

Evidence Doesn't Back Isotretinoin's Rap Sheet

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KOLOA, HAWAII — Most of the reported adverse events associated with the use of isotretinoin for acne—aside from the oral retinoid's long-established teratogenicity risk—don't stand up to scrutiny, Dr. Lee T. Zane said at the annual Hawaii Dermatology Seminar sponsored by the Skin Disease Education Foundation.

Dr. Zane, a dermatologist at the Uni-

versity of California, San Francisco, provided details in the following areas regarding the reported adverse events:

► **Depression and suicidality.** Dr. Zane coauthored a recent systematic review of the medical literature that showed no support for a causal association between isotretinoin for acne and increased risk of depression or suicidal behavior.

But there's a catch: "The studies to date are either too small or otherwise limited enough that they can't rule out a weak as-

sociation," according to Dr. Zane. "Until there is compelling evidence one way or the other, we absolutely must remain vigilant in our patient care in regards to psychiatric symptoms."

Dr. Zane's systematic review included evaluation of 214 published studies addressing this issue. Most were case studies or low-quality research. Only nine reports included primary data—and only four of the nine used standardized depression rating scales. Of those four, none found any

increase in depression scores during isotretinoin therapy when compared with pretreatment. In fact, one showed a statistically significant improvement in depression scores during treatment, and two others demonstrated nonsignificant trends in the same direction (*Semin. Cutan. Med. Surg.* 2005;24:92-102).

► **Hyperlipidemia and transaminases.** Dr. Zane is a coinvestigator in an ongoing retrospective cohort study of laboratory abnormalities in nearly 14,000 acne patients aged 13-50 in a large Northern California HMO. Fourteen percent had hypertriglyceridemia at baseline; this rate jumped to 50% during isotretinoin therapy. These real-world data were surprising; the Physicians' Desk Reference (PDR) describes the hypertriglyceridemia rate in the isotretinoin clinical trials as 25%. The on-treatment incidence of triglyceride levels in excess of 1,500 mg/dL was 0.07% in the HMO study, with no values as high as 5,000 mg/dL.

Elevated transaminase levels were present in 5% of subjects prior to treatment and in 14% at some point during isotretinoin therapy, with 88% of on-treatment elevations being mild.

► **Acute pancreatitis.** Avoidance of this complication is presumably the reason millions of dollars are spent annually in laboratory screening of triglyceride levels in patients on isotretinoin. So it is perhaps surprising, Dr. Zane said, that there are only four published cases of what is believed to be isotretinoin-induced pancreatitis. All four involved overweight or obese women, two in their 40s. Two had triglyceride levels in excess of 5,000 mg/dL at onset. Baseline type IV hyperlipidemia was present in two. One woman had a history of gallbladder disease. Another was on replacement estrogen, which is known to have a strong association with acute pancreatitis.

► **Benign intracranial hypertension.** In an investigation of 179 reports of isotretinoin-associated benign intracranial hypertension, 24 reports involved prior or simultaneous use of tetracyclines. The mean time from isotretinoin exposure to diagnosis was 2.3 months. Symptoms cleared in 48% of patients upon stopping isotretinoin.

Based on the relatively quick onset of pseudotumor cerebri following isotretinoin exposure, the limited number of documented positive rechallenges, and the fact that hypervitaminosis A is a known cause, the investigators concluded that "it seems certain" that there is a direct correlation between isotretinoin use and benign intracranial hypertension (*Ophthalmology* 2004;111:1248-50).

Dr. Zane noted that neuro-ophthalmologic recommendations call for discontinuation of isotretinoin and a workup for intracranial hypertension in patients who develop headache or unexplained blurred vision, along with avoidance of concomitant vitamin A, as well as tetracycline and other medications associated with benign intracranial hypertension.

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COPD



or asthma: Not the same

Chronic obstructive pulmonary disease (COPD)—including chronic bronchitis and emphysema—is a distinct disease, yet often patients who have respiratory symptoms are misdiagnosed with asthma. However, patients can present with symptoms of COPD as early as age 40.¹ Therefore, physicians should think of COPD first in this patient population.

► **Misdiagnosis can lead to suboptimal treatment** COPD and asthma have a similar presentation: cough and/or wheezing as well as an element of airflow limitation reversibility can be present in both diseases.^{2,4} This may present a challenge in making a differential diagnosis.

A diagnosis of COPD should be considered first if patients present with a history of smoking and respiratory symptoms, such as cough, sputum production, dyspnea, or wheezing.^{2,3}

Of course, spirometry must still be used to confirm the diagnosis.² Once COPD is confirmed, a review of the postbronchodilator FEV₁ will help determine the severity level and indicate whether maintenance therapy should be prescribed.³

Some physicians may assume that patients with COPD also have asthma and treat them accordingly. However, the overlap between COPD and asthma is surprisingly low.

Specifically, only 10%–20% of patients with COPD have concomitant asthma.⁵⁻¹⁰

► **Proper diagnosis leads to appropriate intervention** Because the pathophysiology of asthma and COPD are quite distinct, they should be treated differently.⁵ For first-line maintenance therapy, evidence-based guidelines recommend the following:

Recommended first-line maintenance therapy	
COPD	Long-acting bronchodilators ³
Asthma	Inhaled corticosteroids ⁴

► **Improving COPD management** As we enter 2006, Boehringer Ingelheim Pharmaceuticals, Inc. and Pfizer Inc are continuing their efforts to expand the body of knowledge that exists about COPD. This information may help provide physicians with the facts to improve the diagnosis and management of COPD—and improve the quality of care for COPD patients.

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