Background: Some transgender persons undergo cross-sex hormone therapy to align their physical appearance with their gender identity. There is concern that this therapy may lead to increased risk of acute cardiovascular events (ACVEs), including venous thromboembolism (VTE), ischemic stroke, and myocardial infarction. However, population-based evidence for the association between cross-sex hormone therapy and risk of ACVEs is inconsistent and limited. Please note the following definitions as they will be referenced throughout:

- Transgender: Denoting a person whose gender identity differs from their birth sex.
  - Transfeminine: Denoting a person who was assigned male at birth, but identifies with femininity to a greater extent than masculinity
  - Transmasculine: Denoting a person who was assigned female at birth, but identifies with masculinity to a greater extent than femininity.
- Cisgender: Denoting a person whose sense of personal identity and gender corresponds with their birth sex.

Objective: To compare ACVE incidence rates in a cohort of transgender persons with rates in a matched cisgender men and women reference cohort.

Study Design: The Kaiser Permanente Health systems in Georgia and California conducted an electronic medical record–based cohort study of transgender members who had an index date (first evidence of transgender status) from 2006 through 2014. Each transgender participant was matched to ten male or female cisgender enrollees by year of birth, race/ethnicity, study site, and index date enrollment. The total number of participants in the study was 2842 transfeminine (matched to 48,686 cisgender men) and 2118 transmasculine members (matched to 48,774 cisgender women) with a mean follow-up of 4.0 and 3.6 years, respectively. ACVEs were identified from diagnostic codes (ICD-9 and ICD-10) codes through the end of 2016 in transgender and reference cohorts. Multivariable Cox proportional hazards models were utilized to compare ACVE rates between the transfeminine and transmasculine cohorts, the hormone initiation cohorts (transgender participants who started estrogen or testosterone after the index date), and among members in the matched cisgender reference groups, after controlling for confounding factors.
Results: It was found that transfeminine participants had a higher incidence of VTE, with 2- and 8-year risk differences of 4.1 (95% CI, 1.6 to 6.7) and 16.7 (CI, 6.4 to 27.5) per 1000 persons relative to cisgender men; and 3.4 (CI, 1.1 to 5.6) and 13.7 (CI, 4.1 to 22.7) relative to cisgender women.

Conclusions: The evidence was insufficient to draw conclusions regarding risk among transmasculine participants due to limited number of occurring ACVEs in this group. More pronounced differences for VTE and ischemic stroke were observed among transfeminine participants who initiated hormone therapy (estrogen) during the follow-up period. One trend that was observed in this group was that VTE rates increased after 2 years of follow-up and continued to rise for another 5 to 6 years.

Key Point: Results may indicate that clinicians need to increase vigilance in identifying long-term vascular side effects of estrogen therapy in transgender patients. The risk for ACVEs in this population must be weighed against the benefits of treatment.

Not Just a Product of Age: Anticholinergic Medications and Falls in Middle-aged Women

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Background: The risks of anticholinergic medication use in the elderly are well-documented. As anticholinergic burden increases, elderly patients find themselves at an increased risk of confusion, blurred vision, urinary retention, and constipation. A higher anticholinergic burden may also lead to falls, with the potential for catastrophic outcomes, including increased mortality. It is less understood whether the use of anticholinergic medications increases the risk of falls or fractures in younger populations.

Objective: The authors of A high anticholinergic burden is associated with a history of falls in the previous year in middle-aged women: findings from the Aberdeen Prospective Osteoporosis Screening Study (APOSS) wished to examine the association between anticholinergic medication burden (ACB) and a history of falls, bone mineral density, and low trauma fractures in middle-aged women less than 65 years of age in a cross-sectional study utilizing data from APOSS.

Study design: Between the years 1990 and 1993, 7200 women aged 45-54 years were identified from a primary care patient registry for a study in Aberdeen, Scotland. Of these, 5119 elected to participate. Study participants completed both a dual energy X-ray absorptiometry (DXA) scan of the hip and lumbar spine and an osteoporosis risk factor questionnaire. Participants were also asked about comorbidities, including personal history of osteoporosis, rheumatoid arthritis, osteoarthritis, asthma, kidney disease, thyroid disease, diabetes, hypertension, myocardial infarction, and stroke. Information on the use of corticosteroids, calcium supplements, medications for osteoporosis, antiepileptic medications, diuretics, sex hormones and tamoxifen was also gathered. Between 1997 and 2000, these same individuals were invited for a follow-up visit. Participants’ weight, height, and physical activity level were collected, in addition to self-reported falls and fractures within the last 12 months. The ACB of the women who attended the follow-up visit was calculated using the Aging Brain Program’s ACB scoring table. Medications with more anticholinergic properties are assigned higher scores, up to a maximum score of three per medication. Medications such as amitriptyline, diphenhydramine, and scopolamine are examples of medications with the maximum ACB score of three. The sum of the ACB scores of the individual medications was used to determine the patient’s overall ACB score.

