PRIMARY CARE DRUG ALERTS

For Physicians and Nurses



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## Tofacitinib for Ulcerative Colitis

The first oral medication for chronic use in ulcerative colitis has received FDA approval. Previously approved agents were required to be administered via IV infusion or subcutaneous injection. Tofacitinib (*Xeljanz*) is now licensed to treat moderately-to-severely active disease in adults. Clinical efficacy and safety of the agent were demonstrated in clinical trials showing that short-term (8 weeks) treatment with oral tofacitinib could induce sustained, corticosteroid-free remission of ulcerative colitis in nearly half of patients. Common adverse effects of tofacitinib in clinical trials included: diarrhea; increased cholesterol levels; headache; herpes zoster; increased creatine phosphokinase levels; nasopharyngitis; rash; and upper respiratory tract infection. Although less common, serious adverse effects, including malignancy and opportunistic infections, did occur. Tofacitinib carries a boxed warning about the potential for serious infections and malignancy. Use of tofacitinib in combination with biological therapies for ulcerative colitis or with potent immunosuppressants is not recommended.

FDA News Release: FDA approves new treatment for moderately to severely active ulcerative colitis. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm609225.htm.

## Antibiotics and Kidney Stone Risk

Oral antibiotic therapy was associated with increased risk of kidney stones in a large population-based study. This finding may help explain the increase in incidence of nephrolithiasis that has occurred over the past 30 years.

***Methods:*** The study was based on electronic records of patients receiving care in general practices in the U.K. in 1994–2015. For each patient with a diagnosis of nephrolithiasis, 10 age- and gender-matched controls were selected from the same practice. The primary exposure was an outpatient oral antibiotic prescription 3–12 months before the index date. The 3-month lag was included to reflect the biology of kidney-stone formation following alterations in the urinary microbiome and to exclude antibiotics that might have been prescribed for kidney-stone symptoms. Data were analyzed for each of the 12 major classes of antibiotics and also for *H. pylori* treatment, which reduces intestinal colonization by *Oxalobacter* species.

***Results:*** The study included nearly 26,000 patients with nephrolithiasis and 260,000 controls (mean age, 51 years) observed for a median of >5 years. The most common reasons for outpatient antibiotic prescriptions were chest infection, cough, upper respiratory infection, tonsillitis, and urinary tract infection.

Risk of nephrolithiasis was significantly increased in the 3–12 months after exposure to 5 different classes of antibiotics: sulfas (odds ratio* [OR], 2.33); cephalosporins (OR, 1.88); fluoroquinolones (OR, 1.67); nitrofurantoin/methenamine (OR, 1.70); and broad-spectrum penicillins (OR, 1.27). Risk was also increased following antibiotic treatment of *H. pylori* (OR, 1.79), although this increase was not statistically significant in all of the statistical models applied. Antibiotic-associated risk was highest in patients exposed at younger age;

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the exact pattern of age-related risk varied with each antibiotic class. Risk was greatest for antibiotic exposure within 3–6 months of the diagnosis date, but risk was also statistically significantly higher for 3–5 years after exposure for the 5 antibiotic classes except broad-spectrum penicillins.

***Discussion:*** Antibiotics are suspected to increase risk of kidney stones by altering the intestinal and urinary-tract microbiome. Previous studies have shown that patients with kidney stones had reduced diversity of bacteria in the gut microbiome. It is likely that multiple gut organisms, acting as a community, mediate the association of antibiotics and nephrolithiasis.

Exposure to some oral antibiotics might explain the increase in the prevalence of nephrolithiasis, which has been most pronounced in children, adolescents, and young adults. Given that antibiotic use is highest in children, these findings provide another reason to reduce the prevalence of inappropriate prescribing.

Tasian G, et al: Oral antibiotic exposure and kidney stone disease. *Journal of the American Society of Nephrology* 2018; doi 10.1681/ASN.2017111213. From the Children's Hospital of Philadelphia, PA; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

***Common Drug Trade Names*: methenamine—*Hiprex*; nitrofurantoin—*Furadantin***

***See Reference Guide.**

## Flu Shot Recommendation

After reviewing efficacy data, the American Academy of Pediatrics (AAP) has announced they will recommend that families choose the inactivated influenza vaccine (flu shot) over the nasal spray vaccine when they vaccinate their children for the 2018–2019 flu season. The injectable formulation has been shown to be consistently more effective than the nasal spray over the past few flu seasons. Although the AAP will not release their formal policy statement until September, they have announced the decision early so that physicians can order an adequate supply of the injection. The nasal spray remains an option for children who could otherwise not be vaccinated.

AAP News Release: American Academy of Pediatrics advises parents to choose the flu shot for 2018-2019 flu season. Available at https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Advises-Parents-to-Choose-the-Flu-Shot-For-2018-2019-Flu-Season.aspx.

## ACE Inhibitors or ARBS in Diabetes

A meta-analysis found convincing evidence that angiotensin-converting enzyme inhibitors, but not angiotensin II receptor blockers (ARBs), prevented mortality and other adverse cardiovascular outcomes in patients with hypertension and type 2 diabetes.

***Methods:*** The analysis included randomized controlled trials, published since 2000, conducted in patients with both hypertension and type 2 diabetes. The endpoints of the included studies were all-cause mortality, cardiovascular mortality or events, MI, stroke, or heart failure. Additional study requirements were a sample size of >500, patient age >55 years, and >1 year of follow-up. For the meta-analysis, the primary outcomes were all-cause mortality and cardiovascular mortality.

