PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Lorcaserin: Potential Cancer Risk

The FDA has issued a warning that based on the results of a safety study the weight loss agent lorcaserin (*Belviq*) may be associated with an increased risk of cancer. The causality of the cancer in study patients has not been determined, and the FDA will continue to evaluate the study results and communicate recommendations when the review is complete. In the interim, prescribers are urged to consider if the weight loss benefits of lorcaserin outweigh the potential risks and to discuss the potential risk with patients already prescribed the agent.

FDA MedWatch Safety Alert: Belviq, Belviq XR (lorcaserin): drug safety communication - due to possible increased risk of cancer. Available at www.fda.gov/safety/medical-product-safety-information/belviq-belviq-xr-lorcaserin-drug-safety-communication-due-possible-increased-risk-cancer.

Antivirals for Influenza

Influenza is generally self-limiting, but serious complications such as pneumonia, respiratory failure, and death can occur. Antiviral treatment is recommended for patients with confirmed or suspected influenza if they are hospitalized, have a severe, complicated, or progressive illness, or are at high risk for complications. In addition, antiviral therapy can be considered for previously healthy patients with confirmed or suspected influenza who are not at high risk for influenza complications provided it can be initiated within 48 hours of illness onset. Antiviral prophylaxis is recommended in institutional settings to help control influenza outbreaks. It can be considered following exposure for patients at high risk for complications if they have not received the seasonal influenza vaccine, received it within the prior 2 weeks, or are unlikely to have responded to vaccination. Prophylaxis is not recommended for healthy persons exposed to influenza unless it can be initiated within 48 hours of exposure.

The neuraminidase inhibitors oseltamivir and zanamivir are FDA approved for both treatment and prophylaxis of uncomplicated acute influenza. Oseltamivir is administered orally, while zanamivir is inhaled. The IV neuraminidase inhibitor peramivir and the oral polymerase acidic endonuclease inhibitor baloxavir marboxil are approved for treatment, but not for prophylaxis. All of the approved agents are active against both influenza A and B viruses. Amantadine and rimantadine are not currently recommended because they are not active against influenza B viruses and levels of resistance among currently circulating influenza A viruses are high.

There are no data suggesting that one drug is more effective than any other in nonpregnant outpatients with uncomplicated influenza. However, oseltamivir is the preferred option for pregnant women, hospitalized patients, and outpatients with severe, complicated, or progressive influenza. Research suggests that treatment with oseltamivir, zanamivir, or baloxavir shortens to duration of uncomplicated influenza symptoms by about 1 day. For patients who are not high risk, prophylaxis with oseltamivir or zanamivir should be continued for 7 days after exposure. In the case of institutional outbreaks, prophylaxis should last

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for ≥2 weeks and be continued for up to 1 week after the end of the outbreak.

Nausea, vomiting, and headache are the most common adverse effects reported with oseltamivir. Administration with food can reduce the adverse GI effects. Diarrhea, nausea, sinusitis, fever, and arthralgia have been reported with zanamivir. Because zanamivir inhalation can cause bronchospasm, it should not be used by patients with airway disease. Neuropsychiatric effects, including self-injury and delirium, have been reported with use of the neuraminidase inhibitors, but causality has not been established. Clinical trials suggest baloxavir is well tolerated, and it may cause less nausea and vomiting than oseltamivir. Peramivir has been associated with diarrhea and neutropenia.

Antiviral drugs for influenza. *The Medical Letter* 2020; 62 (January 13):1–4.

Common Drug Trade Names*: amantadine—*Symmetrel*; baloxavir marboxil—*Xofluza*; oseltamivir—*Tamiflu*; peramivir—*Rapivab*; rimantadine—*Flumadine*; zanamivir—*Relenza

Antihypertensives: Comparative Effectiveness

According to a large-scale systematic analysis, most classes of antihypertensive drug show comparable effectiveness in new users. However, thiazide diuretics were more effective for several important outcomes and better tolerated than ACE inhibitors, the most commonly prescribed drug class.

Background: Current treatment guidelines recommend any of the major drug classes equally as first-line antihypertensive therapy. The recommendations are based on clinical trials that are in most cases decades old and that are subject to the usual biases such as selective publication. The present analysis was designed to avoid these biases and was carried out using an extremely large network of observational hypertension databases.

