PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Aneurysm Risk with Fluoroquinolones

Fluoroquinolone antibiotics were associated with a 66% increase in risk of aortic aneurysm or dissection in a large cohort study. The risk increase is probably the result of degradation of collagen and related processes, as outlined in a boxed warning in the labeling for the drugs.

Background: Fluoroquinolones were initially observed to increase risk of Achilles tendon rupture and tendinopathy. The agents induce degradation of collagen by stimulating the activity of matrix metalloproteinases, reducing production of new collagen and inducing oxidative stress. Observational studies have suggested a >2-fold increase in aneurysm risk with fluoroquinolones.

Methods: The study was based on nationwide data from Swedish healthcare, demographic, and death-certificate registries. Potential subjects were adults who received a prescription for a fluoroquinolone or amoxicillin in 2006–2013. Amoxicillin, the comparator, is prescribed for similar indications as fluoroquinolones and has no known association with aneurysms. Each fluoroquinolone prescription was propensity score matched* for 47 covariates with an amoxicillin prescription, resulting in 360,088 matched pairs of exposures. Rates of the primary study outcome—a first diagnosis of aortic aneurysm or dissection requiring hospitalization or resulting in death occurring in the 60 days following antibiotic initiation—were compared across the groups.

Results: During the 60-day risk period, there were 64 cases of aortic aneurysm or dissection in patients exposed to fluoroquinolones and 40 cases among those exposed to amoxicillin (1.2 and 0.7 cases per 1000 person-years, respectively). The hazard ratio* for aortic aneurysm with fluoroquinolones was 1.66, which corresponded to an absolute increase of 82 cases per 1 million treatment episodes in the 60-day risk period.

In secondary analyses, risk was increased with fluoroquinolones for the outcome of aortic aneurysm but not for aortic dissection. Fluoroquinolones did not increase risk of death. When the 60-day risk period was divided into 10-day spans, the first 10 days were the peak risk period, with 26 aneurysms in the fluoroquinolone group and 9 in the amoxicillin group. Risk of aneurysm or dissection was not increased with fluoroquinolones between 60 and 120 days after exposure.

Discussion: The present study, which used an active control and propensity score matching to address the limitations of previous observational studies, resulted in a less pronounced but still significant risk estimate. The risk increase is most pronounced in the first 10 days, when treatment is active, which suggests the mechanism is acute and wanes with treatment discontinuation.

Pasternak B, et al: Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018; 10.1136/bmj.k678. From the Karolinska Institutet, Stockholm, Sweden; and other institutions.
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***See Reference Guide.**

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Cardiac Safety of Smoking Cessation Agents

In a large trial in a general population of smokers, smoking cessation medications were not associated with cardiovascular risk.

Background: Early clinical trials of bupropion and varenicline did not show excess risk of cardiovascular events in treated patients. However, in 2011 the FDA mandated that smoking-cessation medications carry warnings of possible cardiovascular events in smokers with established cardiovascular disease. Findings of subsequent studies were mixed, and the FDA mandated the extension of a large clinical trial to monitor cardiovascular safety.

Methods: Participants in the original multinational study were adults, aged 18–75 years, who smoked ≥10 cigarettes per day and wanted to quit. Those with recent clinically significant cardiovascular or cerebrovascular disease were excluded. Randomized treatment, provided for 24 weeks in a triple-dummy fashion, consisted of 1 mg varenicline b.i.d., 150 mg bupropion b.i.d., a nicotine-replacement patch as an active control, or placebo. Patients were invited to participate in the extension study regardless of whether they stopped study medication prematurely, as long as they remained in follow-up throughout the 24-week trial. During the nontreatment extension, patients were evaluated in the clinic every 4 weeks up to week 52. The primary outcome was time to a major adverse cardiovascular event (i.e., cardiovascular death, nonfatal MI, or nonfatal stroke). The incidence of these events was compared during treatment, during the 30 days after completion, and at 1 year.

Results: More than 8000 patients received randomized medication or placebo in the original 24-week study. Their average age was 46 years, 44% were men, and about half had a neuropsychiatric disorder. Between 77% and 79% of each treatment group completed the 24-week trial, and 56% of the original cohort enrolled in the extension trial. Of this group, 90% completed the additional half year of follow-up. Patients were exposed to medication (or placebo) for an average of about 74 days.

