PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXIX / December 2018 / Number 12 www.alertpubs.com

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Fluoroquinolones and Aortic Dissection

Following a safety review, the FDA is requiring a new warning about risk for aortic dissection be added to the prescribing information and patient medication guide for all fluoroquinolone antibiotics. The review found both oral and injectable fluoroquinolone use can increase the occurrence of aortic dissections and ruptures of aortic aneurysms, which can lead to serious bleeding or death. Patients at increased risk include those with or at risk for an aortic aneurysm, those with hypertension, high blood pressure, or genetic disorders that involve blood vessel changes (e.g., Marfan syndrome and Ehlers-Danlos syndrome), and the elderly. Fluoroquinolones should not be prescribed for these patients unless there are no other treatment options available.

FDA Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. Available at www.fda.gov/Drugs/DrugSafety/ucm628753.htm.

Infants' Ibuprofen Recall

Tris Pharma has issued a recall for several lots of 50 mg per 1.25 mL infant's concentrated ibuprofen suspension. The affected lots, sold as Equate, CVS Health, and Family Wellness brands, may have higher than labeled ibuprofen concentrations. Adverse effects of increased ibuprofen doses can include nausea, vomiting, epigastric pain, and diarrhea. Tinnitus, headache, and gastrointestinal bleeding are also possible. Although permanent NSAID-associated renal injury is unlikely, infants—who may be more susceptible to a higher potency level of drug—may be more vulnerable.

FDA Drug Safety Communication: Tris Pharma issues voluntary nationwide recall of infants' ibuprofen concentrated oral suspension, USP (NSAID) 50 mg per 1.25 mL, due to potential higher concentrations of ibuprofen. Available at www.fda.gov/Safety/Recalls/ucm627780.htm.

Gabapentin Abuse

A 51-year-old man with a history of substance-induced mood disorder, as well as opioid, cocaine, and alcohol use disorders, presented to the emergency department following an intentional gabapentin overdose with suicidal intent. His regular medication regimen included sertraline, divalproex, trazodone, and gabapentin. Review of his medication use suggested a pattern of gabapentin abuse characterized by overuse and requests for the medication from different physicians on varying pretexts. On questioning, the patient admitted that for ≥9 months he had been crushing and insufflating 3–4 600-mg gabapentin tablets at 2-hour intervals in bingeing episodes. He described the "high" he achieved as characterized by increased focus, energy, and productivity, followed by a calm/relaxation similar to opioid intoxication. Abrupt discontinuation resulted in withdrawal symptoms. The patient denied misuse of his

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.

other psychotropic medications, and a urine screen for illicit drugs was negative.

Gabapentin is widely used off label as adjunctive treatment for several psychiatric disorders including bipolar disorder, anxiety, PTSD, and depression. It has also shown potential for treatment of withdrawal and craving in alcohol, benzodiazepine, opioid, and cocaine dependence. The drug is well tolerated, has few interactions with other drugs, and is relatively inexpensive. Because it is presumed to have no abuse potential, it is currently not scheduled as a controlled substance. However, there have been other reports of gabapentin abuse and misuse, mainly among patients with a history of substance abuse and psychiatric comorbidity. The pharmacologic properties that underlie gabapentin's abuse potential are unknown. Increasing rates of diversion, comparable to those with oxycontin, have also been documented. Although the present patient denied "cutting" heroine or buprenorphine with gabapentin, there have been reports of gabapentin being used illicitly in combination with opioids and to potentiate the effects of buprenorphine–naloxone. Gabapentin misuse by patients with opioid use disorder is especially concerning, given the recent increases in opioid-related mortality and evidence linking gabapentin use with increased risk of accidental opioid-related overdose deaths. Prescribers should be aware of the potential for gabapentin abuse in at-risk populations and should closely monitor these patients.

Khalid Z, Hennen M-A, Aldana-Bernier L: Gabapentin abuse by nasal insufflation: a case report [letter]. *Journal of Clinical Psychopharmacology* 2018; doi 10.1097/JCP.0000000000000983. From Rutgers New Jersey Medical School, Newark; and VA NJ Healthcare System, East Orange. **The authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine–*Subutex*; naloxone—*Suboxone*; divalproex—*Depakene, Depakote*; gabapentin—*Neurontin, Gralise*; sertraline—*Zoloft*; trazodone—*Desyrel, Oleptro

Contraceptives and Ovarian Cancer

Combined hormonal contraceptives have been shown to reduce ovarian cancer risk; however, most evidence concerns older, relatively high-dose formulations. According to a population-based cohort study, the benefit extends to contemporary, lower-dose contraceptives and the risk reduction persists after discontinuation, although the length of time is not known.

