PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Lorcaserin Market Withdrawal

A review of results from a safety trial assessing cancer risk associated with the weight-loss drug lorcaserin (*Belviq*) has lead the FDA to determine the risks of treatment outweigh the potential benefits. They now recommend the drug be withdrawn from the US market. While special screenings for those treated with lorcaserin are not recommended, patients should stop taking the agent and explore alternate weight-loss strategies.

FDA Drug Safety Communication: FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market: potential risk of cancer outweighs the benefits. Available at www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market.

Rosiglitazone Cardiovascular Risk

A detailed meta-analysis, using both summary data and individual patient-level data from more than 100 clinical trials, confirmed the association of rosiglitazone with cardiovascular risk, especially heart failure. Previous meta-analyses have not resolved uncertainty about these effects, due in part to methodologic concerns including a lack of patient-level data and the possibility of selective adverse event reporting.

Methods: The present analysis included individual patient-level data (i.e., raw clinical trial data supplied by the manufacturer) as well as summary data from published studies, online clinical trial registries, and clinical study reports submitted to regulatory bodies. Included studies were phase II, III, or IV trials lasting 24 weeks and comparing rosiglitazone to another diabetes medication or placebo in adults. The primary endpoint of the meta-analysis was a composite outcome of acute MI, heart failure, cardiovascular related deaths, and noncardiovascular deaths.

Results: The analysis included 33 trials with individual-level data from >21,000 patients, and 103 trials with summary data from nearly 23,700 patients. Comparing the 29 trials with both individual-level and summary data, the authors found that MI events were underreported in most of the latter studies. Analysis of individual patient data found a significant increase in composite events in the rosiglitazone treatment arms (odds ratio, *1.33; p=0.005) that appeared to be driven solely by an increase in risk of heart failure (odds ratio, 1.54; p=0.005).

Analysis of summary-level data was limited to 2 outcomes, heart failure and MI, because of reporting limitations. Risks of both outcomes were attenuated compared with the individual-level analysis, and neither risk was statistically significant. Results were generally similar in analyses by indication (diabetes versus other), trial duration, and comparator (placebo vs. an active drug).

Discussion: Since early reports of cardiovascular adverse effects, rosiglitazone has been removed from the market in most countries but continues to be available with labeled warnings in the US. The required Risk Evaluation Mitigation Strategy (REMS) program was recently dropped after a

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study found cardiovascular risks of rosiglitazone did not differ from other diabetes drugs, but this conclusion has been questioned. Pioglitazone, the only other available thiazolidendione, is the recommended alternative, although it is also associated with some degree of cardiovascular risk.

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

Wallach J, et al: Updating insights into rosiglitazone and cardiovascular risk through shared data: individual patient and summary level meta-analyses. *BMJ* 2020; doi 10.1136/bmj. From Yale School of Public Health, New Haven, CT; and other institutions. **Funded by the Laura and John Arnold Foundation; and other sources. Five of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: pioglitazone—*Actos*; rosiglitazone—*Avandia

***See Reference Guide.**

Breast Cancer Prevention with Anastrozole

In postmenopausal women at high risk for breast cancer, 5 years of anastrozole treatment had a long-term preventive effect, up to 7 years after discontinuation.[1] This is the first evidence of a carryover effect of aromatase inhibitors in the prevention setting, with a larger effect than previously demonstrated for tamoxifen.[2]

Methods: This report presents an updated analysis of the IBIS-II trial, a multinational trial that recruited postmenopausal women, aged 40–70 years, with breast cancer risk 2–4 times that of the general population as determined by an age- and risk factor-based algorithm. Women were randomly assigned to receive 1 mg/day anastrozole or placebo for 5 years. The primary outcome was the development of histological confirmed invasive breast cancer or ductal carcinoma in situ (DCIS). The main trial reported a 69% reduction in breast cancer after 5 years. The present analysis was based on continuing annual follow-up of participants for an additional 7 years.

