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Isotretinoin (Accutane) and serious psychiatric adverse events

To the Editor: The November 2001 issue of the *Journal of the American Academy of Dermatology* included a supplement supported by an educational grant from Hoffman-LaRoche. In the interest of public health, we are commenting on 3 articles in that supplement regarding the association of isotretinoin (Accutane) and psychiatric adverse events.

In the spontaneous adverse event reporting system for isotretinoin, the organ system classification "psychiatric" has, by far, the largest percentage of all serious adverse event reports.¹ "Uses and Complications of Isotretinoin Therapy" by Charles N. Ellis and Kent J. Krach² devotes 2 sentences to psychiatric adverse events, despite the prominence of the warning in the Accutane package insert and the potential for a fatal outcome. The 2 sentences are, inexplicably, found at the end of a section entitled "Neuromuscular Side Effects."

In 1987 Dr Ellis coauthored an article entitled "Hypervitaminosis A Syndrome: A Paradigm of Retinoid Side Effects."³ We are not aware of any reason to abandon the excellent advice offered by Dr Ellis and his coauthors in this 1987 article: "Follow-up of any patient being treated chronically with retinoids should include close attention to neuropsychiatric symptoms. Neuropsychiatric abnormalities may elude detection because these are subtle changes, often ignored or minimized by patients."

Dr Douglas Jacobs is the lead author of "Suicide, Depression, and Isotretinoin: Is There a Causal Link?"⁴ This article addresses dechallenge cases, but resolution of symptoms within days of isotretinoin discontinuation is presented as evidence against a causal association: "Clinical depression would not be expected to lift immediately after removal of a drug, but usually would

require further treatment or, if left untreated, would take many weeks or even several months to lift." In fact, it is the prompt resolution of symptoms that suggests a substance-induced mood disorder instead of a primary (coincidental) psychiatric disorder.⁵

At the Dermatologic Advisory Committee meeting in September 2000,¹ the Food and Drug Administration discussed 40 reports of patients who experienced psychiatric symptoms while taking Accutane, recovered after the Accutane stopped, and had recurrence of symptoms during a second course of Accutane (positive rechallenge). Of these patients, 75% had no reported psychiatric history before Accutane therapy. With the first course, recovery was reported with Accutane discontinuation or course completion in 26 patients, lower dosage for 4 patients, and discontinuation of Accutane and additional medical intervention for 5 patients (insufficient data for remaining 5 patients). The median time to recovery after discontinuation of Accutane was 4.5 days, which is consistent with the terminal elimination half-life of isotretinoin and its metabolites, 10 to 50 hours.⁶ When the drug was restarted, the time to onset of psychiatric symptoms was on average shorter, and 10 patients reported persistent psychiatric symptoms after Accutane discontinuation or medical intervention.

Reports that document positive rechallenge do not prove a causal relationship for events such as depression that have a high background rate and a chronic remitting natural history. Nonetheless, positive rechallenges are very important evidence in overall causality assessment of isotretinoin and psychiatric adverse events. In "Suicide, Depression, and Isotretinoin: Is There a Causal Link?" Dr Jacobs and his colleagues do not address these rechallenge cases.

Dr Jacobs and his coauthors state: "It is important to note that there were no reports of depression in the controlled clinical trials of isotretinoin." No reference is provided for this important statement. If this claim refers to the initial studies that supported the 1982 approval of Accutane, it is more important to note that adverse events in those long-ago trials were reported only if the individual investigator thought they were causally related (a clinical trial practice no longer considered acceptable). As noted by the authors, in-depth psychiatric evaluation is necessary because significant psychiatric symptoms often go unrecognized and undiagnosed. We are not aware of any trial as yet that has included

in-depth psychiatric evaluations as defined by Dr Jacobs.

This article ends with a discussion of biologic plausibility that does not include the reported psychiatric side effects of hypervitaminosis A.³ The authors do discuss research clearly demonstrating an important role for retinoic acid in adult mammalian brain function. We do not think that this research is nonsupportive of plausibility simply because isotretinoin must be isomerized to bind retinoid receptors and there is no direct evidence for such isomerization in the central nervous system. The article does not address whether direct evidence has yet been sought. Even if direct evidence had been adequately sought and found lacking, there is no reason to assume that all biologic actions of retinoids derive from engagement of retinoic acid or retinoid X nuclear receptors.⁷ In fact, studies conducted to date about isotretinoin and the brain have been largely confined to effects on central nervous system development or treatment of brain tumors. A complete discussion of biologic plausibility is beyond the scope of this letter, but we think it important to note that none of what is known about retinoids and the adult mammalian brain is inconsistent with a biologically plausible association between isotretinoin and psychiatric events.

The authors begin their discussion of plausibility by stating that, "There does not appear to be any evidence for a biologic basis to associate isotretinoin with depression or suicidal behavior." They end it by saying: "Thus, despite an intriguing suggestive correlation, there is little evidence to support a molecular mechanism that might underlie putative isotretinoin-induced depressive symptoms." We would add that no one currently knows the molecular mechanism for isotretinoin's efficacy. Absence of this knowledge does not argue against the causal association between isotretinoin and acne resolution.