Methods: The analysis was based on 6 administrative claims databases and 3 electronic health records databases, mostly from the United States but also representing Germany, Japan, and South Korea. Members of the study cohort were patients newly prescribed monotherapy with an antihypertensive from any of the 5 classes recommended as primary therapy in the 2017 American Heart Association/American College of Cardiology guidelines. Primary outcomes were acute MI, heart failure hospitalization, and stroke. Additionally, 6 secondary efficacy outcomes, and 46 safety outcomes corresponding to the major antihypertensive adverse effects were examined. Analyses were adjusted for propensity scores* including a vast number of patient characteristics.

Results: The study included data from nearly 5 million patients. Nearly half (48%) started therapy with an ACE inhibitor, 17% a thiazide diuretic, 16% a dihydropyridine calcium channel blocker (dCCB), 15% an angiotensin receptor blocker (ARB), and 3% a non-dihydropyridine calcium channel blocker (ndCCB). Median on-treatment time at risk varied by drug and database, ranging from 1 to 7 months; 25% of patients received their first drug for >1 year, and median overall follow-up was >2 years. About half of the paired drug comparisons showed no difference between drug classes for the 3 major effectiveness outcomes. However, compared with ACE inhibitors, thiazide diuretics were associated with significantly reduced risk of the 3 major outcomes (see table), with a 15% lower incidence overall. Non-dihydropyridine calcium channel blockers were less effective than several other drug classes for the major outcomes. Of the secondary outcomes, thiazide diuretics were more effective than ACE inhibitors at reducing cardiovascular events, ischemic stroke, hemorrhagic stroke, and unstable angina, but not heart failure or sudden cardiac death. There were few differences in secondary

Statistically Significant Hazard Ratios*				
Target Class	**Comparator**	**Acute MI**	**Heart failure hospitalization**	**Stroke**
Thiazide	ACE inhibitor	0.84 (p=0.01)	0.83 (p=0.01)	0.83 (p=0.01)
Thiazide	ndCCB	0.70 (p<0.01)	0.58 (p<0.01)	0.78 (p=0.01)
ACE inhibitor	ndCCB	0.87 (p=0.04)	0.68 (p<0.01)	0.89 (p=0.02)
ARB	ndCCB	0.78 (p=0.01)	0.71 (p<0.01)	0.84 (p=0.05)
dCCB	ndCCB	0.84 (p<0.01)	0.73 (p<0.01)	0.87 (p=0.01)

outcomes with other comparisons except for nondihydropyridine CCBs, which performed more poorly. Thiazide diuretics also had a more favorable safety profile than the other drug classes, and nondihydropyridine CCBs were the least well tolerated drug class.

Suchard M, et al: Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet* 2019;394(November 16):1816–1826. doi 10.1016/S0140-6736(19)32317-7. From the University of California, Los Angeles; and other institutions. **Funded by Janssen Research and Development; and other sources.**

***See Reference Guide.**

Metabolic Syndrome in Children

Despite a lack of consensus on the definition of metabolic syndrome in children and adolescents, there is general agreement that preventing and treating obesity should be the first-line approach in order to reduce cardiovascular risk due to the syndrome.

In ways that are not fully understood, metabolic syndrome is at least partly the result of an interaction between obesity, insulin resistance, and a pro-inflammatory state. Besides obesity, the other components of the syndrome are hypertension, dyslipidemias, impaired glucose metabolism and type 2 diabetes, and non-alcoholic fatty liver disease. Interventions that address 1 element of the disorder, such as dietary changes and increased physical activity, could be useful in ameliorating others via a common mechanism of weight loss. Evidence suggests these types of behavioral interventions have larger effects in children than in adolescents, emphasizing the importance of early intervention.

Guidelines from the American Academy of Pediatrics describe the appropriate modifications in diet and nutrition. The primary goal of intervention should be reducing caloric intake, but other measures, such as reducing sugar and increasing fiber intake, may improve glucose abnormalities. Physical activity should be encouraged in preschool children, and those aged 6–17 years should engage in moderate to vigorous physical activity for 60 minutes each day. Healthy sleep habits and limiting screen time should be addressed. Pharmacotherapy of obesity in pediatric patients is poorly studied. Orlistat is the only FDA-approved agent for pediatric weight reduction, and only in adolescents aged >12 years. After ruling out substance abuse and eating disorders, bariatric surgery may be considered for patients with extreme obesity who have completed their growth and pubertal development.

