A 12-Year Follow-up on the Long-Term Effectiveness of the Quadrivalent Human Papillomavirus Vaccine in 4 Nordic Countries

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Background: The quadrivalent human papillomavirus vaccine (qHPV), GARDASIL®, was approved in the United States in 2006 for administration to females aged 9-26 years and was subsequently approved for administration to males aged 9-26 years. This 3-dose series vaccine is indicated for the prevention of human papillomavirus (HPV) types 6, 11, 16, and 18 related cervical cancer and precancerous lesions of the vulvar, vaginal, and anal areas, and genital warts.

Purpose/Objective: The primary objective of this study was to assess the long-term effectiveness of qHPV vaccine in Nordic women vaccinated at age 16-23 years and followed for up to 14 years post-vaccination. This assessment was done by monitoring the combined incidence of cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS), and cervical cancer related to HPV type 16 or 18. A secondary objective included assessing the long-term effectiveness of the qHPV vaccine against vulvar and vaginal cancer.

Study Design:
Base Study: The base study, FUTURE II, was a randomized, double blind, placebo-controlled clinical trial that enrolled 12,167 women from 13 countries covering four continents. Participants who were not pregnant, had no abnormal Pap tests, and had a lifetime number of no more than four sexual partners were eligible for enrollment in the base study. These participants were followed for four years.

Long-Term Follow-up (LTFU) Study: This study is an ongoing 10-year extension of the 4-year base study. Only women who received the 3-dose series qHPV vaccine in the base study (n=2,650) were included in the LTFU. Vaccine effectiveness was estimated by comparing the observed incidence with the expected incidence of HPV type 16/18-related CIN2 or worse (CIN2+) via an unvaccinated cohort using historical registry data from the same region. From this historical data, it was found that the incidence of HPV type 16/18-related CIN2+ was estimated to be 0.287 per 100 person-years in unvaccinated women. An adapted 1-sided c chart was used to monitor the incidence rate of HPV 16/18-related CIN2+ in the LTFU study participants over a 12-year period. Based on the estimated historical rate of HPV 16/18-related CIN2+, the vaccine was assumed to have 90% effectiveness. This chart was used to detect any decrease in vaccine effectiveness below 90%.
Results: There were 2,084 evaluated participants, contributing 13,794.9 person-years of follow-up since day 1 of the base study. There were no observed cases of HPV 16/18-related CIN2+. If vaccine efficacy was maintained at 90%, three cases were expected based on the 13,794.9 person-years of follow-up time accrued. Based on the current available data, the qHPV vaccine has continued to be effective at least 10 years post-vaccination. The same pattern was seen in the interval up to 12 years; however, there is insufficient follow-up time in the 10-12 year interval to make a conclusive claim of effectiveness beyond 10 years at this time.

Conclusion: In this LTFU study, the qHPV vaccine is effective against HPV16/18 CIN2+ through at least 10 years after vaccination of women aged 16-23 years with a trend toward 12 years of protection. The results of this study are important because they suggest that the current 3-dose regimen in young women is sufficient to achieve long-term effectiveness; therefore, there is no need for an additional dose of the qHPV vaccine. Future reports will assess effectiveness of up to 14 years or more.

Key Points: The 3-dose series qHPV vaccine shows at least 10 years of protection in women, with a trend for continued protection through 12 years of follow-up. Even though the guidelines regarding the HPV vaccination schedule have been updated, and a new HPV vaccine has been created with more strain coverage since this study was started, it is still important to see the long-lasting protection that the quadrivalent vaccine has provided. Benefit of lowering LDL-C levels is likely dependent on the reduction in apoB containing lipoprotein particles.

Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis²
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Background: Fractures in community-dwelling older adults often involve a complicated recovery and loss of independence. Unfortunately, more than 20% of older adults die within the first year after a hip fracture. Current clinical guidelines recommend calcium and vitamin D supplementation to prevent osteoporosis and fractures, though previous data has yet to show a consistent benefit of supplementation.

Objective: To determine if calcium, vitamin D, or combined supplementation are associated with reduced fractures in community-dwelling older adults.

Study Design: A systematic review and meta-analysis of previously published systematic reviews and meta-analyses was obtained by searching the PubMed, Cochrane library, and EMBASE databases for calcium, vitamin D, and fracture. Publications from December 24, 2006 to December 24, 2016 studying the incidence of fracture in community-dwelling adults were included in the analysis. A similar second search was performed to identify individual studies published from July 16, 2012 to July 16, 2017.

Randomized controlled trials (RCTs) were included if they compared calcium, vitamin D, or both supplements to a placebo or no treatment group, included adults at least 50 years of age living in the community, and provided fracture data. Trials were excluded if they had no placebo or no treatment group, included corticosteroid-induced osteoporosis, included other osteoporotic treatments, used vitamin D analogs or hydroxylated vitamin D, or evaluated dietary intake. Each trial was then designated as low, moderate, or high quality based on blinding, randomization, and bias rating. Trials were assessed for bias by two researchers using the Cochrane risk-of-bias criteria.

