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WHAT'S NEW

- **Federal health agencies** will spend $30 million studying the effects of bisphenol A, a chemical compound used in baby bottles and food containers. **4**
- **Antidepressants trump placebo,** but only for patients with very severe depression. **5**
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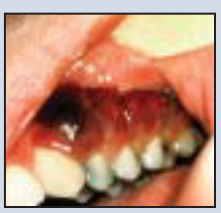
- **Risk of breast cancer death** was up to 91% higher when women took paroxetine during their course of tamoxifen therapy. **22**
- **Kaposi's sarcoma** is coming back in a more deadly form among HIV-positive patients, experts say. **30**



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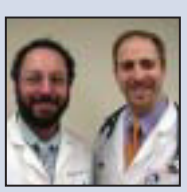

USPSTF: Start Obesity Management at Age 6

"We actually have evidence that this [recommendation]—if there is a referral center available—actually works."

BY JEFF EVANS

New recommendations issued by the U.S. Preventive Services Task Force advise that children aged 6 years and older should be screened for obesity using body mass index calculations, and should be offered or referred to services that provide intensive counseling and behavioral interventions to promote improvements in their weight status.

The task force found enough evidence to rule that the overall benefit is moderate for screening children in that age range and for offering or referring children to moderate- to high-intensity intervention programs (Pediatrics 2010;125:361-7).

Dr. Ned Calonge, the USPSTF chair, said in an interview that many pediatric care providers have been reluctant to perform screening for overweight and obesity and to refer patients for treatment because of "a real sense that it doesn't work." But "the good news is that we actually have evidence that this [recommendation]—if there is a refer-

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COURTESY JAN STAPLEMAN, COMMUNICATIONS, COLORADO DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT

Some patients will not be able to afford counseling and behavioral services, but the evidence in support of the efficacy of moderate- to high-intensity interventions should help to change insurance coverage for them, according to Dr. Ned Calonge.

Little Evidence Guides Noncancer Use of Opioids

BY SHERRY BOSCHERT

One of the first systematic reviews of data on long-term use of opioids found weak evidence to support the idea that adults who take chronic opioids get chronic pain relief, though effects on function or quality of life are unclear.

In a Cochrane Collaboration review of 26 prospective studies with 4,893 participants, 6%-23% of patients dropped out of the clinical trials (depending on the route of drug administration) due to inefficacy or side effects, but those who finished the studies maintained clinically significant reductions in pain during up to 48 months of opioid use, Meredith Noble and her associates reported.

VITALS

Major Finding: When opioids were used long term for noncancer pain, 6%-23% of patients stopped taking them due to inefficacy or side effects and 0.3% developed signs of addiction.

Data Source: Cochrane Collaboration review of 26 clinical studies with 4,893 participants.

Disclosures: None

The review also suggested that opioid abuse or addiction was rare, but acknowledged that the findings are compromised by the limited quantity and poor quality of the studies. Only 7 (0.3%) of 2,613 patients developed signs of addiction or took their medicine inappropriately in the studies that reported those outcomes (Cochrane Database Syst. Rev. 2010 [doi: 10.1002/14651858.CD006605]).

Most of the studies excluded patients with risk factors for abuse. The low rate of addiction may be generalizable only to patients with no history of abuse or addiction, wrote Ms. Noble, a senior research analyst at the Economic Cycle Research Institute, 1 of 14 evidence-based practice centers under the U.S. Agency for Healthcare Research and Quality. A previous study suggested that addiction

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Addiction Figures 'Misleading'

Opioids *from page 1*

or abuse may develop in 3% of patients in all studies of opioid use for chronic pain and in 0.2% of patients in studies that screened out participants with a history of abuse or addiction (Pain Med. 2008;9:444-59).

The evidence of long-term relief of noncancer pain with chronic opioid use was too sparse in the current review to draw firm conclusions about the treatment's effectiveness, including any quantification of mean level of relief from noncancer pain, the investigators concluded. All of the studies had low internal validity, making it highly likely that future studies could overturn their findings.

