Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Federal Agencies, States Move Swiftly to Combat Opioid Overdose Epidemic

CDC Issues New Pain Management Guidelines

The CDC has published sweeping new opioid treatment guidelines that focus on chronic pain management. The guideline is in response to a staggering increase in opioid use nationally and the resultant opioid overdose epidemic. The new guidelines stress that opioids should not be prescribed as first-line therapy for chronic pain but, if needed, should be used with nonpharmacological and non-opioid therapy (the guidelines exclude cancer- and palliative care-related opioid use). The document recommends caution with doses higher than 50 morphine mg equivalent per day (MME/day) and avoiding doses of 90 MME/day. If higher doses cannot be avoided, prescribers need to carefully justify dose escalation due to the increasing risk of harm and overdose with doses > 90 MME/day. Patients initiated on opioids should receive immediate-release products at the lowest effective dose. Physicians should conduct regular reevaluations with assessment of risks and benefits at least every 3 months. State prescription databases should be used to determine whether patients are receiving opioids from other sources or are taking dangerous combinations such as opioids with benzodiazepines (a combination that should be avoided whenever possible). For treatment of acute pain, 3 days of therapy is usually sufficient and more than 7 days is rarely needed. Patients with opioid use disorder should be offered an evidence-based treatment such as methadone or buprenorphine. Naloxone should be considered for patients at high risk of overdose (*JAMA*. Published online March 15, 2016. doi:10.1001/jama.2016.1464; *MMWR* March 18, 2016).

The White House has also announced measures to combat opioid abuse, including increasing the patient limit for clinicians who prescribe buprenorphine for addiction from 100 to 200, providing training for buprenorphine prescribers, and expanding substance use disorder treatment services, particularly in underserved populations.

Meanwhile, several states have taken action individually to curb opioid prescribing. The Massachusetts legislature passed a bill to limit post-surgical opioids to a 7-day supply, and several other New England states are considering similar measures.

More Evidence Supports Timing Hypothesis for Hormone Therapy

The "hormone-timing hypothesis" suggests that estrogen-containing postmenopausal treatment is beneficial for newly menopausal women but not for older women. A new study seems to confirm that, at least with regard to vascular effects. In an NIH-sponsored study in California, 643 healthy, postmenopausal women were stratified according to time since menopause (< 6 years [early postmenopause] or ≥ 10 years [late postmenopause]) and were randomized to estradiol 1 mg or placebo. Women with a uterus also received progesterone vaginal gel or placebo gel, respectively. The primary outcome was carotid artery intima-media thickness (CIMT) measured every 6 months.

Coronary atherosclerosis was also assessed by cardiac CT at the end of the study. After a median of 5 years, estradiol with or without progesterone resulted in a slower progression of CIMT in younger women who were within 6 years of menopause, but not in older women who were ≥ 10 years past menopause (P = 0.007 for the interaction). There was no difference in CT measures of coronary-artery calcium, total stenosis, or plaque between any of the groups. The authors concluded that oral estradiol therapy was associated with less progression of subclinical atherosclerosis (measured by CIMT) than placebo when therapy was initiated within 6 years of menopause but not after 10 years (*NEJM* 2016;374:1221-1231). This is more evidence that supports the timing hypothesis (or the critical window-of-opportunity hypothesis) for hormone therapy to slow atherosclerosis progression.

New Guidelines for Dual Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) — use of aspirin with a P2Y12 inhibitor such as clopidogrel, prasugrel, or ticagrelor — is commonly used after vascular events or procedures in patients with coronary artery disease. The duration of therapy is the subject of a new guideline from the American Heart Association and the American College of Cardiology. The guideline recommends a minimal therapy duration of 6-12 months, while therapy beyond 12 months should be reserved for patients at the highest risk of a vascular event. Low-dose aspirin generally should be continued indefinitely in all coronary artery disease patients. The full guideline was published online in the March 29 issue of *Circulation*.

FDA Actions

The FDA has added a boxed warning to all immediate-release opioids regarding serious risks of misuse and abuse, which can lead to addiction, overdose, and death. The warning includes a recommendation that the drugs only be used for severe pain for which alternative treatment options are inadequate. There also is guidance on initial dosage and dosage changes, with a warning not to abruptly stop treatment in a physically dependent patient. Pregnant women should be warned that opioids put their newborns at risk for neonatal opioid withdrawal syndrome.

The FDA has eased restrictions on mifepristone used with misoprostol used for medical abortions. The new FDA-approved regimen may be used to end pregnancy through day 70 of gestation (after the start of the last menstrual period). Previously, labeling was only approved up until day 49. The dose has also been lowered to 200 mg of mifepristone orally (down from 600 mg) followed 24 to 48 hours later by misoprostol 800 mcg buccally. The new regimen requires a visit with a healthcare provider to prescribe the medication and follow-up 7-14 days later vs the previously required three visits. The new FDA-approved regimen is in line with medical literature and has been the approved regimen in many states.

The FDA has approved reslizumab for the maintenance treatment of severe asthma in patients ≥ 18 years of age with asthma exacerbations despite usual care. Reslizumab is a humanized interleukin-5 antagonist monoclonal antibody produced in murine myeloma non-secreting 0 cells. It is given by IV infusion every 4 weeks in a clinical setting prepared to manage anaphylaxis. Safety and efficacy were established in four double-blind, randomized, placebo-controlled trials in patients with severe asthma on standard therapy. Compared to placebo, reslizumab-treated patients had fewer asthma attacks and longer time to first attack, as well as significant improvement in lung function measured by FEV_1. Serious side effects include hypersensitivity reactions, which can be life-threatening. Other side effects listed by the FDA are cancer and muscle pain. Reslizumab is marketed as Cinqair. Pricing has not been announced.

The FDA has approved ixekizumab for the treatment of adults with moderate-to-severe plaque psoriasis. The new drug is a humanized IgG4 monoclonal antibody that targets the IL-17A cytokine, a different mechanism of action than currently available biologic agents used to treat psoriasis. This is the second IL-17A antagonist after secukinumab. It is given as a subcutaneous injection every 2 weeks for seven doses, then every 4 weeks. Safety and efficacy were established in three randomized, placebo-controlled clinical trials of nearly 4000 participants with plaque psoriasis who were candidates for systemic or phototherapy therapy. Ixekizumab resulted in greater clinical response than placebo with skin that was almost clear on standard psoriasis scoring scales. The drug is an immunosuppressive and comes with the medication guide regarding risk of infection or autoimmune side effects. Ixekizumab is marketed as Taltz. It is priced at $4103 per dose (80 mcg). ■

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