Major adverse cardiovascular events were infrequent, occurring in <0.5% of all groups. Overall there were 14 nonfatal MIs, 8 nonfatal strokes, and 5 cardiovascular deaths. The groups also did not differ in time to major adverse cardiovascular event or a composite outcome consisting of a major adverse cardiovascular event plus new-onset or worsening peripheral vascular disease requiring treatment, coronary revascularization, or hospitalization for unstable angina. Results of the analysis did not differ for each of the 3 observation periods or in patients in low, medium, or high baseline cardiovascular risk categories.

Discussion: Participants in the present study were in generally good health and representative of the population of smokers in general medical practice. No evidence was found in these patients that smoking-cessation agents increase the risk of serious cardiovascular events during or after treatment. In addition, the number of adverse cardiac events that did occur was small and the incidence of serious events was low, suggesting that any absolute increase in risk is low and not clinically meaningful.

Benowitz N, et al: Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.0397. From the University of California, San Francisco; and other institutions. **Funded by Pfizer; and GlaxoSmithKline. All 9 study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

Common Drug Trade Names*: bupropion—*Zyban*; nicotine patch—*Nicoderm*; varenicline—*Chantix

Fostamatinib for Thrombocytopenia

The first-in class spleen tyrosine kinase inhibitor fostamatinib has received FDA approval for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) that has not been sufficiently responsive to previous treatment including steroids, platelet production boosters, or splenectomy.[1] Fostamatinib, which targets the underlying autoimmune cause of ITP by impeding platelet destruction, is expected to be available in late May 2018.

Common adverse reactions to fostamatinib in clinical trials included diarrhea, nausea, dizziness, rash, and neutropenia. The agent can induce hypertension, and patients with preexisting hypertensive disorders may be more susceptible to BP increases. In patients with hypertension, BP should be monitored biweekly until stable, and then monthly. Elevations in liver enzymes (primarily alanine aminotransferase, aspartate aminotransferase) were also reported; liver function should be evaluated monthly during treatment. Because of the risk for neutropenia

with treatment, absolute neutrophil counts should also be monitored monthly. Fostamatinib should not be used by pregnant or breastfeeding women. Interactions are possible with strong CYP3A4 inhibitors (e.g., clarithromycin) or inducers (e.g., carbamazepine), CYP3A4 substrate drugs (e.g., simvastatin),[2] breast cancer resistance protein substrate drugs (e.g., rosuvastatin), and P-glycoprotein substrate drugs (e.g., digoxin).

[1]Rigel announces FDA approval of tavalisse™ (fostamatinib disodium hexahydrate) for chronic immune thrombocytopenia (ITP) in adult patients [press release]. South San Francisco, CA; Rigel Pharmaceuticals: April 17, 2018. Available at http://ir.rigel.com/phoenix.zhtml?c=120936&p=irol-newsArticle&ID=2343080.

[2]Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1.

Common Drug Trade Names*: clarithromycin—*Biaxin*; carbamazepine—*Carbatrol, Epitol, Tegretol*; digoxin—*Lanoxin*; fostamatinib—*Tavalisse*; rosuvastatin—*Crestor*; simvastatin—*Zocor

Trimethoprim Safety in Older Patients

Compared with other antibiotics, trimethoprim was associated with an increase in acute kidney injury and hyperkalemia in older patients receiving treatment for urinary tract infection (UTI), according to a large population-based study. In contrast to previous reports, trimethoprim was not associated with increased risk of sudden death overall or in patients also taking renin-angiotensin system antagonists.

Methods: Electronic medical records from the U.K.'s Clinical Practice Research Datalink were used to identify all patients aged ≥65 years who received a prescription for 1 of 5 commonly used antibiotics for a UTI between mid-1997 and late-2015. Episodes treated with co-trimoxasole were excluded because it is typically used to treat more severe infections. Study outcomes were acute kidney injury, hyperkalemia, and death within 14 days of antibiotic initiation. Rates of these outcomes were compared among patients who received trimethoprim, amoxicillin, cephalexin, ciprofloxacin, and nitrofurantoin, all considered first-line treatment for uncomplicated UTIs during the study years. The analyses were adjusted for an extensive list of covariates. Because evidence suggests that combined use of trimethoprim with renin-angiotensin system antagonists (e.g., ACE inhibitors and ARBs) may increase risk for severe and potentially life-threatening hyperkalemia, a separate analysis restricted to these patients was also conducted.