***Results:*** A total of 13 studies were included in the analysis; 5 trials compared ACE inhibitors with placebo, 6 compared ARBs with placebo, and 2 compared ARBs with an active control drug. Study participants had a mean age of about 65 years and were followed for a mean of about 4 years.

ACE-inhibitor therapy was associated with significant reductions in all-cause and cardiovascular mortality, while ARBs were not. (See table.) ACE inhibitors were also associated with significant reductions in all of the secondary study outcomes—MI, stroke, heart failure, and all cardiovascular events—with odds ratios* ranging from 0.65 to 0.88. Risk reductions with ARBs for all of these events were not statistically significant.

**Effect of antihypertensive treatment on mortality outcomes in patients with type 2 diabetes**

| | All-cause mortality | | Cardiovascular mortality | |
|---|---|---|---|---|
| | Odds Ratio* | Significance | Odds Ratio | Significance |
| ACE Inhibitors (n=24,976) | 0.87 | p=0.0008 | 0.81 | p=0.03 |
| ARBs (n=22,032) | 1.06 | p=ns | 1.02 | p=ns |

***Discussion:*** These results differ somewhat from previous meta-analyses, which showed a beneficial effect of ARBs for several outcomes. The difference is likely the result of requiring a larger

sample size and limiting the present patient population to those aged >55 years with both hypertension and type 2 diabetes.

***Study Rating*—16 (89%):*** This study met most criteria for a systematic review/meta-analysis, but the source of funding was not disclosed.

Xiaodan I, et al: Comparison of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular outcomes in hypertensive patients with type 2 diabetes mellitus: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2018; doi 10.1097/MD.0000000000010256. From Shenyang Pharmaceutical University, China; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential competing interests.**

***See Reference Guide.**

## Antidepressants in Pediatric Anxiety

In children and adolescents with anxiety disorders, antidepressant-related improvements occur quickly and selective serotonin reuptake inhibitors (SSRIs) are associated with earlier and larger improvement than serotonin–norepinephrine reuptake inhibitors (SNRIs), according to the results of a meta-analysis.

***Background:*** SSRIs and SNRIs have both been recommended as first-line treatment of pediatric anxiety disorders. However, duloxetine is the only FDA-approved antidepressant for this indication, and it is unknown whether SSRIs are superior to SNRIs. The present meta-analysis was conducted to evaluate the trajectory of response to antidepressants in pediatric anxiety disorders and to compare the effects of drug class and dose.

***Methods:*** Studies were included if they were prospective, randomized, parallel-group, placebo-controlled trials that evaluated the efficacy of SSRIs or SNRIs in social, generalized, and/or separation anxiety disorder in patients aged ≤18 years. For inclusion, studies were required to use a standardized rating scale to measure anxiety symptoms. The primary outcome of the analysis was change from baseline in a standardized measure of anxiety for the active medication in comparison with placebo. Dose comparisons were based on fluoxetine equivalents of the labeled therapeutic range of each drug. Atomoxetine was included in the analysis because of its potent norepinephrine reuptake blockade and serotonin transporter inhibition.

***Results:*** The comprehensive literature search identified 9 studies conducted in 1805 patients, evaluating 7 different drugs: 4 SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, and sertraline) and 3 SNRIs (i.e., atomoxetine, duloxetine, and venlafaxine). The median study duration was 10 weeks. The Pediatric Anxiety Rating Scale was the outcome measure in all but 2 studies.

Overall, statistically significant differences between drug and placebo appeared at week 2 ($p=0.005$) and reached a clinically significant effect size* of 0.44 by week 6 ($p=0.001$). Both SSRIs and SNRIs were associated with statistically significant improvement, relative to placebo, at treatment week 2 and remained statistically superior to placebo up to week 12. SSRIs were superior to SNRIs beginning at week 2 ($p=0.026$) and continuing to week 12 ($p<0.03$ for all 2-week intervals). The results were essentially unchanged in a sensitivity analysis that excluded data from the atomoxetine trial. Industry-funded and government-funded studies had generally similar results. Low doses of SSRIs (<1.5 fluoxetine equivalents per day) were no less effective than higher doses overall, but high doses were associated with an earlier response.

***Discussion:*** These results suggest that SSRIs may be more effective than SNRIs against pediatric anxiety. It is possible that SSRIs could be superior because the serotonin system matures earlier than the noradrenergic system and may be a more available treatment target. In addition, SNRIs have class-specific tolerability concerns, including suicidality with venlafaxine. The study findings regarding dosage raise questions regarding the long-held belief that antidepressants should be titrated.

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

Strawn J, et al: The impact of antidepressant dose and class on treatment response in pediatric anxiety disorders: a meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2018;57 (April): 235–244. From the University of Cincinnati College of Medicine; and other institutions, OH. **Funded by the NIMH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*Common Drug Trade Names*: **atomoxetine—*Strattera*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor***

***See Reference Guide.**

## Generic Suboxone

The first generic versions of sublingual buprenorphine/naloxone have received FDA approval. This approval advances the FDA commitment to combating the opioid crisis by increasing access to the safe and effective medications needed for pharmacotherapy-assisted treatment of opioid dependence. Two generic versions will now be available; however, as with the branded version, prescribing is limited to physicians with Addiction Treatment Act (DATA)-certification.

FDA News Release: FDA approves first generic versions of Suboxone sublingual film, which may increase access to treatment for opioid dependence. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm610807.htm.

## Reference Guide

**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.

**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.

**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.

**"Change is the law of life and those who look only to the past or present are certain to miss the future."—John F. Kennedy**

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