Hip fracture was selected as the primary outcome because it is considered the most serious type of osteoporotic fracture. Secondary outcomes included rates of nonvertebral, vertebral, and total fractures. Risk ratios (RR), absolute risk differences (ARD), and 95% CIs were calculated using the Mantel-Haenszel method. Pooled data was evaluated using the random-effects model and the I² statistic was used to evaluate heterogeneity between summary data. A sensitivity analysis was also performed that excluded low-quality trials, trials recruiting participants with particular conditions, or trials deemed different from the others. Subgroup analyses were conducted based on medication dosing and schedule differences, sex, fracture history, dietary calcium intake, and baseline vitamin D concentration. If 10 or more trials reported the primary outcome, a funnel plot was used to assess publication bias. All tests were two-tailed and p <0.05 was considered significant.

Results: Overall, 33 RCTs involving 51,145 patients were included after excluding duplicate trials. All studies were randomized and approximately 75% were also double-blind, placebo-controlled trials. Most trials were moderate quality, although one was low quality, and six were high quality. A publication bias analysis was not performed because fewer than 10 trials reported hip fracture in each comparison.

Calcium supplementation, vitamin D supplementation, and combination calcium and vitamin D supplementation
were not significantly associated with hip, nonvertebral, vertebral, or total fractures compared to placebo or no treatment. There was no change in results in the sensitivity and subgroup analyses, except for patients with a baseline serum 25-hydroxyvitamin D level of ≥20 ng/mL, where vitamin D supplementation was associated with a significantly higher incidence of hip fracture (RR 1.49 [95% CI 1.03 - 2.17]; ARD 0.00 [95% CI 0.00 - 0.01]). When compared to patients with serum 25-hydroxyvitamin D level of <20 ng/mL, this result was not statistically significant. Once yearly high-dose vitamin D therapy was also associated with a higher incidence of hip fracture (RR 1.41 [95% CI 1.02 - 1.96]; ARD 0.00 [95% CI 0.00 - 0.01]).

Conclusions: Based on this meta-analysis of RCTs, supplementation with calcium, vitamin D, or combination supplementation compared to placebo or no treatment was not associated with a reduced fracture risk in community-dwelling older adults. The dose of supplementation, patient sex, fracture history, calcium intake, and baseline serum 25-hydroxyvitamin D level did not impact these findings.

Limitations: Not all studies included in the analysis tested baseline vitamin D level and vitamin D deficiency. This may be an area for further research. Due to the process for identifying RCTs, some acceptable trials may have been missed in the meta-analysis and systematic review search. Although the researchers used a relatively objective process for classifying the quality of the trials, some of the criteria could be subjectively interpreted and thus classified differently. Lastly, a few of the included trials used less desirable methods, such as uncertain allocation concealment, and were of poor quality.

Key Point: Supplementing with calcium, vitamin D, or both is not associated with reduced risk of fractures in community-dwelling older adults compared to placebo or no treatment.

Association of Cardiovascular Risk with Inhaled Long-Acting Bronchodilators in Patients with COPD Updates in Research³
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Teaser Summary: Inhaled long-acting β₂-agonists (LABAs) and long-acting antimuscarinic antagonists (LAMAs) newly initiated in patients with chronic obstructive pulmonary disease (COPD) may be associated with an increased risk of cardiovascular disease (CVD) according to a recent study published in January 2018.

Background: Inhaled long-acting β₂-agonists (LABAs) and long-acting antimuscarinic antagonists (LAMAs) used in the treatment of chronic obstructive pulmonary disease (COPD) have been found to increase the risk for cardiovascular disease (CVD) in some studies while other studies have shown no increased risk. Wang and colleagues sought to investigate the use of LABAs and LAMAs in COPD and association of CVD risk, specifically focusing on new use, duration of therapy, individual agents, and concomitant COPD therapy regimens.

Purpose: To determine whether duration or initiation of LABAs or LAMAs used in the treatment of COPD are significant determinants of increased risk of CVD.

Study Design: This case-control, observational study took place in Taiwan and 284,220 patients with COPD who were 40 years of age or older were included. Data was retrieved over five years, from January 1, 2007 to December 31, 2011, through the National Health Insurance Research Database (NHIRD). This database consists of records of medical and pharmacy claims covered under the universal national health insurance in Taiwan. The study cohort included patients who made two outpatient visits or one inpatient visit for COPD in a single year with record of filling at least one COPD medication. Entry date for the cohort was set at the first COPD outpatient visit or discharge date if inpatient hospitalization. Patients were excluded if they had already received LABA-LAMA therapy or lacked continuous health insurance coverage for the year before cohort entry, as this was a means of data retrieval. To identify CVD cases, inpatient or emergency room (ER) visits were monitored and identified if a primary cardiovascular diagnosis was listed based on ICD-9 codes, including the following: coronary heart disease, cardiac arrhythmia, heart failure, or ischemic stroke. Cases were matched with randomly selected controls and a disease risk score was estimated. Covariates were measured and important considerations were made for the following: baseline CVD, CVD risk factors (hypertension, diabetes, hyperlipidemia), cardiotoxic medications, and COPD severity.

