PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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OTC Oral Nicotine Spray

Many nicotine replacement therapies (e.g., gum, lozenges, patches) are available over-the-counter, but nasal sprays and oral inhalers still require a prescription. An expert panel has determined that the smoking cessation benefits of an oral nicotine spray outweigh its risks and has recommended the FDA approve the agent. The oral spray delivers 1 mg of nicotine in each spray and is meant to be used when the patient has the urge to smoke, but no more than 4 times per hour or 64 times per day. Therapy is intended to be continued for 12 weeks, during which the daily dose of nicotine is reduced by using fewer sprays. Concerns raised by the panel include extended use beyond 12 weeks as well as continued smoking while using the spray. Potential misuse by nonsmokers and teens, as has occurred with e-cigarettes, is also an important concern.

Jospeh S, et al: GSK's over-the-counter nicotine oral spray gets FDA backing. Reuters Health News. Available at www. https://www.reuters.com/article/us-gsk-fda/gsks-over-the-counter-nicotine-oral-spray-gets-fda-panel-backing-idUSKBN1W32V2.

Oral Semaglutide for Diabetes

Semaglutide (*Rybelsus*) has become the first oral glucagon-like peptide (GLP-1) receptor agonist to gain FDA approval for the management of blood sugar in type 2 diabetes. Previously, all GLP-1 receptor agonists were injectable formulations. As with injectable semaglutide (*Ozempic*), the oral prescribing information for *Rybelsus* will include a boxed warning about increased risk of thyroid c-cell tumors and contraindicating it for patients with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia syndrome type 2 (MEN 2). *Rybelsus* is not for use in patients with type 1 diabetes or those with diabetic ketoacidosis. *Rybelsus* also carries warnings about pancreatitis, diabetic retinopathy, hypoglycemia, acute kidney injury, and hypersensitivity reactions. It is unclear whether the agent can be used safely by patients who have had pancreatitis.

Rybelsus should be taken daily with no more than 4 ounces of plain water ≥30 minutes before any food, beverage, or other oral medication. Because semaglutide slows digestion, the effects on other prescribed medications should be discussed before starting treatment. The most common adverse effects are nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation.

FDA News Release: FDA approves first oral GLP-1 treatment for type 2 diabetes. Available at www.fda.gov/news-events/press-announcements/ fda-approves-first-oral-glp-1-treatment-type-2-diabetes.

Atomoxetine and Raynaud's Phenomenon

A 7-year-old boy with autism spectrum disorder presented with hyperactivity, impulsivity, and aggressive behavior indicative of ADHD. He was started on 10 mg/day atomoxetine (*Strattera*) that

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was titrated over 3 weeks to 28 mg/day. Within 1 hour of the first 28-mg dose, bilateral digital pallor, cooling, and circumoral cyanosis developed. The symptoms persisted for 2 days before being reported to the patient's physician. On examination, all other physical and laboratory evaluations were unremarkable, and no underlying cause for the cyanosis was identified. He received a diagnosis of Raynaud's phenomenon, which is often associated with stress, cold exposure, or autoimmune disorders, but has been reported less frequently as a medication-associated reaction. Atomoxetine was discontinued and the patient's symptoms resolved.

Raynaud's phenomenon is a rare adverse effect—only 1 previous case has been reported with atomoxetine—and the pathophysiology is unclear. However, it may be related to vasoconstriction in peripheral vessels resulting from atomoxetine-associated increases in norepinephrine and dopamine.

Nur Gulle Z, et al: Raynaud's phenomenon related with atomoxetine treatment in a child with autism and attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2019; doi 10.1089/cap.2019.0025. From Instanbul University, Turkey. **The authors declared no competing interests.**

Antibiotics and Colorectal Cancer

In a large case-control study, colorectal cancer risk was associated with use of oral antibiotics, but risk varied according to anatomic location, with neutral effects in the distal colon and an apparently protective effect for rectal cancer.

Methods: The study was based on prospectively collected data for more than 11 million patients, from the U.K. Clinical Practice Research Datalink. Individuals were included in the analysis if they were aged 40–90 years and were registered in the database for ≥2 years between 1989 and 2012. Each case patient with colorectal cancer was matched with up to 5 controls for age, sex, and other factors. Patients with predisposing conditions or immunosuppressive states were excluded. Antibiotic exposure was ascertained from electronic medical records and classified as occurring 1–10 years or >10 years before the cancer diagnosis and stratified into 5 levels, from 0 to >60 cumulative days.

Results: The analysis included nearly 29,000 cases and more than 137,000 controls, followed for a median of about 8 years before cancer onset. Antibiotics had been prescribed for 70% of case patients and 68.5% of controls.

