PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Tofacitinib and Pulmonary Embolism

A safety study found a dose-related increase in risk of blood clots in the lungs and death in patients with rheumatoid arthritis receiving tofacitinib (*Xeljanz, Xeljanz XR*). Patients in the study were required to be aged ≥50 years and to have ≥1 cardiovascular risk factor. All received either 10 or 20 mg/day tofacitinib in divided doses or a TNF inhibitor. An external data safety monitoring committee found the increased occurrence of pulmonary embolism and death in patients treated with the 10 mg b.i.d. dosage, which is not FDA approved for rheumatoid arthritis. The 10 mg b.i.d. dosage is licensed only in the regimen for patients with ulcerative colitis. Prescribers are reminded to follow the recommendations in the tofacitinib prescribing information for the specific condition they are treating and to monitor patients for the signs and symptoms of pulmonary embolism.

FDA Drug Safety Communication: Xeljanz, Xeljanz XR (tofacitinib): Safety communication - safety trial finds increased risk of blood clots in the lungs and death with higher dose in rheumatoid arthritis patients. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm632016.htm.

Andexanet for Factor Xa Inhibition Reversal

In patients experiencing major bleeding associated with a factor Xa inhibitor (e.g., apixaban, rivaroxaban), treatment with the reversal agent andexanet alfa resulted in good-to-excellent hemostatic efficacy at 12 hours.

Methods: The open-label, single-group study was conducted at 63 centers in North America and Europe. Participants were adults who presented with acute major bleeding within 18 hours of receiving apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at ≥1 mg/kg/day. Acute major bleeding was specified as either potentially life-threatening, associated with a decrease in hemoglobin of ≥2 g/dL, or affecting a critical area or organ. All patients received an andexanet bolus for 15–30 minutes, followed by a 2-hour infusion. The dosage depended on the background anticoagulant. The study had 2 coprimary efficacy outcomes: the percent change from baseline in anti-factor Xa activity and the percentage of patients with excellent or good hemostatic efficacy, as determined by an adjudication committee using prespecified criteria.

Results: The study enrolled a total of 352 patients, who had a mean age of 77 years. A large majority (80%) were being treated for atrial fibrillation. A total of 55% of patients were receiving apixaban, 36% rivaroxaban, 6% enoxaparin, and 3% edoxaban. The primary bleeding site was intracranial in 64% of patients and gastrointestinal in 26%. All patients received andexanet and were followed for ≥30 days or until death.

At the end of the bolus administration, anti-factor Xa activity was reduced by 92% in patients receiving apixaban, by 92% in those receiving

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rivaroxaban, and by 75% in those receiving enoxaparin (edoxaban results not reported). Among the 249 patients who could be evaluated for hemostatic efficacy, 82% were judged to have good or excellent efficacy at 12 hours, with the great majority judged to be excellent. Efficacy was similar for intracranial and GI bleeding. There was no significant correlation between hemostatic efficacy and the reduction in anti-factor Xa activity. Thus a change in anti-factor Xa activity is not likely to be useful for predicting clinical response.

Mild-to-moderate infusion reactions occurred in 2 patients, and no patient developed antibodies to factor X or Xa or to andexanet. During the 30 days post treatment, 34 patients (10%) experienced a thrombotic event and 49 patients (14%) died, 35 of cardiovascular causes.

Discussion: Acute major bleeding associated with factor Xa inhibitors is a medical emergency often associated with a poor prognosis. There are limited treatment options for these episodes. The present results suggest that reversal with andexanet alfa is both safe and effective.

Connolly S, et al: Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *NEJM* 2019; doi 10.1056/ NEJMoa1814051. From McMaster University, Ontario, Canada; and other institutions. **Funded by Portola Pharmaceuticals. Twenty-four of 29 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **apixaban—*Eliquis*; andexanet alfa—*Andexxa*; edoxaban—*Savaysa*; enoxaparin—*Lovenox*; rivaroxaban—*Xarelto***

New Generic Valsartan Approved

The FDA has approved a new generic version of the angiotensin II receptor blocker (ARB) valsartan to treat high blood pressure and heart failure. The prioritized review and approval of the new generic is an attempt to help reduce the current valsartan shortage, which occurred due to multiple recalls because of nitrosamine impurities found in the products. Prior to the approval, the FDA evaluated the manufacturing processes and also made sure the manufacturer used appropriate testing methods to demonstrate that the valsartan product does not contain nitrosamine impurities. The agency has helped facilitate manufacturing process changes that will produce ARBs that are free of nitrosamine impurities and will continue to work with generic manufacturers so that more agents without these impurities can be approved.

