropion (Contrave®).[2,3]

Evidence: Khera et al. conducted a systematic review and network meta-analysis of the FDA-approved obesity pharmacotherapies. Randomized controlled trials were included in the analyses if they compared a FDA-approved weight loss therapy to placebo or another agent in overweight or obese individuals for a period of at least one year. The primary efficacy outcome was proportion of patients achieving 5% weight loss compared to baseline, and the primary safety outcome was the rate of discontinuation due to adverse events.[3]

Twenty-eight randomized controlled trials were included in the analyses representing 29,018 study participants. Only one trial compared two agents head to head (liraglutide and orlistat) and against placebo. Diet restriction and/or exercise were required in most studies, but compliance to these interventions were not always enforced or measured.[3] Khera et al. found that all agents had a greater proportion of participants achieving the 5% weight loss goal than placebo. In addition, a significantly greater proportion of patients discontinued treatment due to adverse events with the active medication than placebo. The most common adverse effects among all drugs were gastrointestinal-related, cholelithiasis, cholecystitis, and acidosis.[3]

In the network meta-analysis, phentermine-topiramate ER was associated with the highest probability of achieving 5% weight loss from baseline when compared to placebo (OR 9.22 [95% CI 6.63-12.85]). Meanwhile, lorcaserin demonstrated the lowest odds of being discontinued because of an adverse event (OR 1.34 [95% CI 1.05-1.76]) whereas liraglutide and naltrexone-bupropion were associated with highest rates of discontinuation (OR 2.95 [95% CI 2.11-4.23]; OR 2.64 [95% CI 2.10-3.35], respectively).[3]
A review in *Metabolism* summarized the results of trials including FDA-approved obesity pharmacotherapies. All of the agents except naltrexone-bupropion have demonstrated cardio-metabolic benefits, including improvements in systolic and diastolic blood pressure, LDL, and HDL, when compared to placebo. Additionally, all therapies have been associated with a reduction in hemoglobin A1c.[2]

Discussion: Currently, there is a lack of comparative efficacy of all of the weight loss agents, which, in conjunction with risk of adverse effects, has deterred providers from utilizing weight-loss medications.[2,3] Khera et al.'s meta-analyses indicate that participants taking an approved weight loss therapy are more likely to achieve the 5% weight loss goal, and adverse effects prevent patients from being adherent and attaining weight loss goals. While sensitivity analyses were utilized in attempt to decrease bias, Khera et al. admit that heterogeneity bias exists and decreases the validity of the meta-analyses. Of note, none of the studies included in the analyses gathered long-term data about lowering the risk

of morbidity or mortality.[3] While studies have indicated that some of the weight loss agents have cardio-metabolic benefits, these results were inconsistent among trials, and the clinical significance and long-term benefits of these improvements are unclear.[2]

Clinical Impact: Lifestyle and behavior modifications are recommended as first-line options for weight loss in obese and overweight individuals with certain comorbidities.[2] The meta-analysis completed by Khera et al. points out the use of obesity pharmacotherapy in addition to lifestyle modifications produces clinically meaningful weight loss but adds risk of adverse effects. Continued research of these weight loss agents is needed to determine their long-term benefits. Nonetheless, consider initiating an anti-obesity therapy in your obese and overweight patients who have failed lifestyle modifications, especially if the patient has numerous comorbidities that would benefit from weight loss.[2] The choice of agent should be patient-specific with consideration of cost, other comorbidities, side effects, and convenience.[2,3]

Deprescribing in Older Adults[22-25]

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Background: Polypharmacy is a healthcare issue that many patients face but can be especially profound in older adults. It is estimated that approximately 30% of patients over the age of 65 take 5 or more chronic medications.[1] While many of these medications are beneficial for chronic disease management, some medications also hold potential risks in older adults due to physiological changes of aging that alter the body's response to drugs. Deprescribing attempts to balance risks and benefits by systematically withdrawing inappropriate medications in order to manage polypharmacy and improve health outcomes.[2]

Evidence: Some state the number of medications a patient takes is the single most important predictor of harm.[3] For example, one study looked at 180,000 adults in Scotland in which 6% of patients had at least one unplanned hospitalization over the past year.[4] Patients taking 10 or more medications were at a statistically greater risk for hospitalization than patients taking one to three chronic medications (24.8% vs. 5.2%; OR 1.25 [95% CI 1.11 - 1.42].[4]

Studies have demonstrated that deprescribing of medications in older people is feasible, may improve health, and decreases risks associated with medications.[2] Deprescribing has been defined as "the systematic process of identifying and discontinuing drugs in situations in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences."[1] An Australian randomized control trial followed 95 participants separated into an active deprescribing group and a control group. After one year, participants in the active deprescribing group were taking 2.0 +/- 0.9 fewer medications and did not experience significant reductions in their health control (one year mortality rate of 26% in the active deprescribing, 40% in the control group; P=0.16, HR 0.60 [95% CI 0.30 - 1.22].[2]

