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Overview of Existing Research and Information Linking Isotretinoin (Accutane), Depression, Psychosis, and Suicide

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Isotretinoin (Accutane; Hoffmann-La Roche, Nutley, NJ) is a drug closely related to the chemical structure of vitamin A. The pharmacology and toxicology of these two retinoids are similar enough to warrant comparison. Accutane is a powerful drug that its manufacturer, Roche, indicates is limited for severe recalcitrant nodular acne. This potency is also reflected in Accutane's well-known ability to produce severe birth defects if taken during pregnancy. Less well known is the risk of this lipid-soluble chemical to affect the central nervous system. Reports of intracranial hypertension, depression, and suicidal ideation with Accutane use have prompted an examination of its serious and life-threatening potential. Although Roche has added a warning to its product label for signs of depression, and suicidal ideation, this product is overprescribed for all forms of acne, including mild and moderate cases that have not been treated with alternative medications with less risk of depression and suicide. There is no contesting that this drug is effective at clearing up the most severe forms of acne, but the public must be informed of the proper limited indication for its use, because depression and suicide can follow in patients with no prior history of psychiatric symptoms or suicide attempts.

Keywords: acne, Accutane, isotretinoin, depression, suicide, vitamin A.

VITAMIN A AND RETINOIDS: CHEMISTRY, TERMINOLOGY, AND METABOLISM

Early this century, animal research revealed modifications of epithelial structure such as increased epidermal keratinization and squamous metaplasia of the mucous membrane under conditions of vitamin A deficiency. The finding that these defects could be reversed by administering vitamin A led to the emergence of vitamin A as an antikeratinizing factor.

Subsequently, vitamin A has been shown to be an essential factor in physiologic growth, visual function, epithelial cell differentiation, and reproduction, exerting its influences at the DNA level, where it plays an important role in regulating transcription of a number of genes.

The first synthesis of vitamin A 50 years ago opened a new era in the chemical synthesis of vitamin A derivatives, collectively known as retinoids. First synthesized in 1955, isotretinoin (Ro 4-3780, Accutane; Hoffmann-La Roche, Nutley, NJ), a first-generation retinoid, was shown to be highly efficacious in the therapy of disorders of keratinization (e.g., Darier disease, ichthyosis).[1] Although the term *vitamin A* has been used to denote specific chemical compounds such as retinol or its esters, this term is now used more as a generic descriptor for compounds that exhibit the biologic properties of retinol. Retinoid refers to the chemical entity retinol and other closely related naturally occurring derivatives. Retinoids also include structurally related synthetic analogs, which need not have retinol-like activity.[2]

Isotretinoin is a metabolic product of dietary vitamin A and provitamin A carotenoids. Retinol (vitamin A) is absorbed from the gastrointestinal tract and metabolized in the liver to retinal. Retinal is then irreversibly oxidized to retinoic acids, which reversibly

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interconvert. The two isomers (retinoic acid and 13-retinoic-acid) have identical chemical structures. Isotretinoin and retinoic acid are further metabolized to oxo-isotretinoin and oxo-retinoic acid, respectively, which also exhibit reversible interconversion.[3] The elimination half-life of isotretinoin and its 4-oxo metabolite are 29 and 22 hours, respectively.[4]

ACCUTANE: MECHANISM OF ACTION IN ACNE AND ADVERSE EFFECTS

Peck et al[1] were the first investigators to demonstrate this drug's value in the treatment of severe acne. In September 1982, the U.S. Food and Drug Administration (FDA) approved it for use in the United States. From 1993 to 1997, prescriptions in the United States jumped 52%, reaching 1.5 million annually.

Acne is caused by an interaction of the normal skin bacteria with the patient's abnormal sebaceous lipids[5] and is associated with increased sebum production and ductal cornification. The acne bacteria, *Propionibacterium acnes*, reside on the surface of the skin in high numbers, especially in oil-rich areas. If they colonize the pilosebaceous duct in the presence of comedones (blackheads and whiteheads), inflammation is often triggered, resulting in papules, pustules, and, if inflammation is more expansive, nodules. Although the exact mechanism of the antiacne action of isotretinoin is unknown, it is unique in its ability to affect to some degree all the known etiologic factors of acne, resulting in reduction of sebum production, lessening of comedogenesis, and a decrease in surface and ductal colonization by *Propionibacterium* acne.[6]

Over the years, Accutane has proven its effectiveness in the treatment of severe recalcitrant acne. Nevertheless, it is associated with a long list of side effects that are frequent, varied, and, at times, severe. The most commonly occurring adverse reactions are those involving the skin and mucous membranes, which occur in all patients treated with Accutane. Other side effects reported include skin fragility, pyogenic granuloma-like lesions and epidermal blistering, paronychia, and alopecia.[7] Gastrointestinal intolerance occurs in 20% of patients treated.[7] Muscular or joint pain is quite common with Accutane use. Myalgia and arthralgias, which occur in 16% of patients treated, usually abate when the medication is discontinued.[8]

Blepharitis and conjunctivitis associated with Accutane use were recognized well before its marketing. Corneal opacities and acute myopia have been reported in government publications and in the ophthalmologic literature. Other ocular reactions include optic neuritis, cataracts, decreased night vision, blurred vision, and photosensitivity. Pseudotumor cerebri (PTC), or benign intracranial hypertension, and headaches are also associated with the drug. In common with other retinoids at pharmacologic doses, Accutane causes elevation of serum lipids, particularly triglycerides.