Antibiotic use increased the overall risk of colon cancer even with minimal exposure and increasing in a dose-dependent manner (odds ratios,* 1.08–1.17). Risk was greatest for cancers in the proximal colon and with antibiotics with anti-anaerobic activity. The association between antibiotic exposure and colon cancer was seen even in patients with antibiotic exposure more than 10 years before cancer detection. Proximal colon cancer risk increased with minimum levels of exposure, up to about 15 days, and then plateaued. Antibiotic use was equivalent in patients with cancer of the distal colon and their controls, and no time trends were observed.

Patients with rectal cancer were less likely than their controls to have been prescribed an antibiotic, with the strongest effect associated with the highest level of antibiotic use, >60 cumulative days (odds ratio, 0.85). The protective effect was not seen until after 30 days of exposure and reached a plateau after 90 days.

The effect of antibiotics on colorectal cancer was most significant after exposure to anti-anaerobic drugs, which markedly disrupt the colon microbiome. For individual antibiotic classes, penicillins were strongly associated with increased colon cancer risk, and tetracyclines were inversely associated with rectal cancer risk.

Zhang J, et al: Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989-2012: a matched case-control study. *Gut* 2019; doi 10.1136/gutjnl-2019-318593. **From Johns Hopkins University School of Medicine, Baltimore, MD; and other institutions. Funded by Johns Hopkins; and the Bloomberg-Kimmel Institute for Cancer Immunotherapy. Three of 9 study authors disclosed potentially relevant financial relationships.**

***See Reference Guide.**

Hormonal Contraception: OTC Access

The American College of Obstetricians and Gynecologists (ACOG) supports changing the status of hormonal contraceptives, including oral contraceptive pills, vaginal rings, transdermal patches, and depot medroxyprogesterone acetate, from prescription to over-the-counter. The committee opinion statement also suggests the change should be made without age restrictions, although label comprehension and self-screening studies may be required in adolescents.

A key factor involved in an FDA consideration of a switch to OTC status is the potential toxicity of a medication. Hormonal contraceptive safety concerns generally focus on risk for venous thromboembolism (VTE). According to the ACOG statement, data support the safety of progestin-only contraceptives, which are associated with minimal VTE risk. In addition, VTE risk with combined oral contraceptives is small compared with risk during pregnancy and in the postpartum period. Despite their safety, hormonal contraceptives are not appropriate for all patients. OTC status would require that women self-screen with a simple checklist for contraindications to their use. Alternatively, behind-the-counter access would allow for pharmacist screening, which could be an intermediate step to increase access.

ACOG Committee opinion: Over-the-counter access to hormonal contraceptives. *Obstetrics and Gynecology* 2019; 134 (October):e96–e105. From the American College of Obstetricians and Gynecologists, Washington, D.C.

Ranitidine Contamination

Product sample of some ranitidine formulations, available both other-the-counter and by prescription, have been found to contain small amounts of a probable human carcinogen N-nitrosodimethylamine (NDMA).[1] The contaminant was previously found in several agents containing the angiotensin receptor blockers (ARBs) irbesartan, losartan, and valsartan, which have been voluntarily recalled.[2] NDMA is a known environmental contaminant and can be found in water and foods, including meats, dairy products, and vegetables. The FDA is not currently recommending that patients stop taking ranitidine. However, as there are multiple drugs approved for the same or similar indications, alternate options exist for patients taking ranitidine who wish to discontinue use.

[1]FDA MedWatch Alert: Zantac (ranitidine): safety information - NDMA found in samples of some ranitidine medicines. Available at www.fda.gov/safety/medwatch-safety-alerts-human-medical-products/zantac-ranitidine-safety-information-ndma-found-samples-some-ranitidine-medicines.

[2]FDA Drug Safety Communication: FDA updates on angiotensin II receptor blocker (ARB) recalls. Available at www.fda.gov/Drugs/DrugSafety/ucm613916.htm. See *Primary Care Drug Alerts* 2018;39 (November):43.

Common Drug Trade Names*: irbesartan—*Avapro*; losartan—*Cozaar*; ranitidine—*Zantac*; valsartan—*Diovan

Loperamide Packaging Limits

In 2016 the FDA issued a drug safety warning regarding serious heart problems including QT interval prolongation, Torsades de pointes or other ventricular arrhythmias, syncope, and cardiac arrest and death associated with the use of much higher than recommended doses of the OTC antidiarrheal loperamide. The events occurred primarily in patients intentionally misusing/abusing the agent to achieve opioid psychoactive effects. Despite the warning, the FDA continued to receive reports of serious cardiac effects and deaths, and in 2018 requested the manufacturers use blister packs or other single-dose packaging and limit the number of doses in each package. Several tablet and capsules formulations of the agent, including *Imodium A-D*, are now available with a maximum loperamide dose of 48 mg packaged in individual doses. The FDA continues to work with the manufacturers of other generic tablets and capsules as well as liquid formulations of the drug to establish appropriate packaging.