Among 3,040 patients treated with oral opioids, 23% discontinued treatment due to adverse effects and 10% dropped out of the trials because of insufficient pain relief. Among 1,628 on transdermal opioids, 12% stopped due to adverse effects and 6% stopped due to insufficient pain relief. Intrathecal pumps delivered opioids in 231 patients who could not find pain relief any other way; of these, 9% stopped due to adverse effects and 8% dropped out due to insufficient pain relief.

One of the studies in the review was a randomized trial comparing two opioids; the other 25 studies were case series or uncontrolled continuations of short-term trials of opioids for noncancer pain. None of the studies included comparisons with placebo or nonopioid therapies.

The only other systematic review of long-term opioid use for chronic noncancer pain was a 2008 study by the same investigators that used somewhat different methodology.

All of the patients had been taking opioids for at least 6 months after failing previous nonopioid therapy for noncancer pain of at least 3 months duration, mainly chronic back pain, severe osteoarthritis, or pain related to nerve damage.

Solid estimates are lacking for the number of people with chronic noncancer pain who are taking opioids long-term and what they are taking. Two U.S. studies suggest that 0.65% of people with medical insurance use opioids chronically and that 10% of people who claimed insurance coverage for opioids had at least a 3-month supply.

The Cochrane Collaboration is an international nonprofit, independent organization focused on systematic reviews of health care interventions.

However, three pain experts said in interviews that they fear clinicians might read too much into the review's limited findings.

The report is "very encouraging, but it's far from the whole story," Dr. Perry Fine said. A literature review does not necessarily reflect concerns in real-life practices. Because there are no good substitutes for opioids on the horizon, physicians need to find ways of making long-term opioid use more effective and safe, he said.

Dr. Fine, who is president-elect of the American Academy of Pain Medicine (AAPM) and professor of anesthesiology at the University of Utah, Salt Lake City, compared current use of long-term opioids for noncancer pain with the use of surgical anesthesia 20-30 years ago when it was associated with significant morbidity and mortality.

"That didn't stop us from doing surgical procedures when necessary," but it did motivate research and improvements in patient selection, monitoring, and dosing that led to the very low rates of morbidity and mortality with anesthesia today, he said.

Dr. Adrian Bartoli, a pain specialist practicing in San Francisco, said he was disappointed that the authors of the review implied that patients who have had a prior problem with addiction should be excluded from opioid therapy for chronic noncancer pain. "There's nothing in this analysis that would suggest that. That was their opinion," he said.

He also noted that the review muddled concepts of pain and addiction, referring to addiction in terms of tolerance and dependence, which are very different concepts.

"I got the sense that they felt that patients could be imbued with addiction by taking a medicine like a narcotic," Dr. Bartoli said. "It's a genetically predisposed condition."

On the other hand, he worried that the report of a very low rate of addiction may lead primary care physicians, in particular, to put patients with chronic noncancer pain on long-term opioids without sufficiently considering other remedies or medications.

"The pharmaceutical industry over the past 10 years has been incredibly strong in trying to move these narcotics onto the market and to put the primary care physicians at ease that they are not prescribing something that has a risk of addiction or abuse," he said. "This review probably is going to reinforce that. Ultimately, there are pros and cons to that occurring."

Primary care internist Roger Chou agreed, saying that the 0.3% rate of addiction reported is "a little misleading, because it's based on pretty crummy data." The review's findings on addiction, pain relief, and adverse events apply to very select groups of patients, not the more complicated cases that raise concerns for physicians considering long-term opioids.

Mainly, the review shows how little is known about prescribing long-term opioids, suggested Dr. Chou, of Oregon Health and Science University, Portland, and lead author of clinical guidelines on chronic opioids for noncancer pain by the American Pain Society and the AAPM. "We really don't have good quality, long-term data on this, which is scary because we're prescribing these medications so much," Dr. Chou said. Over the past 2 decades, "we're prescribing more, but we're also prescribing higher doses and more Schedule II drugs," which have a higher potential for abuse. ■

Disclosures: *None of the commentators was associated with the Cochrane review. Dr. Bartoli and Dr. Chou reported no potential conflicts of interest. Dr. Fine has been a speaker for Wyeth and an adviser and consultant for many pharmaceutical companies that manufacture opioids.*

IL-6 Blocker Approved as Second-Line RA Treatment

BY DIANA MAHONEY

The monoclonal antibody tocilizumab has received approval by the U.S. Food and Drug Administration for the treatment of moderate to severely active rheumatoid arthritis in adult patients who have failed one or more tumor necrosis factor blockers, according to an announcement made last month by the drug's manufacturer, Roche Holding AG.