FDA News Release: FDA approves a new generic valsartan : Agency prioritizing review of ARB applications to help mitigate shortage of valsartan. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633255.htm.

Amphetamine XR Suspension

Results of a pilot study indicate that amphetamine extended-release oral suspension (AMPH EROS; *Dyanavel*) can produce positive effects as early as 30 min post dose in young patients with ADHD.[1]

Background: AMPH EROS was approved in 2015 for treatment of ADHD, based on a placebo-controlled laboratory classroom study that showed an onset of action by 1 hour post dose, the earliest time point assessed.

Methods: Study subjects were 18 children, aged 6–12 years, with ADHD. AMPH EROS was initiated, and the dosage optimized over the first study week. After a practice laboratory classroom session, children were randomly assigned to receive AMPH EROS at a fixed dosage of 15, 17.5, or 20 mg/day or placebo in a randomized, crossover sequence for 2 additional classroom sessions, separated by 5 days. The onset of drug action was assessed as the change in score on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Combined (SKAMP-C) rating scale from pre dose to 30 min post dose, relative to placebo.

Results: The study met its primary efficacy endpoint, with greater changes in the SKAMP-C score from pre dose to 30 min post dose with AMPH EROS, relative to placebo (6-point improvement, vs 2.5-point deterioration with placebo; effect size,* 0.95; $p<0.0118$). AMPH EROS was also superior to placebo at 3 hours post dose (effect size, 1.57; $p=0.0002$). Change in the Permanent Product Measure of Performance, a written math test and secondary study endpoint, did not differ between AMPH EROS and placebo at 30 min, but did differ at 3 hours. During the study, patients were exposed to medication for 11 to 13 days. Three children reported fatigue, 2 reported decreased appetite, and none experienced insomnia.

Discussion: The ideal action profile for an ADHD medication would be a single-dose agent

with a rapid onset of action and an extended duration of effect, sustained into the early evening. Results of this study, although preliminary, support the suggestion of an early onset of action of AMPH EROS. Previous research has shown the agent has demonstrated efficacy for up to 13 hours post dose.[2]

[1]Childress A: et al: Early-onset efficacy and safety pilot study of amphetamine extended-release oral suspension in the treatment of children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2019;29:2–8. doi 10.1089/cap.2018.0078. From the Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV; and Tris Pharma, Inc., Monmouth Junction, NJ. **Funded by Tris Pharma, Inc. All study authors disclosed potentially relevant financial relationships with commercial sources including Tris Pharma.**

[2]Childress A, et al: Efficacy and safety of amphetamine extended-release oral suspension in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (June):306–313.

***See Reference Guide.**

MMR Vaccine and Autism

A large, population-based cohort study confirms previous findings that the measles, mumps, rubella (MMR) vaccination does not increase risk of autism in children. The study also did not support other concerns of vaccination critics: that MMR vaccines trigger autism in susceptible subgroups or that it leads to clusters of cases with onset shortly after vaccination.

Methods: The nationwide cohort study included all children born in Denmark between 1999 and 2010. In Denmark, MMR vaccination is voluntary and provided free of charge; it is offered initially at age 15 months. The analysis was adjusted for many autism risk factors, and an autism risk score based on various pre- and perinatal factors was used to stratify cohort members into 10 risk deciles.

Results: The cohort included >657,000 children. After excluding those who died, emigrated, or were later diagnosed with a genetic abnormality related to autism, the remaining 651,000 were followed until the end of the study. More than 95% of children received a first MMR vaccine, at a median age of 1.34 years. A total of 6517 children received a diagnosis of autism (mean age at diagnosis, 7.2 years), for a calculated rate of 130 per 100,000 person-years.

MMR vaccination was not associated with elevated risk of autism in the entire cohort or in any patient subgroup. Moreover, in 2 subgroups—girls and children born between 1999 and 2001—vaccination was associated with significantly reduced risk of autism. Hazard ratios were not elevated in boys, other birth subcohorts, children who received other early childhood vaccinations, those at high risk, or children with siblings with autism.