Results: During a mean follow-up of two years, 37,719 of 284,220 LABA-LAMA-naive patients in the study cohort were identified with severe CVD (hospitalization or ER visit linked to CVD diagnosis code). The mean age was 71.4 years. Current treatment (≤30 days) with a LABA or LAMA was associated with a 1.50-fold (95% CI 1.35-1.67; P<0.001) and 1.52-fold (95% CI 1.28-1.80; P<0.001) increased risk of CVD, respectively. Use of LABAs was not associated with increased CVD risk with recent initiation of therapy (defined as 31-90 days). For past LABA users (91-180 days), a 10% decrease in CVD risk was identified. Among the LABAs, similar CVD risks were found between salmeterol and formoterol. Similar
risks were found in various LAMA regimens, including tiotropium alone. The risk of CVD was absent or decreased with >30 days of LABA or LAMA use. Researchers found that the greatest risk of a CVD event occurred around the 30th day after initiation of LABA or LAMA treatment, attributed to a “phenomenon of depletion of susceptibles.” This phenomenon is described as an increased event rate after initial exposure to a medication and a subsequent decreased event rate with longer exposure to the drug.

Conclusions: This study investigated CVD risk in COPD patients naive to LABA-LAMA therapy and is one of the first studies not to exclude patients with baseline CVD, a drawback of previous large RCTs. In summary, newly initiated (<30 days) LABA or LAMA use in patients with COPD was associated with an increased risk of CVD. Due to this increased event rate, providers should be attentive to cardiovascular disease symptoms within 30 days of initiating a LABA or LAMA for patients with COPD.

Key Points: LABA or LAMA treatment in patients with COPD is associated with an approximate 1.5-fold increased risk of CVD within 30 days of new initiation. This risk was similar across the LABA agents studied (salmeterol and formoterol) and tiotropium, the LAMA agent studied. Given the results of this study, health care providers should evaluate CVD risk prior to initiating treatment with a LABA or LAMA.

Therapeutic Thoughts

Focusing Primary Efforts on the Right Interventions in Management of Type 2 Diabetes4,6
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Background: Type 2 Diabetes Mellitus (T2DM) is a complex and comorbid disease affecting an estimated 27 million people in the United States. In 2015, diabetes was the seventh leading cause of death in the country, with an estimated $245 billion in annual total direct and indirect costs. Current guidelines for treating and managing T2DM encourage targeting lifestyle interventions as first-line efforts to achieve glycemic control. Despite these recommendations, there is arguably more emphasis on pharmacological therapies and using multiple drug treatments to lower blood glucose and reduce cardiovascular risks associated with the disease.

Pathophysiologi cal research has demonstrated a strong association between T2DM and adult weight gain, specifically linking the disease to the buildup of excess fat within the liver and pancreas. Investigators have discovered that calorie restriction in T2DM can normalize fat content in these organs while restoring liver insulin sensitivity. Studies in newly diagnosed T2DM have also provided evidence that normal glucose control can be achieved through weight loss alone, but until this past year, no trial examining the effects of dietary changes has ever assessed sustained disease remission as a primary outcome.

Evidence: A recent study in the United Kingdom investigated whether intensive weight management in a primary care setting could achieve remission of T2DM. The open-label, intention-to-treat, cluster-randomized trial (DiRECT) recruited 306 patients with T2DM from 49 primary care practices located in Scotland and surrounding regions. Patients were 20-65 years of age with a BMI of 27-45 kg/m², diagnosed with T2DM in the past six years and were not using insulin. Practices were randomized 1:1, providing patients with either a weight management program (intervention) or best-practice care with current guidelines (control) and followed for 12 months. The intervention group underwent withdrawal of all antidiabetic and antihypertensive drugs, and then followed a calorie-restricted diet protocol. Co-primary outcomes were weight loss ≥15 kg and remission of diabetes, defined as achieving a glycated hemoglobin (HbA₁c) <6.5% after two months without antidiabetic medications.

There were 149 participants in each group at the end of the study. In the intervention group, 36 participants recorded weight loss of ≥15 kg (none in control group, P<0.0001) with a mean decrease in body weight of 10 kg compared to 1 kg in the control group (adjusted difference 8.8 kg [95% CI 10.3-7.3; P<0.0001]). There were 68 individuals who achieved disease remission in the intervention group while six met the outcome in the control group, OR 19.7 [95% CI 7.8-49.8; P<0.0001]. Remission of diabetes appeared to correlate with the degree of sustained weight loss in the study population. No serious adverse events led to withdrawal from the study.

Discussion: Results from DiRECT demonstrate the significance of reinforcing appropriate lifestyle changes in patients with T2DM. These findings bring attention to the importance of early detection and prevention of T2DM, highlighting the impact weight loss can have on metabolic pathways and possible remission if successful interventions are made in the early stages of diabetes. The study is limited by a small sample size and homogenous patient population (98% white ethnicity, 59% males). Additionally, those included in the trial had
only slightly elevated HbA1c at baseline despite inclusion criteria of HbA1c <12.0% (mean HbA1c of 7.7% and 7.5% in the intervention and control groups, respectively). Therefore, it is difficult to apply these conclusions to newly diagnosed patients presenting with a significantly higher HbA1c who previously never sought regular medical care. Further investigation is needed to see if there are similar effects in those with longer disease duration and a higher degree of uncontrolled blood glucose. Additionally, studies of longer duration will help determine if these outcomes can be maintained long term. There is also potential for bias in the trial design due to the nature of the studied intervention, which required all study participants to be unblinded.