Tocilizumab (Actemra) is the first interleukin-6 (IL-6) receptor inhibitor to be approved for the treatment of rheumatoid arthritis, and it can be used alone or in combination with methotrexate or other disease modifying antirheumatic drugs (DMARDs), according to the statement. The drug was co-developed by Chugai Pharmaceuticals and its parent company Roche.

The approval comes on the heels of an extensive clinical development program comprising five phase III trials as well as a resubmission of documents, including a proposal for a risk evaluation and mitigation strategy. The pivotal clinical trials include RADIATE (Research on Actemra Determining Efficacy After Anti-TNF Failures), OPTION (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders), TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy), AMBITION (Actemra Versus Methotrexate Double-Blind Investigative Trial in Monotherapy), and LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage).

In the RADIATE trial, 30% of patients who received tocilizumab in combination with methotrexate achieved disease remission compared with 1.6% of patients receiving methotrexate alone. Lead investigator Dr. Paul Emery, professor of rheumatology at the University of Leeds, England, and colleagues wrote that the findings were especially promising for that subset of rheumatoid arthritis patients who have failed to achieve adequate symptom relief with anti–tumor necrosis factor agents (Ann. Rheum. Dis. 2008;67:1516-23).

The results from the OPTION trial showed that 59% of the patients with rheumatoid arthritis who had incomplete responses to methotrexate achieved an ACR20 response following treatment with tocilizumab 8 mg/kg compared with 26% of patients treated with placebo, and 27% of the patients on tocilizumab achieved remission compared with 0.8% in the placebo group (Lancet 2008;371:987-97).

In one trial, 30% of patients who received tocilizumab in combination with methotrexate achieved disease remission, compared with 1.6% of patients receiving methotrexate alone.

Similarly, in the TOWARD trial, 61% of patients who received tocilizumab 8 mg/kg achieved an ACR20 response at 24 weeks compared with 25% of patients treated with placebo plus DMARDs, and approximately 38% of tocilizumab-treated patients met ACR50 criteria for symptom improvement, compared with 9% of patients receiving placebo (Arthritis Rheum. 2008;58:2968-80).

The AMBITION study, in which 70% of patients who received 8 mg/kg achieved an ACR20 response at 24 weeks, was the first to show that treatment with a single biologic agent was superior to methotrexate alone for the treatment of rheumatoid arthritis at 6 months, according to a press release issued by Roche when the phase III results were released in 2008 at the annual Congress of the European League Against Rheumatism

Findings from LITHE, presented by lead investigator Dr. Roy M. Fleischmann of the University of Texas Southwestern Medical Center in Dallas at the 2009 annual meeting of the American College of Rheumatology showed that, over a 2-year period, there was no radiographic progression or joint damage in 75% of rheumatoid arthritis patients taking tocilizumab 4 mg/kg plus methotrexate and 85% of those taking tocilizumab 8 mg/kg and methotrexate compared with 66% of patients taking methotrexate alone.

Among the serious tocilizumab-related adverse events that have been reported in the clinical trials are infections that lead to hospitalization or death, including tuberculosis, and bacterial, invasive fungal, viral, and other infections; gastrointestinal perforations; hypersensitivity reactions; and cellulitis, according to the press release.

In March 2009, Roche's Chugai Pharmaceuticals reported that, among nearly 5,000 rheumatoid arthritis patients in Japan who had been treated with tocilizumab between April 2008 and February 2009, 15 deaths occurred and the possibility of a link to the drug could not be denied, although the exact causes of the deaths were unknown, according to a press release from the company. ■