Methods: Data were collected as part of the ongoing Danish Sex Hormone Register Study. The present analysis included all women aged 15–49 years between 1995 and 2014, excluding those with preexisting cancer, venous thrombosis, or infertility. The cohort of nearly 1.9 million women was followed until the occurrence of ovarian cancer or age 50 years. Women were categorized as current or recent users of hormonal contraceptives, former users (stopping ≥1 year ago), and never-users.

Results: A large majority of contraceptive use (86%) consisted of combined oral preparations. The remaining women used either non-oral combinations or progestogen-only products. There were 1249 incident cases of ovarian cancer, including 478 cases in women who had ever used a hormonal contraceptive. Risk of ovarian cancer was reduced in women who were currently using or had ever used hormonal contraceptives. (See table.) Risk reduction was evident in users of combined oral agents and, by a smaller margin, users of progestogen-only formulations. There was little evidence of important differences between combined oral contraceptives containing different progestogens.

Adjusted relative risk of ovarian cancer		
Use category	**Incidence**	**Relative risk***
Never use	7.5	1.00
Ever use	4.3	0.66
Former use	5.0	0.77

Relative risk of ovarian cancer was lower the longer that women used hormonal contraceptives, reaching a low point of 0.26 in women who had used the contraceptives for >10 years. Women who had stopped taking the contraceptives >10 years in the past had a similar level of risk reduction as women who stopped using them more recently. Protection appeared to wane more rapidly in women who discontinued contraceptives after shorter periods of use.

The investigators estimated that hormonal contraception prevented 21% of the ovarian cancers that would have occurred in this population.

Iversen L, et al: Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. *BMJ* 2018; doi 10.1136/bmj.k3609. From the University of Aberdeen, U.K.; and the University of Copenhagen, Denmark. **Funded by the Novo Nordisk Foundation. Three of 6 study authors disclosed financial relationships with commercial sources including Novo Nordisk; the remaining authors declared no competing interests.**

***See Reference Guide.**

Adverse Events with SGLT2 Inhibitors

In patients receiving second- or third-tier medication for type 2 diabetes, use of a sodium glucose cotransporter 2 (SGLT2) inhibitor was associated with increased risk of lower limb amputation and diabetic ketoacidosis, compared with use of a glucagon-like peptide 1 (GLP1) receptor agonist. Whether these adverse events are a class-wide effect of these drugs remains unknown.

Background: Previous clinical trials have demonstrated increased rates of lower limb amputation and bone fracture in users of SGLT2 inhibitors. There have also been reports of other serious adverse effects. Venous thromboembolism is a theoretical concern because these agents increase blood viscosity by inducing diuresis. There have been no previous large-scale, methodologically valid studies covering the entire spectrum of suspected adverse events of SGLT2 inhibitors.

Methods: The analysis used combined data from nationwide registers in Sweden and Denmark from July 2013 to December 2016. All patients aged ≥35 years who received a first prescription for an SGLT2 inhibitor were compared with patients who received a GLP1 receptor agonist. Patients from the 2 groups were individually matched with controls using a 66-item propensity score.* The primary outcomes were 7 adverse effects suspected to be associated with SGLT2 inhibitors: lower limb amputation, bone fracture, diabetic ketoacidosis, acute knee injury, serious urinary tract infection, venous thromboembolism, and acute pancreatitis.

Results: The study population consisted of >21,000 patients with a new prescription for an SGLT2 inhibitor and >27,000 patients given a GLP1 receptor agonist. Of those who received an SGLT2 inhibitor, 61% were prescribed dapagliflozin, 38% empagliflozin, and 1% canagliflozin. Patients given an SGLT2 inhibitor were older, more likely to be men and to use a dipeptidyl peptidase 4 (DPP4) inhibitor, and less likely have obesity or to require insulin. Propensity score matches were made for about 17,000 pairs of patients, resulting in 2 well balanced groups.

Among patients receiving an SGLT2 inhibitor, risks were significantly elevated for lower limb amputation (hazard ratio,* 2.32) and diabetic ketoacidosis (hazard ratio, 2.14). Risks of the other adverse events were not increased in SGLT2 inhibitor users. Subgroup analyses did not identify any clinical group in which risks differed from the population at large.

Discussion: The mechanisms associated with the potential adverse events are not known. Class-wide mechanisms that could explain some of the suspected associations include volume depletion, increased levels of phosphate, and non-insulin-dependent glucose lowering leading to diabetic ketoacidosis. However, an analysis of individual agents was not conducted and future research should evaluate each agent separately.