While many articles have identified a role and purpose for deprescribing, questions still remain regarding the process of deprescribing. Current use of the American Geriatrics Society Beers criteria and the STOPP/START criteria aim to improve prescribing in older adults and focus on medications that are inappropriate. However, these criteria do not specifically address medications that may no longer be necessary given the patient's expected prognosis and achievable benefit from the drug.[4] Scott et al. suggested a five step protocol to aid in deprescribing:[1]

1. Ascertain all drugs the patient is currently taking and the reasons for each one
2. Consider overall risk of drug-induced harm in individual patients
3. Assess each drug for its eligibility to be discontinued based on indication, evidence or risk of harm versus potential benefit, disease or symptom control, time frame of benefit, and medication burden.
4. Prioritize drugs for discontinuation
5. Implement and monitor drug discontinuation program

The same group identified an algorithm that focuses on medication benefit, potential harm, adverse effects and preventative drugs.[1] These tools can be helpful when evaluating an older adult's medication regimen and initiating an ongoing process of deprescribing.

Another important aspect of deprescribing is who should be responsible for the process. Kouladjian et al. aimed to investigate healthcare practitioners' perspectives on deprescribing anticholinergic and sedative medications through utilization of the Drug Burden Index (DBI). Through the thematic analysis of focus groups and individual interviews with general practitioners, pharmacists, and specialty physicians, the investigators found barriers to deprescribing included individuals responsible, miscommunication and lack of acceptance for recommendations.[3]

Discussion: Ongoing medication review is required to ensure optimal medication use in older adults. Medications do not remain appropriate over time simply because they have been tolerated by patients.[2] Frequent medication review should be conducted in the context of an older adult's individual circumstances to ensure that each medication remains consistent with the patient's care goals. However, more evidence of clinically relevant outcomes of deprescribing in older people is needed to determine efficacy. The current evidence suggests that deprescribing is safe, though a larger evidence base is needed to understand how to implement it in an effective, consistent, and cost-effective manner.[2]

Clinical Impact: Deprescribing of medications in older adults will likely continue to be a strategy to improve health outcomes and safety as the population ages. This provides a crucial role for pharmacists within the healthcare team. Utilizing tools available such as the five step model, in addition to the Beers and STOPP/START criteria, can be beneficial in reducing patients' risks for medication-related harm.

From the Pharmacy Press

Caring for Transgender Patients[26-29]

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Background: Current estimates suggest that close to 1 million adults in the United States identify as transgender. As part of expressing their gender identity, many transgender individuals choose to undergo medical surgeries and/or pharmacological treatments. The purpose of this is to physically and hormonally change their appearance and sex organs to align with the gender with which they identify.[1] The dosage of hormones and extent of treatment and physical alignment is patient-specific, requiring healthcare professionals to have a very good understanding of anatomy, hormones, and pharmacotherapy.

The results of a recent survey published in the *Journal of the American Pharmacists Association* show that a large majority of community pharmacy residents think pharmacists play an important role in providing care for transgender patients and feel a responsibility to treat transgender patients. However, only a small portion of respondents felt comfortable in their ability to provide that care for these patients.[2]

Evidence: The survey (sent to residency directors of ASHP-accredited community pharmacy residency programs across the United States) asked residents to rate the perceptions of managing transgender patients. Responses were graded on a Likert-scale to statements such as "I feel confident in my ability to manage the health concerns of transgender patients" and "I feel comfortable communicating with transgender patients." Respondents were also asked about their pharmacotherapeutic knowledge (including questions regarding appropriate pharmacologic options for feminization and masculinization) and the need for receiving additional education in transgender health care.

Seventy-nine residency program directors were contacted, and 63 residents completed the survey. The survey revealed that 82.7% of community residents think community pharmacists play an important role in providing care for transgender patients, and 98.2% think they have a responsibility to treat transgender patients. Interestingly, only 36.2% felt confident in their ability to do so. These results are not surprising, given that 71.4% of respondents reported they were not educated about transgender patient issues while in pharmacy school. Seventy-three percent of residents agreed that community pharmacists need more education in this area. Eighty-one percent of residents were unaware of local practitioners proficient in transgender health care to which they could refer.

