PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XL / February 2019/ Number 2 www.alertpubs.com

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Pediatric Varenicline Use

Steadily increasing rates of e-cigarette use by adolescents have led to renewed interest in the role of drugs and behavioral therapies for the treatment of nicotine addiction in young patients. Although approved for use in adults, the safety and efficacy of varenicline (*Chantix*) in pediatric patients was not established at the time of approval. Under the Pediatric Research Equity Act, Pfizer was required to study the drug in pediatric patients. Results of a placebo-controlled trial in patients aged 12–16 years indicate that varenicline does not significantly increase abstinence rates in adolescents who smoke. As a result, The FDA has ruled that varenicline should not be used for smoking cessation in patients aged <16 years.

Smoking Cessation Drug Not for Kids, FDA Says. Medscape Medical News February 25, 2019. Available at https://www.medscape.com/viewarticle/909468.

Generic Advair Diskus

The FDA recently approved the first generic formulation of *Advair Diskus* (fluticasone propionate and salmeterol inhalation powder). The combined drug/inhaler device is indicated for the treatment of asthma and chronic obstructive pulmonary disease. The generic version will be available in 3 strengths: 100, 250, and 500 mcg fluticasone each combined with 50 mcg salmeterol.

FDA News Release: FDA approves first generic Advair Diskus. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630151.htm.

ACE Inhibitors and Lung Cancer Risk

According to the results of a population-based cohort study, use of angiotensin-converting enzyme inhibitors is associated with an increase in lung cancer risk.[1]

Methods: The study cohort included nearly 1 million patients registered with the U.K. General Practice Datalink who were newly prescribed an antihypertensive drug after 1994. Those with a history of any cancer diagnosis other than non-melanoma skin cancer were excluded from the analysis. Patients receiving angiotensin receptor blockers (ARBs) were the main comparison group because these drugs are recommended for the same disease stage as ACE inhibitors. Incident lung cancer diagnosis was the primary outcome, and patients were followed through the end of 2016 (mean duration, 7.4 years).

Results: At cohort entry, patients had a mean age of 56 years and 45% were current or past smokers. A total of 21% of patients were prescribed an ACE inhibitor, 1.6% an ARB, and 77.4% another antihypertensive. During follow-up, there were 7952 new cases of lung cancer for an overall incidence of 1.3 per 1000 person-years. Incidence rates were 1.6 and 1.2 per 1000 person-years, respectively, in patients taking ACE inhibitors and ARBs (hazard ratio,* 1.14; see table, next page). ACE inhibitor use for <5 years was not associated with excess risk, but longer durations were, with hazard ratios of 1.22 for 5–10 years of use and 1.31 for

Primary Care Drug Alerts® (ISSN 1559-5668) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: donna@alertpubs.com. Subscription $105.00 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Individual issues are available for $10.00 each. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

>10 years of use. Smoking status did not significantly modify the association between ACE inhibitors and lung cancer risk.

Incident Cases of Lung Cancer in Patients Receiving ACE Inhibitors or ARBS			
Exposure	**# of Events**	**Person Years of Follow-up**	**Incidence Rate**
ACE Inhibitors	3186	1,977,139	1.6
ARBs	266	213,557	1.2

Discussion: The association between ACE inhibitors and lung cancer is biologically plausible: ACE inhibitors cause an accumulation of bradykinin in the lung, which may stimulate the growth of cancer cells, and the accumulation of substance P, which has been associated with tumor proliferation and angiogenesis. Previous studies of lung cancer risk in ACE inhibitor users have had inconsistent results and were flawed by small sample size, short follow-up durations, and various biases. Although the magnitude of excess risk found in the present analysis is small, the effects could translate into a large absolute number of patients at risk, given the prevalent use of ACE inhibitors. However, excess lung cancer risk should be balanced against the gains in life expectancy associated with use of ACE inhibitors in individual patients.[2]

[1]Hicks B, et al: Angiotensin converting enzyme inhibitors and risk of lung cancer: a population based cohort study. *BMJ* 2018; doi 10.1136/bmj.k4209. From Jewish General Hospital, Montreal,Canada; and other institutions. **Funded by the Canadian Institutes of Health Research. One of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Cronin-Fenton D: Angiotensin converting enzyme inhibitors and lung cancer. Any extra risk must be balanced against the mortality benefits of ACEI use [editorial]. *BMJ* 2018; doi 10.1136.bmj.k4337. From Aarhus University,Denmark. **The author declared no competing interests.**

***See Reference Guide.**

Febuxostat Boxed Warning

A large post-marketing safety study in >6000 patients with gout found that compared with allopurinol, patients treated with febuxostat had increased risk of all-cause and heart-related death. In the study, febuxostat was associated with 15 heart-related deaths per 1000 patients treated for 1 year, compared with 11 for allopurinol. Similarly, febuxostat was associated with more all-cause deaths: 26 vs 22 per 1000 patients treated for 1 year. As a result, the FDA will now require a Boxed Warning in the labeling for febuxostat, and prescribers are advised to reserve its use for patients in whom allopurinol is ineffective or intolerable.

FDA Drug Safety Communication: FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat). Available at https://www.fda.gov/Drugs/DrugSafety/ucm631182.htm.

Common Drug Trade Names*: allopurinol—*Zyloprim*; febuxostat—*Uloric

Anticoagulants, PPIs, and GI Bleeding

Upper GI bleeding is a frequent and serious complication of oral anticoagulation. Results of a retrospective cohort study indicate that risk is highest with rivaroxaban and lowest with apixaban. In addition, bleeding risk is reduced in patients receiving concomitant proton pump inhibitor (PPI) therapy.