Results: Nearly 179,000 patients received antibiotics for a total of 422,514 UTI episodes. Trimethoprim was prescribed in 59% of infections, nitrofurantoin and cephalexin each in 15%, and the other antibiotics each in 5%. Within 14 days of antibiotic initiation, there were 1345 episodes of acute kidney injury, 648 episodes of hyperkalemia, and 2214 deaths. Patients who took each of the antibiotics had broadly similar clinical and demographic characteristics.

Trimethoprim was associated with the highest odds of kidney injury compared with amoxicillin, the reference drug (adjusted odds ratio,* 1.72) and of hyperkalemia (odds ratio, 2.27). Ciprofloxacin was also associated with increased risk of acute kidney injury (odds ratio, 1.48), but not hyperkalemia. Cephalexin and nitrofurantoin were not associated with either outcome, and no antibiotic conferred increased risk of death. When the analysis was restricted to patients taking renin-angiotensin system antagonists, risk comparisons were essentially unchanged.

Crellin E, et al: Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. *BMJ* 2018; doi 10.1136/bmj.k341. From the London School of Hygiene and Tropical Medicine. **Funded by the Wellcome Trust. The authors declared no competing interests.**

Common Drug Trade Names*: amoxicillin—*Moxatag*; cephalexin—*Keflex*; ciprofloxacin—*Cipro*; nitrofurantoin—*Macrodantin*; trimethoprim—*Primsol*; trimethoprim–sulfamethoxazole (co-trimoxazole)—*Bactrim

***See Reference Guide.**

Antidepressants: Comparative Efficacy

According to the results of a systematic review and network meta-analysis including 21 different antidepressants, several agents are significantly more effective than others. The analysis also identified differences in patient acceptability among the antidepressants .

Methods: The present analysis was based on randomized controlled trials comparing antidepressants with placebo or other antidepressants as oral monotherapy in adults with major depressive disorder. The primary efficacy outcome was response, defined as a ≥50% improvement in a standardized, observer-rated depression scale score. Acceptability was measured using the rate of withdrawal for any reason.

Results: A total of 522 controlled trials were identified with >116,000 patients enrolled. All medications were more effective than placebo at producing a response. (See table.) Relative to placebo, amitriptyline had the highest odds ratio* of response at 2.13. Odds ratios for other antidepressants compared with placebo ranged from 1.37 to 1.89, with wide confidence intervals. In head-to-head studies, several antidepressants were shown to be superior to others, with odds ratios ranging from 1.19 to 1.96: amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine. The least effective drugs in head-to-head comparisons were fluoxetine, fluvoxamine, and trazodone. Overall, antidepressants were also more effective than placebo at inducing remission (effect size,* 0.30; p<0.0001).

Antidepressant Response Relative to Placebo

Agent	Odds Ratio	Agent	Odds Ratio
Amitriptyline	2.13	Vortioxetine	1.66
Mirtazapine	1.89	Vilazodone	1.60
Duloxetine	1.85	Levomilnacipran	1.59
Venlafaxine	1.78	Bupropion	1.58
Paroxetine	1.75	Fluoxetine	1.52
Milnacipran	1.74	Citalopram	1.52
Fluvoxamine	1.69	Trazodone	1.51
Escitalopram	1.68	Clomipramine	1.49
Nefazodone	1.67	Desvenlafaxine	1.49
Sertraline	1.67		

Citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were significantly better tolerated than other drugs in comparative studies, with odds ratios for dropout ranging from 0.43 to 0.77. Amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine were associated with the highest dropout rates.

Discussion: The summary effect sizes for most antidepressants were relatively modest. However, several agents emerged as combining a relatively high response rate and a low dropout rate: escitalopram, mirtazapine, paroxetine, and sertraline.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Cipriani A, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; doi 10.1016/S0140-6736(17)32802-7. From the University of Oxford, U.K.; and other institutions. **Funded by the National Institute for Health Research Oxford Health Biomedical Research Centre; and the Japan Society for the Promotion of Science. Six of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Drug Trade Names: **amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; nefazodone—*Serzone*; paroxetine—*Paxil*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Brintellix***

***See Reference Guide.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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.