HYPERVITAMINOSIS A

An intake of retinoids greatly in excess of requirement results in a toxic syndrome known as hypervitaminosis A. Some or all the symptoms of hypervitaminosis A also are the major toxic effects that are manifest during the therapeutic use of natural and synthetic retinoids such as Accutane in the treatment of skin disorders. Vitamin A (retinol) is ingested in the diet as retinyl esters, which are transported to the liver and hydrolyzed in hepatic parenchymal cells. Excess retinol is converted to retinyl esters again and stored in the liver. Retinol binds to retinol binding protein. When the amount of vitamin A present exceeds the capacity of retinol binding protein to bind to it, the excess retinol binds to lipoproteins and has toxic effects in this form.[9]

There are two types of hypervitaminosis A: acute and chronic. Acute hypervitaminosis A results from ingestion of a high dose of vitamin A over a short period. Signs and symptoms of acute poisoning include drowsiness, irritability or irresistible desire to sleep, severe headache caused by increased intracranial pressure, dizziness, hepatomegaly, vomiting, papilledema, and, after 24 hours, generalized peeling of the skin.[10] Chronic hypervitaminosis A is more common than the acute form and results from continued ingestion of high doses for months or even years. Symptoms include anorexia, dry itchy skin, alopecia, increased intracranial pressure, fatigue, irritability, somnolence pronounced craniotabes and occipital edema, skin desquamation, fissuring of the lips, pain in the legs and forearms, neurologic disturbances, lethargy, and elevated blood lipids.[11]

Most frequently, high intakes in children are the result of overzealous prophylactic vitamin therapy on the part of parents. Toxicity in adults has resulted from extended self-medication or food fads as well as from the use of retinoids for the therapy of acne or other skin lesions. The toxicity of retinol depends on the age of the patient, the dose, and the duration of administration. Although vitamin A toxicity is uncommon in adults who consume retinol at a rate of less

than 30 mg/d, mild symptoms of chronic retinoid intoxication have been detected in individuals whose intake was approximately 10 mg/d for 6 months.[9] In infants, the daily consumption of as little as 7.5 to 15 mg of retinol for 30 days has induced toxicity. The acute consumption of more than 500 mg of retinol in an adult, 100 mg in a young child, or 30 mg in an infant frequently results in poisoning. Acute and sometimes fatal poisoning in human beings also is known to follow the ingestion of polar bear liver, which contains up to 12 mg of retinol per gram. The Food and Nutrition Board of the National Research Council (1980) has warned that the ingestion of more than 7.5 mg of retinol daily is ill advised. Nevertheless, almost 5% of users of vitamin A in the United States exceed that amount.

PSYCHIATRIC ADVERSE EVENTS

Vitamin A intoxication resulting in generalized as well as central nervous system (CNS) symptoms was first alluded to in 1856 by Elisha Kane,[12] the Arctic explorer. He recorded symptoms of vertigo, headache, drowsiness, and irritability after ingestion of polar bear liver. Over the succeeding 140 years, case reports of the occurrence of acute schizophrenia or remitting psychosis associated with either hypervitaminosis A[13–15] or vitamin A deficiency[16] have appeared in the literature. These provide literature precedent and biologic plausibility for the hypothesized causal role of vitamin A in psychiatric disorders.

In 1972, Restak[17] reported a case of toxic psychosis in a patient after vitamin A treatment (50,000 IU administered two to three times daily) for acne, which required hospitalization. Approximately 6 months after initiating vitamin A therapy, the patient experienced the onset of prolonged depression, bouts of elation alternated with despondency, disturbed sleep, insomnia, and loss of appetite. Twelve months later, while on holiday, she became more agitated and depressed and lost weight. She also developed blurred vision, hyperacusis, vertigo, strong feelings of ego alienation, and lethargy. After psychiatric referral, total remission occurred over 6 months of close observation and antidepressant therapy. The authors cautioned against the "use of the vitamins as preventatives for such benign entities as acne."[18]

In 1992, a case report described a patient with no previous psychiatric history who presented with a 1-year history of depressed mood and poor concentration.[19] Medications included only a multivitamin preparation of 25,000 IU of vitamin A per day for 2 years. The Hamilton Depression Rating Scale confirmed full cessation of depressive symptoms after stopping treatment. Other reports of lethargy, loss of interest in surroundings, insomnia, listlessness, profound daily fatigue, anorexia, and irritability in association with vitamin A have been documented.[20–24]

PSEUDOTUMOR CEREBRI

First described by Gerber et al[43] in 1954, benign intracranial hypertension or PTC has long been associated with vitamin A administration.[25,26] PTC is accompanied by symptoms such as papilledema, vision problems, nausea, and severe headaches. PTC occurs in 30% to 50% of patients with hypervitaminosis A[27] and is characterized clinically by three criteria: neurologic and ocular symptoms and signs of increased intracranial pressure, which may include headache, nausea, transient visual obscurations, sixth-nerve palsies, and papilledema; radiologically demonstrable normal or small-sized cerebral ventricles; and elevated cerebrospinal fluid.[4,28]

PTC has been associated with isotretinoin therapy[29,30] and the retinoid etretinate.[31] The risk of PTC may increase with combination therapy with tetracycline.