Results: The average age of participants at follow-up was 54 years. As ACB score increased, the likelihood the person had fallen within the last year also increased. In fully adjusted logistic regression models, an ACB score greater than or equal to two was associated with a history of falls (1.80 [95% CI 1.25-2.60], P=0.002). Of the 3883 women that completed follow-up, 3293 (84.8%) had an ACB score of zero, 328 (8.4%) had ACB score of one, whereas 262 (6.7%) had an ACB score of two or more. The authors used an ACB score of two or greater in their analysis based on wider literature that associates a score of two or greater with worse outcomes, including increased mortality. As ACB score increased, participants’ age and BMI also increased, while physical activity decreased. It was also noted that patients with an ACB score of two or greater had the highest number of self-reported comorbidities. Additionally, the highest rates of corticosteroid, diuretic, and antiepileptic use was found in patients with ACB scores of two or more. There was no association between ACB and having ever fractured a bone, nor was there an association between ACB and having fractured a bone since the age of 50.

Conclusion: While this cross-sectional study is unable to determine causality, it sheds new light on the risks of anticholinergic medications in younger populations, specifically middle-aged individuals. Nearly one-third of patients with a high ACB score of two or more had fallen in the last year. Some may question whether the patients with high ACB scores in this study were less healthy, as evidenced by the higher rate of comorbidities and medication use. Poor health may have contributed to falling. Additionally, nearly 25% of patients did not complete the follow-up, which leads to questions about the applicability of these results. However, this data may change how we judge the appropriateness of anticholinergic medications in patients under 65 years of age. A history of falling is predictive of future falls, and is the strongest risk factor for low-trauma fractures in elderly patients.

Key Point: The use of multiple anticholinergic medications in younger patient groups, in this case more than 10 years before we consider the Beers criteria, is
likely inappropriate. Pharmacists should educate patients about the risks of anticholinergic medications, regardless of age.

**Sulfonylureas as Second Line Agents: Risk of Cardiovascular and Hypoglycemic Events**

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*Supervalu*

**Background and Study Objective:** Sulfonylureas are a common second line choice after metformin for the treatment of type 2 diabetes. Previous studies have questioned the cardiovascular and hypoglycemic safety profile of sulfonylureas. However, much of this investigation has been in the setting of evaluating sulfonylureas against newer agents or as an alternative to metformin in patients for whom metformin would be suboptimal. The practice of either adding a sulfonylurea to metformin monotherapy, or switching from metformin monotherapy to sulfonylurea monotherapy, is commonplace in primary care; however, the risk burden of this practice is relatively unknown. A recent entry in The BMJ describes an attempt by Douros and colleagues to characterize this risk.

**Objectives and Study Design:** The authors conducted a population-based cohort study using data from the United Kingdom’s Clinical Practice Research Datalink (CPRD), Health Episode Statistics (HES), and the Office of National Statistics (ONS) databases. The study evaluated patients over 40 years old with or without cardiovascular disease who initiated metformin monotherapy between April 1, 1998 and March 31, 2013. Exclusion criteria were a history of other antihyperglycemic drugs prior to enrollment and polycystic ovary syndrome. This population was deemed the base cohort and patients were followed by prescription fill history and health outcomes. Those who continued metformin only were used as controls. Two subsequent cohorts were established: patients who first initiated metformin and later added a sulfonylurea to their regimen and patients who ceased to fill metformin and initiated a sulfonylurea.

The investigators employed several means of eliminating residual confounding. Patients were characterized by A1C at the time of cohort entry, number of metformin prescriptions filled, and propensity score for receiving a sulfonylurea. The propensity score was calculated using a logistic regression model to evaluate 500 measures expressing the likelihood of receiving a sulfonylurea prescription. Patients were matched 1:1 according to propensity scores, A1C, and number of metformin prescriptions received at entry. Patients were followed forward from entry into a cohort and evaluated on time to event basis until the end of the study period or when they either discontinued treatment, stopped receiving care at an enrolled practice, or experienced one of the following five primary outcomes: myocardial infarction, ischemic stroke, cardiovascular death, all cause mortality, or severe hypoglycemia. Analysis was conducted by person time per cohort. The investigators evaluated and compared the risk for occurrence of one of the outcomes in each of the three cohorts.