Discussion: Since the now-retracted article linking MMR vaccination with autism, no study or meta-analysis has confirmed an association. The present study, by far the largest to date, confirms the lack of association and extends the findings to various subgroups.

Hviid A, Hansen J, Frisch M, Melbye M: Measles, mumps, rubella vaccine and autism. A nation wide cohort study. *Annals of Internal Medicine* 2019; doi 10.7326/M18-2101. From Statens Serum Institut, Copenhagen, Denmark; and other institutions. **Funded by the Novo Nordisk Foundation; and the Danish Ministry of Health. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Oral Testosterone Approval

An oral testosterone undecanoate capsule (*Jatenzo*) has received FDA approval for the treatment of hypogonadism due to genetic disorders such as Klinefelter syndrome or tumors in men that have damaged the pituitary gland. In a clinical trial, 87% of men who received *Jatenzo* achieved an average testosterone level within the normal range. Common adverse effects in the trial included headache, an increase in hematocrit, a decrease in high-density lipoprotein cholesterol, high blood pressure, nausea, and an increase in prostate specific antigen (PSA). Treated patients should undergo regular monitoring of hematocrit, cholesterol, and PSA. Men with benign prostate hyperplasia should be monitored for worsening of symptoms.

Jatenzo should not be used in men with age-related hypogonadism. In these patients, the benefits of *Jatenzo* do not outweigh the risks of treatment, particularly blood pressure increases that can raise the risks of heart attack, stroke, and cardiovascular death. The drug labeling will include a boxed warning about these effects.

FDA News Release: FDA approves new oral testosterone capsule for treatment of men with certain forms of hypogonadism. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm63 4585.htm.

Beta-Blockers and COPD Hospitalization

Use of beta-blockers was associated with reduced risk of hospitalization for chronic obstructive pulmonary disease, compared with use of other antihypertensive agents. This observation, from a population-based cohort study, suggests beta-blockers can be prescribed safely in patients with COPD.

Background: There is some reluctance to prescribe beta-blockers in patient with airway symptoms or a history of smoking. Some studies have shown that beta-blockers are associated with worsening of airway symptoms and reduced lung function in patients with COPD. Other studies have shown beneficial effects on COPD symptoms in patients treated after an MI. There appear to be no previous large-scale population-based studies of beta-blockers' effects on COPD.

Methods: Study data were collected from Danish national registries of prescriptions, hospitalization, and deaths. Study subjects were adults, aged 30–90 years, with no prior history of hospitalization for COPD, treated between 1995 and 2015. Patients were followed from the date a second prescription for a beta-blocker or other antihypertensive agent was filled. The primary study outcome was first hospitalization for COPD.

Results: The cohort included >300,000 patients treated with a beta-blocker and >1 million treated with other antihypertensive medications. Patients had average ages of 50–60 years at the start of therapy and were evenly divided between men and women. During follow-up, beta-blocker users were hospitalized for COPD at a rate of 649 per 100,000 person-years, compared with 919 per 100,000 person-years in the group taking other medications. After adjusting for all available covariates, the rate of COPD hospitalization was nearly 20% lower in beta-blocker users (adjusted hazard ratio,* 0.80). Risk estimates were unchanged in analyses limited to COPD hospitalization in the first 5 years after the start of treatment or excluding these early hospitalizations. Risk reductions were similar in men and women, in different age groups, and regardless of beta-blocker selectivity. Beta-blockers reduced COPD hospitalization risk in patients with or without ischemic heart disease, cardiac arrhythmias, asthma, hypertension, or diseases of the pulmonary circulation. All-cause mortality and COPD mortality were also reduced in patients taking beta-blockers.

Discussion: The analysis of hospitalizations beginning 5 years after the start of therapy was carried out to avoid the "healthy user effect," which assumes beta-blockers are prescribed more often in healthier patients. Presumably patients hospitalized 5 years after the start of therapy would have been free of COPD symptoms at baseline.

Nielsen A, Pedersen L, Sode B, Dahl M: Beta-blocker therapy and risk of chronic obstructive pulmonary disease—a Danish nationwide study of 1.3 million individuals. *EClinical Medicine* 2019; doi 10.1016/j.eclinm.2019.01.004. From Zealand University Hospital, Køge, Denmark; and other institutions.
Funded by the Danish Council for Independent Research in Denmark; and other sources. The authors declared no competing interests.

***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.