The overview of this supplement ("Isotretinoin: A State of the Art Conference") by David R. Bickers and Jean-Hilaire Saurat⁸ wraps up the subject by stating that, "These studies demonstrate that isotretinoin is not associated with major depression or suicide." The authors support their conclusion with 2 statements, the first of which is: "A careful review of existing data indicates that isotretinoin is associated with mood disturbances but with no other symptoms of depression." The article by Dr Jacobs, in fact, references published cases that document other well-established symptoms of depression. Many spontaneous reports also note additional symptoms, such as appetite

and sleep disturbances, malaise/fatigue, and marked behavioral changes characterized by irritability, aggression, and anger.

The second statement is: "Between 1991 and 1997...34 suicides occurred... This is approximately one fifth the number of suicides that would be expected to occur in that population, based on epidemiologic data related to suicide." Here, the observed events equal only the *reported* events. It is not known how many suicides have actually occurred among patients taking isotretinoin.

We are not aware of any study, or combination of studies, adequate to support a conclusion that there is no causal association between isotretinoin and serious psychiatric events. Faced with uncertainty about causality, we urge clinicians to consider very carefully the possibility of isotretinoin-induced psychiatric adverse events. Recognizing these events and implementing appropriate intervention may prevent significant morbidity, and even be lifesaving.

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Reply

To the Editor: I am pleased that our correspondents are complimenting an article that I coauthored 15 years ago. My coauthors' and my goal is for all our articles to stand up so well to the test of time. The 2001 article¹ covers many of the same points as the 1987 article.² However, the 2001 article mentions the new information about suicide, suicide attempts, and suicidal ideation that have been reported during and after isotretinoin therapy. The 2001 article does not conflict with the 1987 article. I agree that patients taking isotretinoin must be monitored appropriately.

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Dapsone and sulfones in dermatology: Overview and update

To the Editor: We enjoyed reading this clinical review by Zhu and Stiller¹ in the September 2001 issue of the Journal that confirms the ongoing interest for dapsone therapy in dermatology, undiminished after more than 50 years of clinical application. We wish to add some information to this excellent and thorough overview.

Not only dapsone's side effects, as discussed by Zhu and Stiller, but also dapsone's anti-inflammatory action may be primarily effectuated by its metabolites dapsonehydroxylamine (DDS-NOH) and monoacetyldapsone, in vitro and in vivo.² Thus, the parent compound, dapsone, suppresses

human polymorphonuclear leukocytes (PMN) 5-lipoxygenase activity with an inhibitory concentration of 50% (IC₅₀) of 15 μ mol/L for leukotriene B₄ (LTB₄), whereas DDS-NOH's IC₅₀ is 0.0049 μ mol/L. Consequently, on topical application of dapsone and its metabolites in healthy human volunteers, and studying PMN chemotaxis to subsequently applied LTB₄, we could observe no inhibitory action of the parent compound, dapsone, whereas DDS-NOH inhibited PMN chemotaxis to subsequently applied LTB₄.³ Our experiments confirmed the observation of Prendiville and Russell-Jones⁴ who, in studying patients with acne that was dapsone treated, could not demonstrate any inhibition in LTB₄-induced PMN chemotaxis in vivo. Those metabolite-mediated effects on 5-lipoxygenase can be observed at clinically meaningful concentrations, in contrast to the parent compound-mediated inhibition of binding of LTB₄ to its receptor and dapsone's inhibition of lysosomal enzymes discussed by Zhu and Stiller, which only occur at supra-physiologic concentrations.

One of us could also establish a reduction of UVB-induced erythema by systemic intake and topical application of dapsone, albeit this sulfone exerted no effect on anthralin- or sodium dodecylsulfate-induced erythema.⁵

The hypersensitivity syndrome to dapsone is an *extremely rare* side effect. Although dapsone is applied million-fold throughout the world, in a retrospective study including all published cases and all material available through the World Health Organization and the main dapsone-producing companies, 103 cases could be compiled. The hypersensitivity syndrome occurred over a wide dose range (from 100 mg/wk to 300 mg/d), but all cases developed within the first 2 months of treatment. Of those affected, 15% died, most often from hepatic coma.⁶ Thus, frequent measurements of laboratory values during the first 2 months of treatment are reasonable. A recently recognized possible rare side effect of dapsone therapy is eosinophilic pneumonia remitting after omission of the drug and relapsing after dapsone reintroduction.⁷ Rarely, dapsone can also induce photosensitivity.⁸

As published by Coleman et al⁹ and cited by Zhu and Stiller, coadministration of cimetidine at 3 \times 400 mg/d partially prevents the metabolic conversion of dapsone to DDS-NOH and, thereby, decreases methemoglobinemia. Rhodes et al,¹⁰ however, observed that this effect vanishes after about 3 months of codosing, probably because of C-P450-enzyme induction. Therefore, if using this