**Results:** Out of 77,138 metformin initiators, 25,699 either added or switched to a sulfonylurea. Of these, 23,592 were selected for analysis based on the availability of a match in the base cohort. Mean time to follow-up was 1.1 (SD 1.4) years. Patients who added or switched to a sulfonylurea experienced significantly higher rates of myocardial infarction (HR = 1.26 [95% CI 1.01 – 1.56]), all-cause mortality (1.28, [95% CI 1.15 – 1.44]), and severe hypoglycemia (5.5 [95% CI 4.64 – 12.44]) compared to those remaining on metformin only. Rates of ischemic stroke and cardiovascular death were non-significant but trended in favor of metformin monotherapy. The increased risk of sulfonylureas was driven by their use as monotherapy. Compared to combination therapy, patients only on sulfonylureas were at increased risk for myocardial infarction (HR 1.51 [95% CI 1.03 – 2.24]) and all-cause mortality (1.23 [95% CI 1.00 – 1.50]). There was no difference in risk for severe hypoglycemia between patients receiving both drugs as compared to sulfonylurea monotherapy (1.06 [95% CI 0.65 – 1.71]).

**Conclusions:** This data suggests that the addition of or the switching to sulfonylureas in patients initially treated with metformin carries a significant risk. Patients taking sulfonylureas experienced significantly higher rates of myocardial infarction, all cause mortality, and severe hypoglycemia. With the exception of hypoglycemia, this risk appears to be driven primarily by the replacement of metformin monotherapy by a sulfonylurea. Clinicians should employ sulfonylurea drugs judiciously and sparingly. When they are added to therapy, it would seem preferable to supplement metformin rather than replace it entirely. Admittedly, some patients are unable to continue metformin due to absolute contraindications or repeated history of intolerance. These patients may be better candidates for newer second line agents with demonstrated cardiovascular benefits as opposed to sulfonylureas which may be cardiotoxic and carry a high risk for hypoglycemia.

**Key Points:** Compared to metformin, sulfonylureas appear to confer a significant risk of mortality, including cardiovascular and severe hypoglycemic events. Concurrent therapy with metformin appears to be safer than sulfonylurea monotherapy. Sulfonylurea monotherapy appears to carry the greatest risk of adverse cardiovascular events; however, any sulfonylurea therapy carries risk for hypoglycemic events.
1. Omega-3 Fatty Acids: Do Cardiovascular Benefits Exist? a–8

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**Background:** Omega-3 fatty acids have been widely used and recommended due to the belief that increased intake would prevent cardiovascular (CV) disease. Compounds with potential benefit are the long-chain omega-3 fatty acids (LCn3) from oily fish including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the plant sourced alpha-linolenic acid (ALA). Many proposed mechanisms by which LCn3 might improve CV health exist including: membrane-stability effect by enrichment of the myocardial membrane, electrophysiologic effects on various ion channels, autonomic effects such as reduction in heart rate variability and increased vagal tone, reduction in perfusion arrhythmias, anti-inflammatory effects, and antithrombotic effects. It is well established that high doses of DHA and EPA effectively treat hypertriglyceridemia (TG>500 mg/dL). This therapy is currently recommended by most major guidelines as a first line option, primarily to reduce the risk of pancreatitis. However, CV benefits in the wider population are less well established. There has been some promising evidence supporting the use of fish oil, however recent reviews and meta-analyses seem to conclude there is no benefit with regards to CV outcomes.

**Evidence:** The most recent update on the potential role for fish oil was a large 2018 systematic Cochrane review by Abdelhamid et al. The review encompassed 79 randomized controlled trials lasting at least 12 months, totaling 112,059 patients. The included study interventions were LCn3 supplementation and/or advice to increase LCn3; and the comparison groups were usual or lower intake of LCn3. The results showed little or no effect of increasing LCn3 on all-cause mortality (RR 0.98 [95% CI 0.90–1.03]), CV mortality (RR 0.95 [95% CI 0.87–1.03]), CV events (RR 0.99 [95% CI 0.94–1.04]), coronary heart disease (CHD) mortality (RR 0.93 [95% CI 0.79–1.09]), stroke (RR 1.06 [95% CI 0.96–1.16]), or arrhythmia (RR 0.97 [95% CI 0.90–1.05]). Results were graded based on moderate- and high-quality evidence. When the authors conducted a sensitivity analysis retaining only trials with a low risk of bias, the effect sizes for LCn3 on all primary outcomes, with the exception of arrhythmia, moved the RR toward 1.0 suggesting no difference.