Background: Non-vitamin K oral anticoagulants (NOACs) are at least as effective as warfarin in preventing strokes, but their comparative risks of inducing upper GI bleeding have not been compared in large clinical trials.

Methods: The study cohort consisted of U.S. Medicare patients who received a first prescription for an oral anticoagulant from January 2011 through September 2015. Patients receiving edoxaban were excluded because too few initiated treatment with the drug during the study period. Exposure was defined as filling ≥1 prescription for apixaban, dabigatran, rivaroxaban, or warfarin; concomitant users of multiple anticoagulants were also excluded. The exposure period was the number of days covered by the prescription, plus an additional 3 days for warfarin. The primary study outcome was hospitalization for any upper GI tract bleeding considered potentially preventable by PPI therapy.

Results: The cohort included >1.7 million episodes of anticoagulant treatment in >1.6 million patients (mean age, 76 years). The indication for anticoagulation was atrial fibrillation in 75% of cases. Regardless of concomitant PPI therapy, the overall risk of an upper GI bleed was lowest with apixaban and higher with rivaroxaban than with warfarin or dabigatran.

Concomitant PPI therapy reduced the overall risk of an upper GI bleed by one-third (incidence rate ratio,* 0.66). For each individual anticoagulant, risk was substantially reduced in patients also receiving a PPI. (See table.) Risk reduction with a PPI was most pronounced with dabigatran and least pronounced with rivaroxaban.

Incidence of hospitalization for upper GI bleeding for oral anticoagulants with and without PPI therapy		
Anticoagulant	**Adjusted incidence per 10,000 person-years**	
	No PPI	**Concomitant PPI**
Apixaban	73	49
Dabigatran	120	59
Rivaroxaban	144	108
Warfarin	113	74

Discussion: The present study confirms the suggestion from previous observational studies that risks differ between individual NOACs. The study results are consistent with the observation that rivaroxaban, which is taken once daily, results in higher peak concentrations, leading to increased bleeding risk. PPIs may have a particularly large protective effect with dabigatran because they lessen the direct GI mucosal injury that this drug's formulation may cause.

Ray W, et al: Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA* 2018;320 (December 4):2221–2230. doi 10.1001/jama.2018.17242. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by National Heart, Lung, and Blood Institute; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: **apixaban—*Eliquis*; dabigatran—*Pradaxa*; edoxaban—*Savaysa*; rivaroxaban—*Xarelto*; warfarin—*Coumadin***

***See Reference Guide.**

Medication for Cannabis Withdrawal

In a small placebo-controlled trial, the investigational drug PF-04457845 reduced withdrawal symptoms and cannabis use in men seeking treatment for cannabis dependence.

Background: Cannabis use disorder is associated with long-term adaptive changes to the endocannabinoid system, and substitution therapy with THC (δ-9-tetrahydrocannabinol), which creates a state of controlled dependence, has little effect on relapse prevention. An alternative approach to treatment is to potentiate endocannabinoid function by increasing concentrations of primary endocannabinoids. The investigational agent PF-04457845 inhibits fatty acid amide hydroxylase (FAAH), an enzyme that degrades the endocannabinoid anandamide. Drugs in this class offer a novel approach to treating cannabis use disorder by increasing levels of the endocannabinoid as cannabis itself is withdrawn.

Methods: The study enrolled self-referred men, aged 18–55 years, with varying levels of desire to discontinue cannabis use. Participants met criteria for cannabis dependence and had made ≥1 prior attempt to quit that was accompanied by withdrawal symptoms. Participants were admitted to an inpatient unit for 5–8 days to achieve abstinence. From the first day, they received randomly assigned 4 mg/day PF-04457845 or placebo. They were directly observed taking the medication while hospitalized and discharged with the remaining supply, with a smartphone app to monitor adherence. The study had multiple primary outcomes: cannabis withdrawal symptoms during the first 4 days of abstinence, measured using the Marijuana Withdrawal Checklist (MWC); and self-reported cannabis use and urinary THC metabolite (THC-COOH) concentrations at 4 weeks.

Results: By design, two-thirds of the 70 participants were assigned to active medication and one-third to placebo. A total of 8 patients dropped out of treatment with PF-04457845 and 4 dropped out from the placebo group. Medication adherence was 95% during the inpatient portion of the study and an estimated 88% after patients were discharged.

On the first 2 days of abstinence, scores on the MWC were significantly lower in the active treatment group than the placebo group ($p \leq 0.048$). Afterward, the 2 groups had similar symptom scores through the remaining inpatient days.

At baseline, the men were smoking an average of 3 joints per day. After 4 weeks, mean daily consumption was 0.4 in the PF-04457845 group

and 1.27 in the placebo group (p=0.0003). Urine concentrations of THC-COOH were higher in the placebo group than the group receiving active treatment. Exploratory analyses also found PF-04457845 reduced self-reported depression, anxiety, and irritability and improved sleep. Adverse events were mild and did not differ between the active medication and placebo.

Discussion: BIA 10-2474, another FAAH inhibitor, was withdrawn from development because of serious adverse events, including 1 death, that occurred in a clinical trial. The FDA had determined this to be a unique toxicity that does not extend to other drugs in this class. The positive effects and apparent safety of PF-04457845 suggest further study of endocannabinoid modulation via FAAH inhibition for the treatment of cannabis use disorder may be warranted.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

D'Souza D, et al: Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. *Lancet Psychiatry* 2019; doi 10.1016/S2215-0366(18)30427-9. From the VA Connecticut Healthcare System, West Haven; and other institutions. **Funded by the U.S. δ-9-tetrahydrocannabinol National Institute on Drug Abuse. Five of 17 study authors declared potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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Primary Care Drug Alerts 2018 Volume XXXIX.

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