Results: Of the initial 3864 study participants, 96% were still at risk for breast cancer after the 5-year treatment period. Median follow-up for this analysis was nearly 11 years post-randomization. Anastrozole was associated with about a 50% reduction in breast cancer risk over 12 years of post-randomization follow-up (hazard ratio [HR],* 0.51; p<0.0001). The reduction was larger during treatment (HR, 0.39; p<0.0001), but remained significant 7 years after discontinuation of randomized treatment (HR, 0.64; p=0. 014). At the last follow-up, the estimated cumulative risk of developing breast cancer was 8.8% in the placebo group and 5.3% in the anastrozole group. The number needed to treat* for 5 years to prevent 1 breast cancer was 29. Anastrozole reduced the incidence of all cancer types, regardless of invasiveness, HER2 status, and estrogen receptor status, and had similar effects in subgroups stratified by age, body mass index, previous hormone replacement therapy, or previous precancerous breast lesions. Anastrozole had no long-term effect on fractures or other adverse events. Owing to the small number of breast cancer deaths, anastrozole had no discernible effect on that outcome (3 with anastrozole, 2 with placebo).

Discussion: Early research on breast cancer prevention focused on selective estrogen receptor modifiers (SERMs) like tamoxifen, which was associated with a 5-year number needed to treat of 58 in an early study. Like anastrozole, SERMs are associated with a carryover effect, but the effect with anastrozole appears to be larger. The IBIS-II study did not collect long-term data on less serious adverse effects that might influence treatment adherence, but 25% of patients were nonadherent with and did not complete the 5-year randomized phase.

[1]Cuzick J, et al: Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomized controlled trial. *Lancet* 2020;395 (January 11):117–122. doi 10.1016/S0140-6736(19)32955-1. From Queen Mary University, London, UK; and other institutions. **Funded by Cancer Research UK; and other sources including Sanofi Aventis and AstraZeneca. Three of 10 study authors disclosed potentially relevant financial relationships the remaining authors declared no competing interests.**

[2]Chumsri S, Thompson EA: Carryover effects of aromatase inhibitors in prevention [Editorial]. *Lancet* 2020;395 (January 11):91-92. doi 10.1016/S0140-6736(19)33102-2. From the Mayo Clinic, Jacksonville, FL. **The authors declared no competing interests.**

Common Drug Trade Names*: anastrozole—*Arimidex*; tamoxifen—*Nolvadex

***See Reference Guide.**

Opioid Use Disorder Treatment Approaches

In a large nationwide sample of insured patients with opioid use disorder, treatment with buprenorphine or methadone was associated with a lower rate of recurrence than other models of treatment. However, few patients received these treatments.

Background: Despite better access to medical care, commercially insured patients with opioid use disorder rarely receive medications and

commonly undergo psychosocial-only treatments. The comparative effectiveness of different treatment pathways has not been well studied previously.

Methods: The investigators analyzed administrative claims data from a large, diverse cohort of patients with opioid use disorder, enrolled in commercial insurance or Medicare Advantage plans. A total of 6 mutually exclusive treatment pathways were compared: no treatment; inpatient detoxification or residential services; intensive behavioral health; buprenorphine or methadone; naltrexone; and nonintensive outpatient counseling. Patients were followed for at least 90 days and up to 1 year after beginning treatment, or from a randomly selected index date for those who received no treatment. As proxies for recurrence, overdose, either fatal or nonfatal, and opioid-related acute hospitalization were the primary study outcomes.

Results: The cohort included nearly 41,000 patients (mean age, 48 years; 54% men), 58% with commercial insurance and 42% covered by Medicare Advantage (the latter including 25% who were under age 65 years). The most common treatment pathway was nonintensive behavioral health (59%), followed by inpatient or residential services (16%) and buprenorphine or methadone (12.5%). Nearly half of patients were no longer enrolled in their insurance plan after 1 year, but it could not be determined whether this was due to death or loss of coverage. Patients treated with medication had the highest coverage discontinuation rates, about 54%.

During 3 months of follow-up, 707 patients (1.7%) experienced an overdose and 773 (1.9%) had a serious episode of opioid-related care. Compared with patients receiving no treatment, those who received buprenorphine or methadone had a lower rate of overdose (hazard ratio [HR],* 0.24) or acute care (HR, 0.68) within the 3 months after starting treatment. Rates of these outcomes were also lower at 1 year (HR, 0.41 and 0.74, respectively). Intensive behavioral health interventions were also better than no treatment (HRs, 0.59–0.79). Inpatient detoxification or residential services, intensive behavioral health interventions, and naltrexone were not associated with statistically significant reductions in recurrence outcomes.

Compared with buprenorphine or methadone, all other treatment options were associated with higher rates of eventual admission to inpatient detoxification. Duration of pharmacotherapy was relatively short, with means of 74 and 150 days, in the buprenorphine or methadone and naltrexone groups respectively. Longer duration of buprenorphine or methadone treatment was associated with lower rates of overdose or acute care use.