The Agency for Healthcare Research and Quality performed a review in 2016, which also suggested no CV benefits with LCn3 supplementation (Balk et al). However, previous systematic reviews have suggested CV protection in specific patient populations such as post heart surgery patients (He et al. 2013) and post myocardial infarction patients (Zhao et al. 2009).

Public health advice from professional organizations on LCn3 supplementation is also variable. The UK’s National Institute for Health and Clinical Excellence supports dietary fish intake, but does not support using dietary supplements. The American Heart Association encourages patients with CHD to consult with their doctor, as they may benefit from omega-3 supplements.

**Discussion:** While the 2018 Cochrane review seems quite convincing, it may not tell the whole story for LCn3 supplementation. Generally a large sample size is desirable, however the patient populations in the various studies included in this meta-analysis may be too heterogeneous. Patients included had variable baseline CV risk and medical histories. An overly heterogeneous patient population could mean that specific populations who do benefit from increased LCn3 intake are not seen in the analysis because of large numbers of patients with different baseline characteristics. Additionally, many of the trials included in the meta-analysis had limitations such as not controlling for dietary intake in control populations, having too short of a follow-up period when evaluating long term outcomes, and using inadequate doses of LCn3s. Most recent evidence has suggested little to no benefit when supplementing with LCn3; however, the conclusions of the Cochrane review may be too broad.

**Clinical Impact:** The body of evidence allows for few conclusions related to the use of LCn3s. It is likely that most patients would benefit from a healthy diet, including fish rich in omega 3 fatty acids, instead of consuming omega 3 dietary supplements. However, evidence suggests that specific populations, such as those with TG>500 mg/dL, could benefit from increased LCn3 intake. Increased LCn3 intake may also benefit other patient populations, such as those identified in the aforementioned reviews, in addition to other patient populations currently being investigated.

Additional studies are needed to identify appropriate patients for LCn3 supplements. Several ongoing randomized controlled trials may provide better evidence for the role of LCn3s in cardiovascular prevention. The
Reduction of Cardiovascular Events With EPA – Intervention Trial (REDUCE IT) and Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGH CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trials are long-term studies comparing CV morbidity and mortality for patients using statin medications plus high dose prescription LCn3 compared to a placebo group. The Study of Cardiovascular Events in Diabetes (ASCEND) and Vitamin D and Omega-3 Trial (VITAL) are ongoing studies looking at supplement doses of LCn3 one gram per day for primary prevention of cardiovascular outcomes. Results of these trials may provide further guidance and recommendations with regards to LCn3 supplementation. Pharmacists should consider LCn3 supplements for patients with elevated triglycerides, however current evidence suggests they are not useful for everyone, and money may be better spent on healthy food consumption, including fatty fish.

As-needed Budesonide-formoterol in Mild Asthma

Background: The 2018 Global Initiative for Asthma (GINA) guidelines recommend as-needed short-acting beta agonists (SABAs) with or without low-dose inhaled corticosteroids as maintenance therapy in patients with mild asthma. Similarly, the 2007 National Heart, Lung, and Blood Institute (NHLBI) guidelines prefer low-dose inhaled corticosteroids along with as-needed SABAs for these patients. Many patients rely on SABAs for symptom relief, but these medications do not treat underlying inflammation and overuse is associated with a higher risk of asthma exacerbation. Additionally, poor adherence to maintenance inhaled corticosteroids is a critical issue in clinical practice. Two recent studies have investigated the use of as-needed budesonide-formoterol as an alternative to conventional therapy in adolescent and adult patients with mild asthma.