Discussion: The majority of residents listed discrimination and lack of provider knowledge as the major barriers to care experienced by this population. Residents surveyed believe transgender education should be integrated into pharmacy school curricula and continuing-education programs. Lesbian, gay, bisexual, transgender, and queer (LGBTQ) health has recently been added to the Healthy People 2020 initiative, highlighting the need for special attention across all professions to ensure future providers are prepared to deliver the care needed by this underserved population.[3] It is worth noting that the results broadly mirror the same lack of knowledge and education identified amongst 204 medical school students on a family medicine clerkship, in which 74% of the respondents reported receiving two hours or less of transgender education in medical school.[4] Many other health professions are publishing policy statements in effort to bridge the gap in care for these patients, including the American Medical Association, the American Psychiatric Association, and

the American Nurses Association. However, there is no public policy statement from the American Pharmacists Association regarding the pharmacist's role in caring for the transgender patient.[3]

This study had several limitations. The results are not necessarily representative of the wider new pharmacist population given the small sample size, with only 63 respondents yielding an approximate 50% response rate. The survey was sent only to directors of the community pharmacy residency programs, thus increasing response bias if the director thought the survey was worth distributing to residents. Finally, it is difficult to generalize the sense of responsibility and confidence among new practitioners in different settings as the survey targeted community pharmacy residents, with no mention if "community pharmacy" refers solely to pharmacists in a retail setting or if it also included pharmacists in ambulatory care community settings.

Clinical Impact: In order to bridge the gap and provide community-level care for transgender patients, pharmacists must first be educated in transgender health management. Incorporating transgender health into pharmacy education and continuing education programming can empower pharmacists with a unique opportunity to apply therapeutic knowledge to care for this underserved population.

Pharmacists' Role in Pharmacogenomics Increasing in an Age of Precision Medicine[30]

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Background: Pharmacogenomics is an area of science that has been expanding for many years. It is a useful tool that can help guide healthcare professionals in the choices they make for their patients. Pharmacogenetics analyzes gene-to-drug interactions and provides information on a patient's response to medications as well as the rate of metabolism. For example, about 25% of the population cannot convert clopidogrel to its active form properly. Pharmacogenetic testing could identify a gene variation in cytochrome 2C19 enzyme, which is the enzyme that metabolizes clopidogrel to its active form. More and more medications are being labeled with genetic variations in metabolism. Currently there are more than 160 prescription labels that include this information. Pharmacists have the potential to play a big role in this new development.

The Model: Several pharmacies have developed a medication therapy management (MTM) practice based on pharmacogenetic testing. Working with community physicians, pharmacists can develop collaborative practice agreements. This agreement would allow the pharmacist to bill for the lab test and provide the results to the patient. It also helps to develop a relationship between the provider and the pharmacist so the provider feels comfortable referring his/her patients for this test. However, patients do not need a referral from their physicians to set up an appointment and receive testing.

Once a referral is made or a patient decides to get tested, an initial appointment is scheduled. At the first appointment, the pharmacist will gather background history, perform a thorough review of current medications, and get a DNA sample. Some important information that could affect the results of the test include whether or not the patient drinks, smokes, or uses illicit drugs. DNA is then collected from a buccal swab and is shipped to the lab for analysis.

Once the results are received, the pharmacist will make a follow-up appointment with the patient. Results are made available to the physician and patient as well through an online portal. A follow-up appointment will take place after the results are received. The pharmacist will interpret these results and provide clinical recommendations to the physician regarding a patient's medication regimen. Once all the information is obtained, the pharmacist will sit down with the patient and discuss all results and recommendations. Recommendations are approved by the patient's physician before the pharmacist goes over the results with the patient. Pharmacists will generally work closely with the physician to provide the best comprehensive care.

Discussion: With pharmacogenomics being so new, it can be a challenge to know how to interpret the results. One great resource available to help with recommendations is, Clinical Pharmacogenetics Implementation Consortium (CPIC). This is an organization that provides guidelines and prescribing recommendations based on genetic testing. All recommendations have a standard system for grading levels of evidence.

One of the biggest challenges is reimbursement for both the genetic testing and the pharmacist's time. New American Medical Association Molecular Pathology CPT codes are in the process of being developed to help with reimbursement issues.

Key Point: Pharmacogenomic testing is an area that will continue to grow and pharmacists have the opportunity to lead the way. They are the most qualified for this job

as they know about the pharmacokinetics and pharmacodynamics of medications. The information obtained from pharmacogenomic testing is useful to both patients and physicians, and pharmacists can be at the forefront of guiding clinical decisions based on this information.

Miscellaneous News

New Update Issued by FDA for Fluoroquinolone Antibiotics[31-32]

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At the end of July 2016, the U.S. Food and Drug Administration (FDA) required that manufactures of all fluoroquinolone antibiotics update the package inserts and Medication Guides to include warnings about the risk of disabling and potentially permanent adverse reactions that can occur from this class of antibiotics. Specifically, a FDA safety review found that both oral and injectable fluoroquinolones are associated with disabling side effects that involve tendons, muscles, joints, nerves, and the central nervous system.
The FDA recommends that fluoroquinolones be reserved for conditions where there are no alternative treatment options, such as for serious bacterial infections, including anthrax, plague, and bacterial pneumonia. For conditions such as acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and uncomplicated urinary tract infections, the risk of these serious adverse effects typically outweigh the benefits. It is recommended that another class of antibiotics be used to treat these infections.
Should a patient start on a fluoroquinolone, healthcare providers are encouraged to discuss with patients the serious adverse effects and instruct them to notify their provider immediately if they have any concerns. Healthcare professionals and patients should report adverse events to the FDA's MedWatch Safety Information and Adverse Event Reporting program.