**Clinical Impact:** Primary care practitioners are often required to dedicate considerable direct patient care time attempting to resolve adherence issues, medication side effects, and financial barriers to pharmacological therapies, rather than focusing on supportive lifestyle coaching and developing patients’ self-management skills. The observations in DiRECT should encourage clinicians in primary care settings to continue focusing on lifestyle modifications in T2DM in order to achieve desired outcomes. Although the diagnosis is often overwhelming, patients with new onset T2DM can feel empowered by these promising findings while those opposed to medication therapies may be further motivated to make meaningful lifestyle changes to improve their health.

**2017 ACC/AHA Hypertension Guidelines: Influential or Controversial?**

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**Background:** The American Heart Association (AHA), American College of Cardiology (ACC), as well as nine other health professional organizations released a new hypertension guideline November 2017. The 2017 hypertension guideline discusses detection, prevention, management, and treatment of high blood pressure. Contrary to the previous JNC8 guideline released in 2014, in which hypertension was classified as a blood pressure of ≥140/90 mmHg, the 2017 guideline changes the definition of hypertension to either systolic blood pressure (SBP) measurement of 130 mmHg or higher or diastolic blood pressure (DBP) measurement of 80 mmHg or higher, regardless of comorbidities. The new guideline also provides new treatment recommendations with emphasis on lifestyle modifications. An important component of the new guideline recommendations includes results of the Systolic Blood Pressure Intervention Trial (SPRINT), which has sparked much discussion within the field. The 2017 ACC/AHA hypertension guidelines offer a more stringent hypertension definition with the basis of this change being the results from the SPRINT trial.

**Evidence:** Although other trials are denoted within the new ACC/AHA hypertension guidelines, the SPRINT trial receives substantial weight, comparatively. The SPRINT trial is the largest trial to date specifically designed to evaluate blood pressure targets (n=9,361). The purpose of the SPRINT trial was to determine if treatment to a goal SBP of less than 120 mmHg is superior to treating to less than 140 mmHg (control group) in adults 50 years or older with hypertension who are at risk for cardiovascular disease. The control group target of less than 140 mmHg was selected due to previous guideline recommendations for treating to a SBP target of less than 140 mmHg. SPRINT showed that more intensive management of SBP to a goal of less than 120 mmHg reduced heart attacks, heart failure, and stroke by 25% (HR 0.75 [95% CI 0.64-0.89]; P<0.001) and lowered the risk of death by 27% (HR 0.73 [95% CI 0.60-0.90]; P=0.003). SPRINT also showed that ambulatory adults age 75 years or older treated to a more stringent blood pressure goal of less than 120 mmHg also showed significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause. It was also found that serious adverse events (hypotension, syncope, electrolyte abnormalities, acute kidney injury), although not statistically significant, were higher within the more stringent blood pressure group.

While the results of the trial were quite influential, there has been discussion around the limitations to the SPRINT trial. Limitations to the SPRINT trial include participants being on antihypertensive medications at baseline (skewing hypertension staging categorization), randomization of the trial did not follow age stratification, stopping the trial early due to clinical impact (limiting evaluation of long term safety), and excluding older adults living in nursing homes with type 2 diabetes mellitus, previous stroke, and individuals with symptomatic heart failure.

**Discussion:** It is well understood that hypertension elevates the risk for heart disease, heart attack, and stroke. The argument from the new ACC/AHA hypertension guidelines for a more stringent hypertension definition is due to the risks of blood pressure at levels even between 130-139/80-89 mmHg. The basis of this change is due to the results from the SPRINT trial, one of the only clinical trials to show this. It has been postulated that as a result of the ACC/AHA guideline, half of the U.S. adult population will now be diagnosed with hypertension. Authors of the new guidelines, however, have estimated that only a small number of those newly diagnosed will require antihypertensive medications since more emphasis will be placed on discussing lifestyle modifications. This is
because the decision of initiating pharmacotherapy is not only based on SBP/DBP but also cardiovascular disease risk. The striking change in proposed guideline recommendations has caused the SPRINT trial to be the subject of discussion.

After identifying the limitations of SPRINT and the exclusion criteria, it is crucial to use the results of SPRINT within the appropriate patient population. Some argue that risk associated with high blood pressure is a continuum and that patient individualization is critical, with some individuals benefiting from more stringent targets, but may also lead to unnecessary treatment and potential side effects.

Some organizations have chosen to not endorse the ACC/AHA hypertension guidelines. An editorial from the Annals of Internal Medicine discussed how the 2017 ACC/AHA hypertension guideline publishing organizations differ from previous guidelines. Specifically, the American College of Physicians and the American Academy of Family Physicians were not a part of updating or publishing of the new guidelines. The editorial discussed how the new definition of hypertension may lead to worries of harm, cost, and increased complexity of care. It also speaks to the differing opinions on when pharmacological therapy is or is not appropriate due to lack of consistent evidence within clinical trials and how benefits may be overestimated and harms underestimated.