Evidence: The Symbicort® given as needed in mild asthma 1 (SYGMA 1) trial randomized 3,849 participants to one of three regimens: twice-daily placebo plus terbutaline (0.5mg) used as-needed, twice-daily placebo plus budesonide-formoterol (200mcg-6mcg) used as-needed, or twice-daily budesonide (200mcg) plus terbutaline (0.5mg) used as-needed. Subjects were 12 years of age and older with a clinical diagnosis of asthma requiring GINA guideline step two treatment. Inhaler use was measured according to inhaler monitor data, and symptom control was recorded electronically in a daily diary, also serving as an adherence reminder. With respect to percentage of weeks with well-controlled asthma, as-needed budesonide-formoterol was found to be superior to as-needed terbutaline (34.4% vs. 31.1%; OR 1.14 [95% CI 1.00-1.30]; P=0.046), but inferior to budesonide maintenance therapy (34.4% vs. 44.4%; OR 0.64 [95% CI 0.57-0.73]). Additionally, as-needed budesonide-formoterol was associated with a 64% lower rate of severe asthma exacerbations as compared to as-needed terbutaline (RR 0.36 [95% CI 0.27-0.49]). The rate of exacerbations in the as-needed budesonide-formoterol group did not differ significantly from the budesonide maintenance group. When comparing the median daily dose of inhaled glucocorticoid, the as-needed budesonide-formoterol group received 17% of the dose in the budesonide maintenance group.

With a more pragmatic study design eliminating daily adherence reminders, the Symbicort® given as needed in mild asthma 2 (SYGMA 2) trial examined whether as-needed budesonide-formoterol would be noninferior to budesonide maintenance therapy in preventing severe asthma exacerbations in patients with mild asthma. The 4,215 participants were randomized to receive either twice-daily placebo plus budesonide-formoterol (200mcg-6mcg) used as-needed, or twice-daily budesonide (200mcg) plus terbutaline (0.5mg) used as-needed. Similar to SYGMA 1, subjects were 12 years of age and older with a clinical diagnosis of asthma that required GINA guideline step two treatment. With regards to the annualized rate of severe exacerbations, budesonide-formoterol used as-needed was noninferior to budesonide maintenance therapy (RR 0.97 [95% CI upper limit, 1.16]), as the confidence interval upper limit remained below the prespecified noninferiority limit of 1.2. There was no significant difference in time to first severe exacerbation between the two groups (P=0.66). Secondary efficacy outcomes assessing asthma symptom control, asthma quality of life, and change in FEV1 from baseline favored the budesonide maintenance group. The as-needed budesonide-formoterol group had a 75% lower median daily dose of inhaled glucocorticoid compared to the budesonide maintenance group.

Discussion: SYGMA 1 demonstrated a 3.3% increase in weeks with well-controlled asthma and a 64% lower rate of severe asthma exacerbation with as-needed budesonide-formoterol as compared to as-needed terbutaline. However, budesonide maintenance therapy was superior to as-needed budesonide-formoterol with a 10% increase in weeks with well-controlled asthma in this study. Both SYGMA 1 and SYGMA 2 trials demonstrated similar rates of severe asthma exacerbations with as-needed budesonide-formoterol and budesonide maintenance therapy. Furthermore, as-needed budesonide-formoterol significantly decreased exposure to inhaled corticosteroids. Although both trials revealed inferior symptom control with as-needed budesonide-formoterol when compared to budesonide maintenance therapy, researchers found adherence rates to maintenance treatment in these trials were much...
higher than in clinical practice. Interestingly, SYGMA 2 initially aimed to evaluate the superiority of as-needed budesonide-formoterol, but the protocol was modified to test for inferiority due to a pre-specified sample size review of blinded results that confirmed lower exacerbation rates and higher adherence rates than anticipated. Additionally, all groups were required to use twice-daily maintenance inhalers, either budesonide or placebo, which would not be necessary in real-world situations.

Clinical Impact: In patients with mild asthma who qualify for GINA step two treatment, budesonide-formoterol used as-needed may be preferred over SABAs alone and may be used as an alternative to budesonide maintenance therapy in select situations. Clinicians should consider patient preference, medication adherence, and the reason for treating mild asthma when selecting therapy. Although current GINA and NHLBI guidelines have not addressed the results of these new trials, as-needed budesonide-formoterol may be acceptable for the treatment of mild asthma in patients unwilling to use daily maintenance inhaled corticosteroids, those struggling with medication adherence, and when treating to decrease asthma exacerbation risk rather than control symptoms. Moreover, additional studies with more practical study designs are needed to determine the effectiveness of as-needed budesonide-formoterol when compared to maintenance inhaled corticosteroids in a clinical practice setting.

Efficacy of the New Intranasal Live Attenuated Influenza Vaccine for the 2018-2019 Season15-17
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Background: The intranasal live attenuated influenza vaccine (LAIV) was approved in 2003 and remained part of the Center for Disease Control’s (CDC) Advisory Committee on Immunization Practices (ACIP) until its removal before the 2016-2017 flu season. This intranasal option was used primarily in patients aged between 2-49 years old who preferred to avoid intramuscular injections. After several years of being outside of the recommendations, the CDC’s ACIP reviewed the new formulation of the intranasal LAIV for the 2018-2019 flu season.