Entresto's Role in Heart Failure Guidelines[33-34]

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The American College of Cardiology (ACC) along with American Heart Association (AHA) and Heart Failure society of America (HFSA) have updated the 2013 ACC/AHA Guideline for the Management of Heart Failure, which includes recommendations on Entresto's® place in therapy.

Entresto® (valsartan/sacubitril) is an angiotensin receptor-neprilysin inhibitor (ARNI). Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin, and other vasoactive peptides. By inhibiting angiotensin and neprilysin, Entresto® causes vasodilation, natriuresis, aldosterone suppression, and antifiboris. However, the use of this ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema in some patients. In one large, randomized clinical trial (PARADIGM-HF), Entresto® was compared with enalapril and found to be superior in reducing the risks of cardiovascular death or hospitalization by 20% in symptomatic patients diagnosed with heart failure with reduced ejection fraction (HFrEF).

Entresto® is approved for patients in NYHA Class II-IV HFrEF. Previous guidelines only included an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as appropriate therapies to inhibit the renin-angiotensin system and therefore reduce morbidity and mortality (Level of Evidence (LOE) A). Now guidelines recommend using an ACEI, ARB (LOE A (for both)), or ARNI (LOE B-R) to reduce morbidity and mortality.

Because of the PARADIGM-HF trial, guidelines recommend replacing an ACEI or ARB with an ARNI in chronic, symptomatic patients who have NYHA class II/III HFrEF with adequate blood pressure and who have tolerated a reasonable dose of ACEI or ARB to further reduce morbidity and mortality (LOE B-R).

New Drug Updates

Zinbryta® (daclizumab), developed by Biogen

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Indication: Daclizumab was approved by the FDA in May 2016 for relapsing forms of multiple sclerosis (RMS). It is recommended to be reserved for patients who have had an inadequate response with two or more medications indicated for the treatment of MS.

Mechanism of Action: Daclizumab's therapeutic effect in MS is unknown. However, it is an interleukin-2 receptor blocking humanized monoclonal antibody thought to bind to CD25, a subunit located on IL-2 receptor, causing activation of the IL-2 mediated lymphocytes and inactivation of T-cells which can reduce nerve damage and MS symptoms.

Dosage and Administration: The recommended dose is 150 mg injected subcutaneously once monthly. Missed doses should be administered as soon as possible but no more than two weeks late. If two or more weeks have passed, skip the missed dose and take the next dose on schedule.

Effectiveness: The FDA approval of daclizumab was based on two randomized, double-blind, controlled studies. In study one, daclizumab vs Avonex® (interferon beta-1a) was conducted with 1841 patients. Nine-hundred nineteen patients received daclizumab (150 mg subcutaneously, every four weeks) and 922 patients received interferon beta-1a (30 mcg intramuscularly, weekly). Duration of treatment consisted of two to three years. Daclizumab showed a statistically significant ($p<0.0001$) effect on the primary outcome of annualized relapse rate and on the number of new or newly enlarging T2 hyperintense lesions, which provides indication of patients' disease burden.

In study two, daclizumab vs. placebo was conducted with 412 patients. Two hundred eight patients received daclizumab (150 mg subcutaneously, every four weeks), and 204 received placebo every 4 weeks. Median length of treatment was approximately 11 months. Daclizumab showed a statistically significant ($p<0.0001$) effect on the primary outcome of annualized relapse rate and the proportion of patients relapse free, the number of new T1 Gd-enhancing lesions, and the number of new or newly enlarging T2 hyperintense lesions.

Safety: The most common adverse reactions reported for daclizumab may include, but are not limited to, the following: nasopharyngitis, upper respiratory tract infection, rash, depression, influenza, and dermatitis. Daclizumab has a black box warning for potential hepatic injury including autoimmune hepatitis and other immune-mediated disorders. Hepatic lab monitoring is required before and during treatment. It is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

Place in therapy: Daclizumab may be considered as an alternative treatment option for patients with relapsing forms of MS, who have tried and received inadequate response to two or more medications for the treatment of MS with no pre-existing hepatic disease or hepatic impairment. Additionally, as a once a month injection, daclizumab may improve convenience for the patient and provide added benefit from the standpoint of adherence. Exact cost of daclizumab is not yet available; however, estimated cost of a single-dose syringe is $7000. Patients may benefit from prescription assistance programs if available.

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