**Clinical Impact:** The 2017 ACC/AHA hypertension guidelines have provoked much discussion and debate amongst clinicians. Although there are opposing thoughts regarding endorsement of the new guidelines, approach to hypertension targets and treatment should be made on an individualized basis, taking into account patient history, characteristics, risk factors, and preferences.

**Does the Type and Duration of Hormonal Contraceptives Used Increase Cancer Risk?**

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**Background:** Evidence suggests an association between the use of hormonal contraception, particularly estrogen, and an increased risk of breast cancer may exist. Historical studies used only oral products that contain far more estrogen than current products on the market. Further exploration to review these new dosing regimens and hormonal products is necessary. New research takes a look at various routes of delivery including patches, rings, and implants that have differing doses of estrogen or progestin only to see if these products carry similar risks. Long term use data was also analyzed to see if duration of therapy or various lifestyle choices influenced the risks of specific cancers including breast, colon, ovarian, and endometrial.

**Evidence:** The Danish Sex Hormone study followed 1.8 million women between the ages of 15-49 years for an average of 10.9 years via Danish nationwide registries. These women had no history of cancer or venous thromboembolism (VTE) and had not received infertility treatments. Participants were taking either both combination estrogen and progestin products or progestin only products, both with various routes of administration. The researchers also looked at whether the risk of breast cancer was influenced by duration of use.

Of the 1.8 million women followed, a total of 11,517 cases of breast cancer occurred. When looking at women who were current or recent (discontinuation within the previous 6 months) users of hormonal contraception, the relative risk of breast cancer was 1.20 [95% CI 1.14 - 1.26] compared to women who had never used hormonal contraception. Less than one year of use correlated to a risk of 1.09 [95% CI 0.96 - 1.23] increasing to 1.38 [95% CI 1.26 - 1.51] with more than 10 years of use (P=0.002). Women who currently or recently used the progestin-only IUD also had a higher risk of breast cancer than women who had never used hormonal products RR 1.21 [95% CI 1.11 - 1.33]. The overall absolute increase in breast cancers diagnosed among current and recent users of any hormonal contraceptive was 13 [95% CI 10 - 16] per 100,000 person-years, which equals approximately one case of breast cancer per 7,690 women using hormonal contraception for one year.

A prospective study by the National Institutes of Health and the American Association of Retired Persons (NIH-AARP) Diet and Health reviewed over 100,000 women who were using oral hormonal contraception and aged 50-71 at time of enrollment (1995-1996). A baseline questionnaire was sent to women to obtain duration of oral contraceptive use, demographics, and health and lifestyle characteristics. Women were followed from enrollment until cancer diagnosis, death, or the end-of-study follow up in 2011. Participants were predominantly white and excluded patients with a history of cancer, had menses stop due to chemotherapy or radiation, or who did not provide information on contraceptive use.

Data analysis conducted from September 2016 through April 2017 identified no significant correlation between oral contraception use and colorectal cancer risk or breast cancer risk, regardless of family history. However, long-term users (use of oral contraception for longer than 10 years) who were current smokers were found to have an increased risk of breast cancer HR 1.21 [95% CI 1.01 - 1.44]. Longer duration of use was associated
with an increased risk reduction of ovarian cancer HR 0.60 [95% CI 0.47-0.76]; P<0.001 for trend. This trend was similar across all lifestyle modifiers including smoking, obesity, alcohol use, and physical activity. Analysis of endometrial cancer showed similar risk reductions with increased duration of use HR 0.66 [95% CI 0.56 - 0.78]; P<0.001 for trend. Risk reduction was stronger in patients who were smokers, were obese, and exercised rarely.

Discussion: Regardless of what type of hormonal contraception is being used, there is still data showing a potential risk of breast cancer that seems to increase with duration of use. It appears that even progestin only methods present an increased risk. Lifestyle choices do not appear to modify the risk of breast or colorectal cancer when using oral contraception, but may have a protective effect on ovarian and endometrial cancers. Further research is needed specifically addressing various hormone dosing in each formulation available and their associated risks/benefits of long term use to decipher how big of an impact hormonal contraceptives play in cancer risk and protection.

Clinical Impact: Prescribers should obtain a full health history and assess risk factors for each patient individually prior to prescribing hormonal contraceptives. Patients should be educated regarding duration of use of these products and the possible progression of risks or benefits of cancer. The decision to use hormonal contraceptives should be carefully considered based upon the patients’ full health profile and personal preference.

Pharmacy Student Involvement in Student-Run Free Clinics

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Background: According to recent data, there are 85 Student Run Free Clinics (SRFCs) in the United States associated with medical schools and of these, 35 are partnering with pharmacy students. SRFCs are known for their ability to improve community health and to teach students clinical skills along with professional generosity. SRFCs primarily differ in the services they offer, student roles, preceptor models, and interprofessional interactions.