Evidence: The intranasal LAIV was officially removed from recommendation before the 2016-2017 season following several years of reduced efficacy in what was speculated to be the H1N1 strain. Influenza vaccines include two influenza A viruses (H1N1 and H3N2) and one or two influenza B viruses for trivalent or quadrivalent vaccines, respectively. The study Vaccine failure and serologic response to live attenuated and inactivated influenza vaccines in children during the 2013–2014 season examined this issue. Hemagglutination inhibition (HI) assays were used against vaccine reference strains before and after vaccine administration to test for seroconversion. Seroconversion was used as a surrogate marker to assess for protection against the H1N1 strain. Baseline H1N1 geometric mean titers (GMTs), a marker used to measure effective serologic responses, were similar at baseline between the inactivated influenza vaccine (IIV) and LAIV. However, after vaccination they discovered 40% of IIV patients experienced seroconversion as compared with only 2% of LAIV patients.

The efficacy of this intermediate marker was demonstrated when three (3%) IIV recipients and eight (13%) LAIV recipients (P=0.02) tested positive for H1N1 on swabs. After completing an age-adjusted, multivariable logistic regression, LAIV was the only factor associated associated with vaccine failure against H1N1. This gap in efficacy in protecting against the H1N1 strain led to the vaccine’s loss in favor by the CDC in 2016.

The CDC states that the new LAIV, which includes A/Slovenia/2903/2015, has much higher seroconversion rates than the previous vaccine, which had A/Bolivia/559/2013. The increased seroconversion is believed to be produced by an improved replicative fitness. This means that the new strain has a higher capacity and greater adaptability to be replicated, and therefore produce a seroconversion.

Discussion: Based on the new formulation for the LAIV, the CDC’s ACIP includes the new intranasal LAIV in its recommended 2018-2019 influenza vaccine options. While the new LAIV has much higher seroconversion rates, there are unfortunately no efficacy studies on the new LAIV for preventing influenza in a patient population. The American Academy of Pediatrics (AAP) convened to discuss the updated ACIP recommendation and is officially giving preference to IIV over LAIV, stating that the nasal vaccine may not offer full protection against influenza. Their rationale is that the LAIV’s efficacy was inferior to IIV against H1N1 during past seasons and is currently unknown for H1N1 for this upcoming season.

Clinical Impact: It is important to note that while seroconversion has been proven, the effectiveness of the updated LAIV against currently circulating H1N1 viruses is not yet known. Due to this lack of efficacy against the currently circulating H1N1 viruses, the AAP recommends using the IIV intramuscular vaccine instead of the LAIV intranasal vaccine. Based on the evidence available, it is reasonable to use the intranasal LAIV in patients who would otherwise not receive a flu vaccine.
Impact of Pharmacist-Physician Collaborative Care Model on Patient Outcomes and Health Services Utilization

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Background: Pharmacists make interventions, in both hospital and clinical settings, to improve outcomes for patients with both acute and chronic disease states. Six rural hospitals from the Carilion Clinic health system in southwest Virginia participated in a project to look deeper into this concept. The primary goal of the project was to assess the impact of a pharmacist-physician collaborative care model on patient outcomes and health services utilization.

Methods: The majority of patients enrolled in the study were identified while hospitalized. Patients were considered eligible if they had a documented diagnosis of two or more of the seven core chronic conditions (congestive heart failure, hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and depression), prescriptions for four or more medications, and a primary care physician in the Carilion Clinic health system. The usual care group, or control group, was retrospectively identified by applying an EMR algorithm to patients in a health-system without an embedded clinical pharmacist. Resulting patients were not screened for additional pharmacist contact outside of their primary health-system. Primary clinical outcomes were differences in absolute change in measures associated with diabetes mellitus, hypertension, and hyperlipidemia management from baseline to the end of the two-year study between collaborative care and usual care groups. Pharmacists called patients within 72 hours of any hospital discharge, then scheduled an in-office follow-up within 14 days. Patients were contacted quarterly by the pharmacist thereafter to address patient-specific problems or concerns.

Results: A statistically significant decrease in hemoglobin A1c (mean difference of -0.46%, P<0.001), systolic blood pressure (mean difference of -6.28 mm Hg, P<0.0001), and diastolic blood pressure (mean difference of -2.69 mm Hg, P=0.0071) was seen in the collaborative care group compared to the usual care group. Differences seen in LDL cholesterol and total cholesterol were not statistically significant between groups. Since improvements were significant in three of the five clinical measures for patients in the collaborative care model, study investigators deemed the primary outcome achieved. Cost savings was also analyzed, with the collaborative care program providing a return on investment calculated at 504%.

