PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Dupilumab for Nasal Polyps

The FDA has approved dupilumab (*Dupixent*) injection for the treatment of adults with chronic rhinosinusitis with nasal polyps that has not been adequately controlled with intranasal steroids. In clinical trials, nasal polyp size and nasal congestion were significantly reduced in patients who received dupilumab, compared with placebo. Actively treated patients also reported increased ability to smell and required less oral steroid use and nasal polyp surgery. Dupilumab, which is also approved for treatment of eczema not controlled by topical therapies as well as moderate-to-severe eosinophilic and corticosteroid-dependent asthma, has been associated with serious allergic reactions and with conjunctivitis and keratitis. Injection site reactions are also common. Patients receiving treatment with dupilumab should not receive live vaccines.

FDA News Release: FDA approves first treatment for chronic rhinosinusitis with nasal polyps. Available at www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-chronic-rhinosinusitis-nasal-polyps.

PSA Suppression and Cancer Detection

In a large, population-based cohort study, use of 5α-reductase inhibitors (5-ARIs) was associated with delayed diagnosis of prostate cancer, more advanced disease at diagnosis, and increased prostate cancer mortality.

Background: Benign prostatic hyperplasia affects more than half of men aged ≥50 years and is commonly treated with 5-ARIs (e.g., finasteride, dutasteride). These agents are known to depress serum prostate-specific antigen (PSA) levels by 50%. However, 5-ARI-induced PSA suppression may not be routinely taken into account when using PSA to screen for prostate cancer.

Methods: Study data were collected from the Veterans Administration health system. Subjects were >80,000 men who received a diagnosis of Stage I to IV prostate cancer between 2001 and 2015 and who had ≥2 years of prediagnosis medical care at the VA. Exposure consisted of prescription for a 5-ARI ≥1 year before prostate cancer diagnosis. Elevated PSA was defined as >4 ng/mL in unexposed men and >2 ng/mL in men prescribed a 5-ARI. Study patients were followed until death, last follow-up within the VA, or December 31, 2017. The primary study outcome was prostate cancer-specific mortality.

Results: Prostate cancer diagnosis was made at a mean patient age of 67 years. 5-ARIs were prescribed ≥1 year before diagnosis in 8587 men (10.6%), the vast majority of whom (98%) received finasteride. Patients were treated with 5-ARIs for a median of almost 5 years before prostate cancer diagnosis, and the median follow-up after cancer diagnosis was 6 years.

During follow-up, a total of 19,065 deaths occurred, 4513 of which were attributed to prostate cancer. After adjusting for multiple other factors, prostate cancer mortality was increased by about 40% in men who had been taking 5-ARIs (hazard ratio,* 1.39; p<0.001). Users of 5-ARIs had longer delays from the first elevated PSA to prostate biopsy

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compared with men treated with α-blockers alone or receiving no prostate medication (3.6 versus 6.4 years; p<0.001). The unadjusted PSA level at the time of diagnosis was similar in all groups, but the adjusted PSA was twice as high in patients receiving 5-ARIs as other groups. Biopsy occurred within 2 years of the first elevated PSA level in 29% of 5-ARI users, compared with 59% of nonusers. 5-ARI users were more likely than nonusers to present with higher grade, lymph node positive, and metastatic disease than nonusers. Use of 5-ARIs was associated with a 10% increase in all-cause mortality, which was entirely accounted for by prostate cancer.

Discussion: This study does not suggest that 5-ARIs are inherently unsafe or that PSA screening is ineffective in men taking these drugs. Rather, the results highlight the need for greater awareness of 5-ARI-induced PSA suppression as well as published guidelines that provide clear recommendations for cancer detection in patients treated with the agents. Systems-based solutions, such as building the adjustment into clinical decision support tools and lab value alert systems, would also be useful.