Purpose or Objective: This study sought to evaluate pharmacy student involvement and interprofessional collaboration in SRFCs. Specifically, the study explored pharmacy students’ roles in SRFCs, perceptions of the benefit of being involved in SRFCs, the feedback and preceptorship of student volunteers, interprofessional involvement, and educational credit associated with volunteer time in the SRFCs.

Study Design: The 139 pharmacy schools registered with American Association of Colleges of Pharmacy (ACCP) were polled to determine if they were associated with a SFRC or not. Those that were associated with a SFRC were asked to respond to a 29-questionnaire survey using Qualtrics Survey Software. Follow-up emails and calls were sent to schools that did not respond.

Results: There were 45 survey respondents (32% response rate), with 29 schools responding that they did not have a SRFC while 16 of the schools were associated with one or more SFRCs. The roles of student pharmacists in SRFCs were variable and included point-of-care-testing, health screenings, and vaccine administration. Seven (44%) of the schools offered medication therapy management services. Twenty-four (83%) of the respondents had pharmacy students involved in administrative or leadership roles. The majority (81%) of respondents stated that their SRFC involved other health care professional students and preceptors. Fifty percent of schools that responded described the care provided by pharmacy students to be interprofessional in nature for more than 50% of their time spent in clinic. From the student perspective, the most common benefits of involvement were applying clinical knowledge and interacting with interprofessional students. Students most commonly received feedback from preceptors via interprofessional huddles, during downtime, and electronically (especially in regards to documentation).

Conclusions: SRFCs allow a unique opportunity for pharmacy students to take on leadership opportunities in an interprofessional environment. There appears to be variability in amount of time spent interacting with students from other professions. Therefore, the design of care teams and clinic flow in SRFCs should be intentional to maximize engagement in interprofessional work. The results of this study demonstrate the potential benefits that pharmacy schools may experience when they have an established partnership with a SFRC.

Key Point: SRFCs allow a unique opportunity for pharmacy students to take on leadership opportunities in an interprofessional environment and are an important resource to local communities.
Specialty Pharmacy and Specialty Clinic Collaboration in Treatment of Hepatitis C

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**Background:** An estimated 2.7 to 3.9 million people in the United States are living with chronic Hepatitis C virus (HCV) infection, per the Center for Disease Control and Prevention, many of whom are asymptomatic and unaware. Additionally, HCV is the leading cause of liver transplant and liver cancer in the United States. FDA approval of various second generation direct-acting antivirals (DAAs) for the treatment of HCV and their incorporation into current infectious disease and hepatic disease guidelines have changed the landscape of treating this disease. Minimal toxicities and high rates of achieved sustained virologic responses (SVRs) make this class of agents optimal for clinical use. Pharmacists, as one of the most accessible healthcare professionals, have a great opportunity to identify patients for screening. Furthermore, pharmacists can help navigate prescription coverage issues, drug-drug interactions, and offer close monitoring of patients who are subsequently treated for HCV.

**Methods:** A recent descriptive, retrospective study analyzed 364 patients in a single-center hepatology clinic who used the therapy management program at a local specialty pharmacy (LSP) and assessed the time to therapy (TTT) and rates of achieved SVRs. The definition of TTT is the number of days between the initial prescribing of the DAA and when the patient took his/her first dose. The review also evaluated the effects of the LSP’s financial assistance intervention on the out-of-pocket costs to the patients filling at the LSP. In this model, the LSP obtained a thorough medication history from the patient and developed a plan for managing pharmacist identified drug-interactions with the prescribed DAA, prior to initiating the medication. The LSP managed the prior authorization process and appeals as well as explored other financial assistance programs available for patients with copays greater than $20. Additionally, they recorded the start date of the medications, called with refill reminders seven days prior to the due date, and screened for adverse effects monthly while the patient was on the therapy. If any concerning adverse effects were identified, the LSP contacted the hepatology clinic to determine the appropriate course of action. Lastly, the LSP verified when a full treatment course was completed and helped determine when viral loads should be obtained. As dictated by insurance requirements, some patients were required to fill their DAAs outside of this LSP and copay assistance was not performed for these patients.

**Outcomes:** Using intention-to-treat analysis, the rates of SVR among all patients was 86.8%. However, 27 (7.4%) patients did not complete a full course of therapy; 15 of whom were lost to follow up and 12 of whom died prior to completion. Excluding the patients who did not complete a full course of DAA therapy, the rates of achieved SVR increased to 93.8%. The average TTT was 12 ± 18 days with a maximum of 86 days. Among the subgroup whose prior authorizations were approved upon first submission, the average TTT was seven days. Copay assistance was conducted by the LSP for 42.8% of patients. Among this group, 95.5% were able to reach a copay of $5 or less after the pharmacy intervention.

**Discussion:** The results of this study showed comparable rates of achieved SVR to DAA clinical trials data among a “real-world” patient population in a hepatology clinic. However, this study decreased TTT significantly from prior reviews where average TTT ranged from 18 to 31 days. Prior studies had varying rates of pharmacy intervention, some of which had none at all. Therefore, this study demonstrates that collaborating with a specialty pharmacy can impact the clinical outcomes of patients with HCV infection by achieving high rates of SVR with decreased TTT. Secondly, this study was able to quantify the effects of copay assistance among patients who were able to use this benefit. Analyzing the outcomes of copay assistance is unique to this study as compared to prior reviews. Further analysis would be warranted in terms of a similar program based out of a primary care clinic setting as well as the impact a non-specialty pharmacy team could make on these outcomes.