Conclusions: Inclusion of clinical pharmacists in this physician-pharmacist collaborative care-based model was associated with significant improvements in patients’ medication-related clinical health outcomes.

Analysis of 2017 Prescription Drug Expenditure in the United States

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Background: In 2016, $3.3 trillion were spent on healthcare in the United States. This accounted for 17.9% of gross domestic product (GDP) and was a 4.3% increase from 2015. In contrast, GDP only grew by 2.8% from 2015 to 2016. Multiple factors play into increasing health costs including increased Medicare enrollment due to aging baby boomers and increasing prices for medical goods and services, including prescription drugs. Schumock and coauthors published a special edition article, National trends in prescription drug expenditures and projections for 2018 in the American Journal of Health-Systems Pharmacists in July 2018 to analyze prescription drug expenditures and make projections for the year.

Methods: Data was collected and analyzed from the IQVIA (formerly QuintileIMS) National Sales Perspective databases. In addition, new drug approvals and patent expirations were reviewed. Focused analyses were completed on drug classes more likely to impact expenditures including antimicrobials, biosimilars, and oncology medications.

Results: In 2017, $455.9 billion was spent on prescription drug sales in the US. This was a 1.7% increase from 2016. Retail pharmacies account for 46.2% ($210.5 billion) of total expenditures, followed by mail-order pharmacies (24.1%), and clinics (15.6%). Prescription drug expenditures grew in clinics by 10.9% in 2017 compared to 2016, which is the healthcare sector with the biggest growth. Retail pharmacies had a 2.2% decline in expenditure in 2017 compared to 2016. Three factors driving growth in all settings include 1) new products, 2) price changes of existing products, and 3) increased purchasing (and utilization) of products.

The top five drugs by expenditure in 2017 overall were adalimumab, insulin glargine, etanercept, ledipasvir-sofosbuvir, and insulin aspart. Adalimumab was the top...
Objective: The primary objective of the study “Evaluating patient satisfaction with pharmacist-administered long-acting injectable antipsychotics in the community pharmacy” assessed patient satisfaction with community pharmacist-administered LAIAs. Secondary objectives evaluated satisfaction with the current service compared to a similar service received elsewhere, and determined the relationship between patient demographics and likelihood of recommending the service to others.

Study Design: This prospective study occurred from December 2016 to February 2017 in Albertsons community pharmacies in Arizona, California, Hawaii, Idaho, Oregon, Texas, Virginia, and Washington. The survey, administered after the injection was received, included four sections: satisfaction in eleven areas (5 point Likert scale); open-ended items about positive aspects of the service and what could be improved; comparison of current service to a similar service provided elsewhere; and demographic information.

Results: The 104 surveys collected (of 716 sent out) showed the majority of patients resided in CA or TX, were males younger than 40 years old, and had their current diagnosis for one to five years. Of the 11 survey statements pertaining to the primary objective of patient satisfaction, nine received at least 95% positive responses (agreed or strongly agreed). Among the nine were: comfort with service, trust in pharmacist, unrushed appointment, and likelihood of recommending service. Only 64% of patients responded positively regarding the location of the service, which may indicate the patient’s usual pharmacy is farther away from the pharmacy at which they receive their injection. Open-ended questions reflected similar responses as the likert-scale survey questions did. No feedback was provided regarding ways to improve the service.

In the secondary objective of comparing satisfaction with the current service to a similar service received elsewhere (n = 57), responses acknowledged clear


**Fluoroquinolone Impact on Mental Health and Blood Sugars**

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Fluoroquinolone antibiotics are used to treat many serious bacterial infections, including some bacterial pneumonias. Previously, the Food and Drug Administration (FDA) has associated an increased risk of tendon rupture, tendonitis, and peripheral neuropathy with the use of fluoroquinolones. The FDA is now requiring additional risks be added to the labels and patient Medication Guides of all brand and generic fluoroquinolones (levofloxacin, ciprofloxacin, moxifloxacin, ofloxacin, gemifloxacin, and delafloxacin).