Ueda P, et al: Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ* 2018; doi 10.1136/bmj.k4365. From Karolinska University Hospital, Stockholm, Sweden; and other institutions. **Funded by the Swedish Heart-Lung Foundation; and other sources. Three of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: canagliflozin—*Invokana*; dapagliflozin—*Farxiga*; empagliflozin—*Jardiance

***See Reference Guide.**

Baloxavir Efficacy

A single dose of the newly-approved antiviral drug baloxavir reduced the duration of influenza symptoms as well as viral load in randomized, active- and placebo-controlled trials. Its mechanism of action distinguishes baloxavir from existing anti-influenza drugs, to which recent influenza strains are developing resistance.

Methods: A phase II trial, conducted in Japan, enrolled patients aged 20–64 years who were randomly assigned a single dose of baloxavir (10, 20, or 40 mg) or placebo. A phase III trial, conducted in Japan and the U.S., enrolled patients aged 12–64 years. Those aged ≥20 years received a single weight-based dose of baloxavir (40 or 80 mg), oseltamivir 75 mg b.i.d. for 5 days, or placebo. All adult patients in this study received a 5-day regimen, with placebos as appropriate. Patients aged 12–19 years received a single dose of baloxavir or placebo.

For both trials, patients were enrolled if they had been experiencing fever (axillary temperature, ≥100.4), ≥1 systemic symptom, and ≥1 respiratory symptom for ≤48 hours. Twice a day, patients rated the severity of 7 influenza symptoms on a 4-point scale. The primary study endpoint was alleviation of flu symptoms, defined as ratings of mild or absent for all 7 symptoms for ≥21.5 hours.

Results: A total of 389 patients completed the phase II study. The median time to symptom

alleviation ranged from 49.5 hours to 54.2 hours in the 3 baloxavir dosage groups, compared with 77.7 hours in the placebo group. All 3 dosage groups showed greater reductions than the placebo group in influenza virus titers on days 2 and 3.

A total of 1064 patients were included in the efficacy analysis of the phase III trial. The median time to alleviation of symptoms was 65.4 hours with baloxavir and 88.6 hours with placebo. Symptoms were alleviated 38.6 hours earlier with baloxavir than placebo in adolescents and 25.6 hours earlier in adults. The effects of baloxavir were greater in the 53% of patients who started treatment within 24 hours of symptom onset. The median time to symptom resolution was similar with baloxavir and oseltamivir. Baloxavir was associated with more rapid declines in viral load than oseltamivir or placebo.

Discussion: Baloxavir targets the viral polymerase complex that binds to the cap of host cell RNA as a step in transcribing viral messenger RNA. Several other agents in this category are in clinical development. Two other classes of antiviral drugs are widely available, but circulating influenza viruses are largely resistant to 1 class and developing resistance to the other. Viral variants with reduced susceptibility to baloxavir were detected in 2% of patients in the phase II trial and nearly 10% in the phase III trial. Nevertheless, baloxavir may provide an option for patients with infections caused by viruses resistant to other drugs.

Hayden F, et al: Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *NEJM* 2018;379 (September 6):913–923. From the University of Virginia College of Medicine, Charlottesville; and other institutions. **Funded by Shionogi. Thirteen of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: baloxavir marboxil—*Xofluza*; oseltamivir—*Tamiflu

Prucalopride for Constipation

The serotonin-4 receptor agonist prucalopride (*Motegrity*) has received FDA approval for the treatment of chronic idiopathic constipation in adults. The first serotonin agonist approved for the indication, prucalopride works by enhancing colonic peristalsis to increase bowel motility.

In clinical trials, significantly more patients taking prucalopride than placebo achieved normalization of bowel movement frequency. Response was rapid, in some cases as early as week 1, with improvement maintained over 12 weeks of treatment. In the trials, the most common adverse reactions were headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue. Suicides, suicide attempts, and suicidal ideation were also reported. Although a causal association with prucalopride has not been established, treated patients should be monitored for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Prucalopride is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, or severe inflammatory conditions of the intestinal tract (e.g., Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum). The manufacturer will be required to conduct postmarketing studies evaluating the pharmacokinetics, efficacy, and safety of prucalopride in pediatric patients and in pregnant and lactating women.

FDA approves Shire's Motegrity™ (prucalopride), the only serotonin-4 receptor agonist for adults with chronic idiopathic constipation (CIC) [press release]: Cambridge, MA; Shire: December 17, 2018. Available at www.shire.com/en/newsroom/2018/december/qmmwqk.

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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.

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.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.