**Medication Management in Minnesota schools: A Unique Partnership Opportunity**

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**Background:** In 2012, nearly 10 million children nationwide experienced a health problem that required a prescription medication for at least 3 months. Ideally, these prescriptions would be managed at home (e.g. before and after school). However, a large responsibility falls on school nurses when medications are required to be administered during the school day. The National Center for Health Statistics reported that selected prescription drug classes used in the past 30 days for those younger than 18 years from 2009 to 2012 included: bronchodilators, leukotriene modifiers, respiratory inhalant products, psychostimulants, and antidepressants. School nurses are responsible for...
increasingly complex medication management (MM) and administration in schools.

**Objectives:** The purpose of this study was to assess the MM needs of school nurses in Minnesota and determine if opportunity exists for collaboration between nurses and pharmacists to optimize MM for students.

**Methods:** The University of Minnesota (UMN) College of Pharmacy researchers partnered with the School Nurses Organization of Minnesota (SNOM) and the Minnesota Department of Health to conduct a 32-item online survey. The survey was created with the use of the Qualtrics system sponsored by UMN and consisted of the following question types: demographic, yes or no, rank order, open-ended, and defined selection options. A link to the online survey was distributed to the SNOM listserv via email. The email is estimated to have reached 200 SNOM members. Respondents received a gift card for participation.

**Results:** A total of 155 survey responses (77% response rate, estimated) were submitted. Minnesota nurses administered the majority of medications at their school (70%) compared with unlicensed assistive personnel (29%). Similar to national statistics, stimulants (38%) and asthma medications (26%) were the most common classes of medications administered in Minnesota schools; others included over-the-counter analgesics (18%) and insulin (7%).

The top MM concerns included 1) availability of students’ medications and required documentation, 2) health literacy, 3) pharmacist consultations, 4) lack of time available for nurses to follow up with and evaluate students, 5) family-centered care, 6) delegation, 7) communication, and 8) professional development. The main barriers identified included delayed ordering or transport; missing prescriber or parent documentation; lack of care coordination among multiple providers; and lost, stolen, or diverted medications from students transporting medication to school.

Most of the nurses expressed interest in interprofessional partnerships with pharmacists: 90% reported that a pharmacist could assist them with MM, 80% would consult with a pharmacist if one were available, and 12% had informal access to a pharmacist. Topics that nurses anticipated discussing with a pharmacist included new medications (72%), drug-drug interactions (67%), proper administration (52%), and storage (39%). However, nurses emphasized a need for better understanding among pharmacists of school nurse practice and the potential benefits of interprofessional MM.

**Conclusion:** While a clear majority of school nurses were interested in partnering with pharmacists to improve school MM, few had an established collaboration to do so. Results from this study indicate opportunity exists for collaboration between school nurses and pharmacists. Interprofessional partnerships focused on MM and education were the most requested pharmacy services by school nurses. While the results from this study were helpful, the authors discussed the need for future studies to incorporate the survey results into practice.

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**The First Pill Goes Digital: Abilify MyCite ®**

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This past November, the first digital pill was approved by the FDA. The antipsychotic, aripiprazole, which is approved for acute manic and mixed episodes of bipolar I disorder, schizophrenia, and as adjunctive treatment for major depressive disorder, will be manufactured as Abilify MyCite®. Abilify MyCite®'s embedded sensor will allow for patients and clinicians to track when a pill was ingested.

The sensor within the pill contains magnesium and cuprous chloride which is activated upon contact with gastric fluids. It signals to a skin patch worn on the patient’s abdomen. The skin patch then sends a signal to a patient’s cell phone app when it is time for a dose and if it is not taken. Patients may allow their healthcare providers and others access to the pill tracking information on a website.

There is not currently evidence that this technology will increase adherence. Critics have commented that patients with paranoia may already have fears of being tracked; although others argue that these patients build a trusting relationship with their clinician and may find benefit in pill-tracking technology to improve medication adherence.

A small feasibility study with Abilify MyCite® in 28 people with mild bipolar disorder or schizophrenia showed no increase in psychoses exacerbations. Overall, 21 of the 27 participants who completed the study agreed that...
they would like to receive reminders on their phones if they missed a dose, 24 agreed the technology could be useful to them, and 19 thought the technology was easy to understand.

The manufacturers, Proteus Digital Health, Inc and Otsuka Pharmaceutical, aim for a limited roll-out to gauge feedback for this new product. Some speculate this could be the next disruptive technology: could this become the mainstay of medication use in the future?

Center for Disease Control and Prevention’s Yellow Book: What is new in 2018?23-28
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Every two years, the Centers for Disease Control and Prevention (CDC) updates the CDC Health for International Travel, commonly called the Yellow Book. It serves as a reference for health professionals providing care to international travelers. The 2018 update, recently released online and in print, provides updates on travel vaccinations, antibiotic recommendations for traveler’s diarrhea, special consideration for unique types of travel, and the latest information about emerging infectious disease threats such as Zika, Ebola, and Middle Eastern respiratory syndrome (MERS).