In July 2018, the U.S. FDA released a statement regarding the safety of fluoroquinolones, which included an increased risk of mental health side effects and changes in blood glucose. Associated mental health side effects include attention disturbances, disorientation, agitation, nervousness, memory impairment, and delirium. Warnings and precautions about central nervous system changes associated with various fluoroquinolones were previously described on their labels, however this new warning makes mental health risks more prominent and will apply to all fluoroquinolones. Blood sugar disturbances due to fluoroquinolones have already been established by the FDA; however, the FDA is now expanding the warning to include the risk of hypoglycemia which can lead to life-threatening coma. Elderly patients and/or patients taking oral hypoglycemic medications or insulin are at much higher risk of developing hypoglycemia or coma due to fluoroquinolone use than the general public.

As healthcare professionals, it is important to understand the new risks associated with fluoroquinolones. This new information can be important in determining the best antibiotic for patients, especially the elderly, those with mental health disease, and those with diabetes at a high risk for hypoglycemia. Fluoroquinolones have a valid place in therapy and should be considered for treatment as long as the risk and benefits are evaluated for each individual patient.

**Ibogaine for Opioid Withdrawal**

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Ibogaine is a psychedelic drug that has been used for opioid withdrawal in other countries. It is a naturally occurring compound found in the roots of an African rainforest shrub called Tabernanthe iboga. Because ibogaine is a schedule I controlled substance in the United States, its data has come from use in Canada and Mexico treatment centers; however, data is limited. Its potential use for reducing opioid withdrawal symptoms has not gone unnoticed in the United States. New York, Maryland, Vermont, and New Hampshire have introduced ibogaine into legislation for use in pilot studies but none have yet passed.

Of clinical note, ibogaine has been shown to cause a dream-like state in those who use it. Initial dosing of the drug has shown to first produce vivid waking dreams. After the initial period, the individual may then experience a feeling of personal insight and mental clarity. Research is still being done on clinical dosing and duration of use. Significant adverse effects of...
ibogaine are its cardiotoxic effects, including delayed cardiac repolarization and prolonged QT interval. Because of these potential adverse effects, it is important to discourage individuals from purchasing ibogaine illicitly or using it without direct medical supervision. Sudden death and neurotoxicity have also been reported.

Drug-drug interactions may be associated with ibogaine as it is metabolized through CYP2D6, CYP2C9 (minor), and CYP3A4 (minor). Ibogaine also interacts with multiple neurotransmitters, including kappa and mu opioid receptors, N-methyl-D-aspartate (NMDA) receptors, acetylcholine, dopamine, and serotonin. Its use in patients on medications for mood disorders needs to be considered, weighing the risks and benefits of potential interactions.

With limited medications currently approved for opioid withdrawal, new drugs are always of interest. Especially with the rise in opioid use disorder and the difficulties associated with opioid withdrawal management, new therapies provide another avenue of possibility in helping lessen the patient’s symptoms and achieving success in abstinence. More research and data are needed to fully evaluate the safety considerations with its use and the potential ibogaine has for treating opioid withdrawal symptoms. Because of the safety implications and minimal evidence currently available to support its use, healthcare practitioners should discourage patients from using or purchasing ibogaine over the internet if a patient is interested in it.

Type 2 Diabetes and Depression - Updates from the ADA Symposium
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Diabetes and depression are two of the most common conditions seen in ambulatory care, and many patients live with both diagnoses simultaneously. It is important to note that these two diseases do not occur in isolation of each other, but instead share a bidirectional relationship. Diabetes patients are twice as likely to have depression when compared to patients without diabetes.

Conversely, the Multi-Ethnic Study of Atherosclerosis (MESA), sponsored by the National Institute of Health, found that patients living with depression have a 21 percent higher risk of developing diabetes.

The correlation between diabetes and depression may have biological origins. Abnormal patterns of cortisol and adrenaline in the hypothalamic pituitary adrenal axis have been associated with both disease states. Sherita Hill Golden, MD, of Johns Hopkins University School of Medicine, a researcher with the MESA, describes that this atypical stress hormone profile may explain the elevated diabetes risk in patients with depression. As we begin to better understand the mechanisms involved, new drug targets may emerge that allow for treatment of both conditions simultaneously.

Pharmacists play an important role in the management of patients with comorbid depression and diabetes. We can assist with management of medications, encourage healthy lifestyle modifications, provide education, and direct patients to appropriate resources. A variety of initiatives exist to combat diabetes, such as the National Diabetes Prevention Program. The CDC is working to ensure that this evidence-based lifestyle change program is available to people with prediabetes living anywhere in the nation. It is important that patients have access to coordinated comprehensive care that addresses both the physical and mental aspects of their health.

References


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