FDA Drug Safety Communication: FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use. Available at www.fda.gov/drugs/drug-safety-and-availability/fda-limits-packaging-anti-diarrhea-medicine-loperamide-imodium-encourage-safe-use.

Pediatric Migraine: Treatment Guideline

An updated recommendation on treatment of migraine in children and adolescents has been issued by the American Academy of Neurology and the American Headache Society. The recommendation, which includes evidence from 10 new studies of acute migraine treatments, focuses on the importance of early treatment, individualized choice of the route of administration, and counseling on avoidance of risk factors such as triggers and medication overuse.

The updated guideline stresses the importance of early diagnosis. Diagnostic criteria for pediatric migraine require ≥5 attacks per year, ≥2 of 4 associated features (i.e., pulsatile quality, unilaterality, activity-limiting or worsening with activity, and moderate to severe intensity), and association with nausea, vomiting photophobia, or phonophobia. Premonitory and aura symptoms, clinical characteristics of the headache, and pain-related disability should also be assessed.

Treatment should aim for fast, complete pain relief and control of associated symptoms. Most children and adolescents benefit from nonprescription oral analgesics such as acetaminophen, ibuprofen, and naproxen. Triptans are less commonly used in young patients. Although 4 have received FDA approval, 3 are limited to patients aged ≥12 years: almotriptan, sumatriptan/naproxen, and zolmitriptan. The fourth, rizatriptan, is approved for use in patients as young as 6 years. Failure to respond to 1 triptan does not preclude trying another; and ibuprofen or naproxen can be added to a partially effective triptan. The only high-confidence evidence supports oral sumatriptan/naproxen or zolmitriptan nasal spray in adolescents who are more likely to be pain-free at 2 hours than those receiving placebo. Moderate evidence supports the use of ibuprofen and intranasal sumatriptan for pain and sumatriptan/naproxen for photophobia and phonophobia. No acute treatments were effective for migraine-related nausea or vomiting.

Oskoui M, et al: Practice guideline update summary: acute treatment of migraine in children and adolescents: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2019;91:1-13. doi 10.1212/WNL0000000000008095. From McGill University, Montreal, Canada; and other institutions. **Funded by the American Academy of Neurology.**

Common Drug Trade Names*: almotriptan—*Axert*; rizatriptan—*Maxalt*; sumatriptan—*Imitrex*; zolmitriptan—*Zolmig

Duloxetine Metabolism in Smokers

Analysis of a therapeutic drug monitoring database found that despite receiving higher doses, patients who smoked cigarettes had significantly lower serum concentrations of duloxetine (*Cymbalta*) than nonsmokers. Tobacco smoking induces CYP1A2, which metabolizes duloxetine, reducing serum concentrations.

Methods: Study subjects were 125 inpatients receiving duloxetine treatment who had undergone routine therapeutic drug monitoring at a psychiatric hospital in Germany. Patients were allowed to smoke in special areas of this hospital, so there was little likelihood of the study results being influenced by smoking cessation. Subjects were excluded from the analysis if they were taking other drugs with CYP activity. Duloxetine serum concentrations were retrospectively compared between patients who smoked and those who did not.

Results: The analysis was based on 36 active smokers and 89 nonsmokers. On average, smokers received higher daily doses of duloxetine: 90 mg/day vs 60 mg/day in nonsmokers (p=0.001). However, serum concentrations were significantly lower in smokers (29.25 ng/mL vs 47.5 ng/mL; p=0.002). The concentration-to-dose ratio was also significantly lower in smokers (0.325 vs. 0.7; p<0.001).

Discussion: Smoking status should be evaluated in patients who are prescribed duloxetine as smokers may require higher maintenance doses of duloxetine than nonsmokers. Dosage should be individualized because of the high interindividual variability of duloxetine metabolism. In addition, smoking cessation by a patient receiving a stable dose will likely be followed by a rapid and considerable increase in duloxetine concentrations. Therapeutic drug monitoring can avoid adverse drug reactions in these patients.

Augustin M, et al: Differences in duloxetine dosing strategies in smoking and nonsmoking patients: therapeutic drug monitoring uncovers the impact on drug metabolism. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.17m12086. From Aachen University, Germany; and other institutions. **This study was conducted without funding. Three of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Reference Guide

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.