The oral cholera vaccine (Vaxchora®) is now recommended to be given to adult travelers age 18-64 who are traveling to an area of active cholera transmission. Vaxchora® is a live oral vaccine, and has not been studied in immunocompromised patients. Patients also on antimalarial prophylaxis with chloroquine should start taking chloroquine 10 days after the administration of Vaxchora® due to decreased response to the vaccine if chloroquine is started sooner than 10 days after Vaxchora® administration. Antibiotics may also decrease the immune response to Vaxchora®, so the vaccine should not be given to patients who have received antibiotics in the previous 14 days. Vaxchora® may be shed in the stool for at least seven days, and the vaccine strain may be transmitted to unvaccinated close contacts. Clinicians and travelers should use caution when considering whether to use the vaccine in people with immunocompromised close contacts.

Recommendations for traveler’s diarrhea and antibiotic use were also updated. Prophylactic antibiotics should not be recommended for most travelers. The CDC does state, however, that prophylactic antibiotics can be considered in patients who are high-risk hosts, such as those who are immunosuppressed or who are taking critical trips (such as engaging in a sporting event) without the opportunity for time off in the event of sickness. This recommendation was updated due to increasing evidence of resistance of bacterial pathogens to prophylactic antibiotics and association with allergic and adverse reactions.

Several different categories of travel were updated to provide more specific guidance to travelers. Specifically, the section on “Traveling with Infants and Children” saw significant updates around cooking food and safe consumption of various food groups during travel. Emerging diseases like Zika, Ebola, and MERS also saw significant updates as evidence is becoming available regarding threats. Finally, additional travel destination specific recommendations for Cuba and Burma were added in the 2018 update.

New Drug Updates

Semaglutide (Ozempic®) - Novo Nordisk29-30
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**Indication:** Semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

**Mechanism of Action:** Semaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist that reduces fasting and postprandial blood glucose by stimulating insulin secretion and inhibiting glucagon secretion. By selectively binding to and activating the GLP-1 receptor, there is also a minor delay in gastric emptying in the early postprandial phase. Semaglutide has a long half-life due to albumin binding, which results in decreased renal clearance and protection from metabolic degradation.

**Dosage and Administration:** Semaglutide is a subcutaneous injection used in the abdomen, thigh, or upper arm. The dose starts at 0.25 mg once weekly for the first four weeks, then increases to 0.5 mg once weekly thereafter. The dose can be increased to a maximum of 1 mg once weekly if additional glycemic control is needed after four weeks of the 0.5 mg weekly dosage. Semaglutide can be administered at any time of day, with or without meals. If a dose is missed, it is recommended to administer within five days of the missed dose.
Effectiveness:

Monotherapy: In a 30-week double-blind trial, 388 patients with T2DM inadequately controlled with diet and exercise were randomized to semaglutide 0.5 mg or semaglutide 1 mg or placebo once weekly. The mean changes from baseline to week 30 compared to placebo for Hemoglobin A1c (HbA1c) were -1.2% for the 0.5 mg dose and -1.4% for the 1 mg dose. The mean changes from baseline to week 30 compared to placebo for weight were -2.6 kg for the 0.5 mg dose and -3.5 kg for the 1 mg dose.

Combination with metformin and/or sulfonylurea: In a 56-week open-label trial, 813 patients with T2DM on one to two oral antidiabetic medications (metformin, sulfonylurea, or thiazolidinedione) were randomized to semaglutide 1 mg or exenatide 2 mg once weekly. Treatment with semaglutide resulted in a statistically significant -0.5% HbA1c improvement compared to exenatide.

Safety:

Adverse effects: Hypoglycemia, abdominal pain, constipation, diarrhea, nausea, vomiting

Serious adverse effects: Medullary thyroid carcinoma, pancreatitis, diabetic retinopathy

Contraindications: Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2

Place in Therapy: Semaglutide 0.5 and 1 mg subcutaneous weekly injections as monotherapy or in combination with other antihyperglycemic therapies significantly improved HbA1c compared with placebo or active antihyperglycemic comparators, including weekly exenatide 2 mg subcutaneous injections. Fasting plasma glucose, percentage of patients attaining HbA1c less than 7%, and weight were also improved versus comparator groups. Per the 2018 American Diabetes Association Standards of Medical Care in Diabetes, metformin is still regarded as the first-line therapy of choice. Semaglutide, and other GLP-1 agonists, can be recommended second-line or as add-on therapy to metformin.

Cardiovascular and Renal Benefits: The SUSTAIN-6 clinical trial in patients with T2DM and high cardiovascular risk showed that once-weekly semaglutide 0.5 mg or 1 mg in addition to standard care was non-inferior and superior to placebo with regard to a reduction in major adverse cardiovascular events after 105 weeks of therapy. In this study, there was also a significant 23% absolute reduction in the risk of new or worsening nephropathy with semaglutide compared with placebo.

References


12. Brook RD, Rajagopalan S. 2017