The other components of metabolic syndrome are likely to improve with weight loss and lifestyle modifications, but may also require specific treatment. Hypertension should be addressed with lifestyle modification, followed by medication if necessary. The current target blood pressure in adolescents is <130/80 mmHg. ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics are all similarly effective in children. Dyslipidemia in children with metabolic syndrome usually consists of elevated triglycerides and low HDL cholesterol. Fish oil supplements may be considered. Glucose impairment seldom requires medication, but type 2 diabetes calls for treatment with metformin, followed by insulin. Probiotics and omega-3 fatty acids may ameliorate liver disease.

Fornari E, Maffeis C: Treatment of metabolic syndrome in children. *Frontiers in Endocrinology* 2019; doi 10.3389/endo.2019.00702. From the University of Verona, Italy. **Funded by the University of Verona. The authors declared no competing interests.**

Common Drug Trade Names*: metformin—*Glucophage*; orlistat—*Xenical

Trends in Generic ARB Prescribing

Angiotensin receptor blockers are among the most commonly prescribed drugs for hypertension, heart failure, and diabetic nephropathy in the U.S. The discovery of potentially carcinogenic nitrosamine impurities in generic ARBs has led to recalls of 139 lots of valsartan, 57 lots of losartan, and 16 lots of irbesartan from different manufacturers. Although FDA statements indicate the potential cancer risk associated with exposure to these impurities is very small, the recalls were concerning to both patients and physicians.

Using data from a large commercial prescription claims database, utilization patterns of generic ARBs (i.e., losartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan) were evaluated between January 2018 (prior to the recalls) and March 2019. Prior to the recalls, the affected lots represented 37% of total ARBs dispensed. Following the FDA warning, neither the total volume of generic ARB prescriptions nor the proportion of ARB prescriptions relative to other antihypertensives (e.g., ACE inhibitors, β-blockers, calcium channel blockers, and diuretics) was reduced, suggesting prescribing shifts within the

class. However, as the proportion of overall ARB prescribing, generic valsartan use decreased substantially after the recalls (see table), while use of losartan and irbesartan were not substantially changed, possibly because fewer lots of these agents were affected by the recall.

Prescribing patterns for generic ARBS from before to after recalls

	% total prescriptions before recalls	% total precriptions after recalls
Losartan	67%	74%
Valsartan	21%	10%
Olmesartan	6%	8%
Irbesartan	4%	6%
Telmisartan	2%	4%
Candesartan	1%	1%

Desai R, et al: Changes in utilization of generic angiotensin receptor blockers following product recalls in the United States. *JAMA* 2020; 323 (January):87–89. From Brigham and Women's Hospital, Boston, MA. **Source of funding not stated. Three of 6 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: candesartan—*Atacand*; irbesartan—*Avapro*; losartan—*Cozaar*; olmesartan—*Benicar*; telmisartan—*Micardis*; valsartan—*Diovan

Lemborexant Approved for Insomnia

The FDA has approved the orexin receptor antagonist lemborexant (*Dayvigo*) for the treatment of insomnia in adults.[1] The agent will be available in 5- and 10-mg doses following scheduling by the Drug Enforcement Administration. Efficacy was demonstrated in clinical trials comparing lemborexant with placebo and active comparators in approximately 2000 adults treated for 1–6 months. The agent was not associated with rebound insomnia or withdrawal effects after discontinuation.

According to the package insert,[2] lemborexant should only be taken before bed and only if the patient can remain in bed for ≥7 hours. Patients should be advised that onset of action can be delayed if lemborexant is taken with or soon after a meal. Lemborexant has the potential to impair daytime wakefulness and next-morning driving performance even when used as directed. In addition, sleep paralysis and complex sleep behaviors (e.g., sleep-walking, sleep-driving, preparing and eating food while not fully awake) have occurred. Worsening depression and suicidal thoughts have also been reported during lemborexant treatment.

[1]FDA approves lemborexant (Dayvigo) for insomnia—Medscape—December 23, 2019.

[2]Dayvigo Package insert: Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf.

Reference Guide

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.