Sarkar R, et al: Association of treatment with 5a-reductase inhibitors with time to diagnosis and mortality in prostate cancer. *JAMA Internal Medicine* 2019; doi 10.1001/jamainternmed.2019.0280. From the University of California, San Diego; and other institutions. **Funded by the NIH. Three of 14 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: dutasteride—*Avodart*; finasteride—*Proscar

***See Reference Guide.**

Bremelanotide for HSDD

In 2012, the FDA identified female sexual dysfunction as one of 20 disease areas of high priority. As part of their commitment to protect and advance womens' health, they have granted approval for bremelanotide (*Vyleesi*) injection to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women.

Bremelanotide activates melanocortin receptors, but the mechanism by which it improves sexual desire and related distress is unknown. The agent is self-injected subcutaneously in the abdomen or thigh ≥45 minutes before anticipated sexual activity. Patients should not use >1 dose within 24 hours or >8 doses per month.

Women who participated in bremelanotide clinical trials experienced increases in sexual desire and decreases in distress. However, there was no difference between the active and placebo groups in the change from the start of the study to end of the study in the number of satisfying sexual events. Bremelanotide does not enhance sexual performance.

The most commonly reported adverse effects of bremelanotide in clinical trials were nausea and vomiting, flushing, injection site reactions, and headache. In the trials, about 40% of patients experienced nausea, usually with the first injection. However, 13% required medication control the nausea. Blood pressure increases were also reported after injection. Although these typically resolved within 12 hours, bremelanotide should not be used by women with uncontrolled high blood pressure, those with known cardiovascular disease, or those at high risk for cardiovascular disease. Although rare, about 1% of treated patients reported hyperpigmentation of the gums and skin, including the face and breasts. This did not resolve with treatment discontinuation in about half of the patients. Hyperpigmentation was more common in women with darker skin.

FDA News Release: FDA approves new treatment for hypoactive sexual desire disorder in premenopausal women. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-hypoactive-sexual-desire-disorder-premenopausal-women.

OCs and Bone Loss in Anorexia

Oral contraceptive treatment of osteopenia in young women with anorexia nervosa is fairly widespread but remains a matter of considerable debate. In a case-control study of patients treated in routine clinical practice, OC use was associated with increased areal bone mineral density (aBMD) that improved with an early start and longer duration of use. Effects were most pronounced in women with more severe forms of anorexia.

Methods: Study subjects were 305 young women (aged 14.5–35 years) with a diagnosis of anorexia nervosa who were consecutively treated at a university hospital between 2009 and 2016 and a control group of 121 healthy, normal-weight adolescents and young women with normal menstrual cycles. All participants completed a medical questionnaire, assays for hormones and bone metabolism markers, and DXA scans of areal bone mineral density of the whole body and the lumbar spine, femoral neck, hip, and radius. To determine the effects of OC use, 99 patients with

anorexia taking OCs were compared with 206 nonusers with anorexia.

Results: As expected, patients with anorexia had lower anthropometric characteristics (body mass index, body fat mass, fat-free soft tissue, and aBMD) than controls, as well as increased levels of CTX, a marker of bone resorption, and lower values of 2 markers of bone formation, osteocalcin and PINP.

OC users had significantly higher aBMD values for whole body and the 4 individual sites than nonusers. Most of these differences remained statistically significant after adjusting for age, weight, fat-free soft tissue, and age of anorexia onset. However, compared with the healthy control group, all aBMD measures were lower in women with anorexia who were taking OCs.

Of multiple makers of bone metabolism, the bone resorption marker CTX and the formation marker osteocalcin were significantly lower in patients taking OCs than patients not taking OCs. The type of OC, estrogen-progestin versus progestin-only, generally did not affect aBMD or bone metabolism markers. After adjustments for other factors, aBMD (whole-body and at all sites) increased with longer duration of OC use; and shorter times between anorexia onset and the start of OC use favorably affected most aBMD measurements.

Discussion: Earlier studies have not resolved the controversy about the effects on bone of OC use in anorexia because of inconsistent results, generally attributable to small sample size and short periods of observation. In the present study, the largest gain in aBMD was observed in women with >3 years of OC use and in women with the lowest BMIs. However, the favorable effects of OCs do not appear to completely offset the effects of anorexia nervosa on bone tissue. It is likely that the onset of anorexia preceded the start of OC use, leaving a period when bone tissue was not protected. Although OCs may limit bone loss in this population, they should not be used as the sole method of bone protection.