Discussion: Most individuals in this cohort received only psychosocial services or inpatient detoxification, both of which were less effective than pharmacotherapy. Numerous barriers, including a lack of access to waivered practitioners, high copayments and/or prior authorization requirements, and other restrictions, limit the use of pharmacotherapy to treat opioid use disorder and can lead to premature discontinuation in patients who do receive it. The present findings suggest coverage of buprenorphine and methadone should be expanded and include fewer restrictions and that patient-centered treatment models should focus on retaining opioid users on medications.

Wakeman S, et al: Comparative effectiveness of different treatment pathways for opioid use disorder. *JAMA Network Open* 2020; doi 10.1001/jamanetworkopen.20109.20622. From Massachusetts General Hospital, Boston; and other institutions. F**unded by Boston Medical Center; and other sources. Six of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine—*Subutex;* naltrexone—*ReVia, Vivitrol

***See Reference Guide.**

Buprenorphine/Cannabis Interaction

A small retrospective study in patients undergoing opioid maintenance therapy (OMT) found buprenorphine concentrations were nearly 3-fold higher in patients who used cannabis. Given the increasing medical and recreational use of cannabis, therapeutic drug monitoring of buprenorphine may be prudent.

Methods: Data were analyzed from patients undergoing OMT with either buprenorphine or buprenorphine/naloxone. Patients were required to be receiving OMT for 5 years, clinically stable, and to be receiving a stable buprenorphine dosage with a take-home prescription. Patients were free of HIV infection and active hepatitis, not using other legal or illegal drugs, and not taking medications with known interactions with CYP3A4 or CYP2C8, the enzymes affected by buprenorphine. Participants underwent monthly immunologic urine testing for drugs and serum

levels of buprenorphine and norbuprenorphine. The probability of a cannabis/buprenorphine interaction was rated using the 10-item Drug Interaction Probability Scale.

Results: A total of 10 patients provided 32 eligible serum buprenorphine measurements over the course of 5 years: 5 patients were consistently negative for all drugs of abuse except nicotine and 5 tested positive for cannabis only. No patient reported cannabis use by prescription. Urine cannabis concentrations in the exposed group were consistent with frequent use of moderate amounts, in agreement with the patients' self-reports of once-daily consumption via smoking.

Mean buprenorphine dosages did not differ between cannabis exposed and unexposed patients (8.6 and 8.8 mg/day, respectively). Cannabis use was strongly associated with serum buprenorphine level, with mean concentrations of 5.4 ng/mL (range, 2–10) in the cannabis group and 2 ng/mL (range, 0.2–12.6) in the comparison group ($p<.0002$). On average, norbuprenorphine levels were higher in the cannabis group than controls, though not statistically significantly. The total active moiety and the dose-related active moiety were at least twice as high in the cannabis group as the control group. Three patients who discontinued cannabis use during the study period showed substantial declines in buprenorphine concentrations after cessation, further supporting the probable interaction.

Discussion: These results suggest cannabis consumption lowers the rate of buprenorphine metabolism, most likely due to CYP3A4 inhibition. The possibility of interaction should be taken into consideration when attempting to wean OMT patients from cannabis use, as it may contribute to buprenorphine withdrawal symptoms and an increased dosage requirement. Caution should be taken when prescribing medical cannabis to patients receiving OMT.

Vierke C, et al: Buprenorphine-cannabis interaction in patients undergoing opioid maintenance therapy. *European Archives of Psychiatry and Clinical Neuroscience* 2020; doi 10.1007/s00406-019-01091-0. From the University Medical Center Göttingen, Göttingen, Germany, and other institutions. **Funded by the Deutsche Forschungs Gesellschaft. Two of 5 study authors disclosed potentially relevant financial relationships; 2 declared no competing interests; and no disclosure included for the remaining author.**

Common Drug Trade Names*:** **buprenorphine—*Subutex*; buprenorphine/naloxone—*Suboxone

Generic ProAir HFA Approval

The first generic version of *ProAir HFA Inhalation Aerosol* (albuterol sulfate) has received FDA approval for use in patients aged ≥4 years. The metered-dose inhaler is indicated for treatment of bronchospasm in patients with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm. The approval is noteworthy in part because complex generics, such as this metered-dose inhaler, can be more difficult to formulate.

FDA News Release: FDA approves first generic ProAir HFA: agency supports development of complex generic drugs to improve competition and access to more affordable medicines. Available at www.fda.gov/news-events/press-announcements/fda-approves-first-generic-proair-hfa.

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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.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

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.