Maimoun L, et al: Oral contraceptives partially protect from bone loss in young women with anorexia nervosa. *Fertility and Sterility* 2019;111 (May):1020–1029. doi 10.1016/j.fertnstert. 2019.01.008. From the University of Montpellier, France; and other institutions. **Funded by the Centre Hospitalier Régional Universitaire of Montpellier. The authors declared no competing interests.**

New Stimulant Formulations Reviewed

In recent years, many new stimulant formulations have become available to treat ADHD. Most innovations involve the 2 existing drugs most commonly used to treat ADHD: methylphenidate and amphetamine. These new formulations offer physicians unprecedented ability to personalize treatment of ADHD.

Since the last major review of new stimulant formulations in 2004, the emphasis in drug development has been on long-acting formulations and novel delivery systems but several new immediate-release (IR) formulations have also been developed. All of the new IR formulations were designed for or can be modified for use by children who have difficulty swallowing. Some are available as solutions or chewable tablets; others are water soluble or can be crushed and mixed with food. As with older IR formulations, twice- or thrice-daily dosing is still required.

Some of the newer long-acting formulations have also been designed for ease in swallowing, as orally dissolving tablets (ODT), suspensions, solutions, or chewable tablets. Some provide a mixture of immediate- and delayed-release particles, allowing once-daily dosing. Efficacy, tolerability, and safety of these formulations are similar to earlier extended-release formulations. Lisdexamfetamine, a d-amphetamine prodrug, has also been developed as capsules and chewable tablets.

A methylphenidate transdermal patch has been introduced that delivers drug for the duration of wear time (no more than 9 hours is recommended), with absorption continuing but declining for several hours afterward. Because the onset of action takes 2 hours, IR methylphenidate may be co-prescribed to reduce the lag. Transdermal methylphenidate has comparable safety and efficacy to other formulations, but there are some unique risks: local contact dermatitis, discomfort when removing the patch, and the risk of accidental poisoning. Previously used patches still contain a large amount of the drug and could pose a hazard to children.

Several new long-acting methylphenidate formulations make use of a novel "beaded" technology, containing varying proportions of microbeads that release methylphenidate in IR and extended release forms, with a duration of action of 12–16

New Stimulant Formulations		
Methylphenidate	**Amphetamine**	**Lisdexamfetamine (amphetamine pro-drug)**
Immediate Release		
Generics formulations of *Methylin* oral solution and chewable tablets	*Evekeo* tablets *Evekeo* ODT *Zenzedi* tablet *Procentra* oral solution	—
Long-Acting Formulations		
Contempla XR ODT *Quillivant XR* oral solution *Quillichew ER* chewable tablet *Daytrana* transdermal patch *Aptensio XR* multilayer bead capsule *Adhansia XR* multilayer bead capsule	*Adzenys XR*-ODT *Adzenys ER* oral suspension *Dyanavel XR* suspension *Mydayis* triple bead capsule	*Vyvanse* capsule *Vyvanse* chewable tablet
Delayed, Extended-Release		
Jornay PM microbead capsule	—	—

hours. A delayed release/extended release methylphenidate formulation, based on a proprietary delivery system contains microbeads with 2 layers of coating, 1 that delays drug release and a second that regulates release in an extended pattern. This formulation is meant to be taken in the evening, delays release for 8–10 hours, and then provides clinical action up to 22 to 24 hours post-dose. In addition, a new triple-bead amphetamine formulation provides up to 16 hours of pharmacologic action; these capsules can be opened and sprinkled on food without altering absorption.

Steingard R, et al: New formulations of stimulants: an update for clinicians. *Journal of Child and Adolescent Psychopharmacology* 2019;29 (5):1–16. doi 10.1089/cap.2019.0043. From the Child Mind Institute, New York; and other institutions. **Source of funding not stated. Three of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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.