CASE REPORT

A consumer brought a products liability action against Roche, alleging that the defendant failed to adequately warn of the association of Accutane with PTC and the dangers of concomitant use of Accutane and certain antibiotics such as minocycline (Minocin), a tetracycline derivative. A female patient was prescribed Accutane on November 8, 1982, for acne in addition to continuation of Minocin therapy. Six weeks later, a neurologist diagnosed papilledema and PTC. Steroids were prescribed to treat the PTC; as a result, the appellant experienced avascular necrosis. The appellant underwent several surgeries to replace both hip joints and a shoulder joint. The appellant's theory of recovery at trial was premised on her presentation that (1) "Accutane is so similar chemically to vitamin A that appellees either were aware, or should have been aware, that Accutane also had the potential to cause PTC" and (2) "because the two antibiotics the appellant was receiving were both associated with PTC, the combination of the two increased that risk." Dr. Elias, one of the physician investigators who participated in the clinical trials of Accutane, testified that the testing done by the appellees before FDA approval was

deficient because it failed to monitor for neurologic toxicity and that because of the similarity to vitamin A, Roche should have predicted the same association of Accutane with PTC. In addition, even in the absence of specific instances of PTC in clinical trials, Roche should have predicted an association and should have warned of this possible effect. In fact, the *Investigational Drug Brochure* dated March 20, 1978, which contains an extensive listing of abnormalities in its Precautions and Warnings section, stated that in patients with chronic vitamin A intoxication, "papilledema with increased intracranial hypertension" was a reported associated abnormality. The same document also stated, "A review of the clinical studies discussed in this brochure indicates that the adverse reactions seen with the use of orally administered Accutane are essentially those of hypervitaminosis A."

:ETINOIDS IMPLICATED N SCHIZOPHRENIA

Goodman[32] has recently proposed retinoid dysregulation as a possible cause of schizophrenia. Schizophrenia is now considered to be a neurodevelopmental disorder, with first evidence of the disorder occurring in the midgestational period, the time when the fetal brain is actively developing. Vitamin A, which is essential in gene regulation and expression, is particularly active in brain neurodevelopment at this time. Goodman[32] has put forward three lines of evidence for an association. The first is the resemblance of symptom presentations of retinoid toxicity to the stigmata of schizophrenia (e.g., thought disorder, mental deficit, enlarged ventricles, microcephaly, congenital malformations). The second line of evidence comes from the finding that specific gene loci linked to schizophre- n re also known loci of genes within the retinoid signaling system. Retinoids are handled in the body t a complex genetic cascade necessary for the metabolism of retinol to retinoic acids. The major genes in the retinoid cascade are the nuclear retinoid receptors RAR and RXR. The loci of two of the genes involved in the regulation of this cascade, RXR_ and RAR_, have been suggestively linked to schizophrenia. Recently, RXR was shown to be necessary for the expression of dopaminergic neurons in the midbrain region in mice, which have been implicated by numerous studies as abnormal in schizophrenia.[33] The third line of evidence shows schizophrenia genes as targets of retinoid regulation. Retinoic acid binds to RARs and RXRs, and these complexes then bind to specific regions of target genes, thus regulating the expression of multiple target genes. Among the many genes shown to be targets of retinoic acid are dopamine and serotonin, both of which have been proposed as candidate schizophrenia genes.[18] Alteration of neurotransmitters is a classic hallmark of the psychoses. Recent work has shown that retinoic acid is a major regulator of several of the genes involved in neurotransmission.[34]

ACCUTANE AND DEPRESSION LITERATURE REPORTS

In the past, depression associated with Accutane therapy has been described as idiosyncratic. The increasing number of reports of depression associated with Accutane use suggests that it is not the rarity it was once considered to be. Between 1982 and 1998, 24 cases of psychologic distress associated with the use of this drug were reported in the literature. Most of these cases reported the subsequent emergence of depression with features similar to those of hypervitaminosis A.[18] Other authors have published case reports of vitamin A poisoning.[35–46]

Systemic side effects are generally less significant if therapy is short term. Whereas transitory abnormal elevations in serum transaminases are rare, hyperlipidemia is frequent, with 25% of patients developing increased triglyceride levels and, less frequently, increased cholesterol and low-density lipoproteins and decreased high-density lipoproteins.[47] Myalgia and arthralgia are common complaints. Headaches occur and rarely are a symptom of PTC. Occasionally, patients have drug-associated depressive episodes. Long-term therapy may produce skeletal side effects, including diffuse idiopathic skeletal hyperostoses, extraskeletal ossification (particularly at tendinous insertions), and, in children, premature epiphyseal closure.[4]

In 1983, 1 year after market release, Hazen et al[48] reported that 5.5% (6 of 110) of patients with acne experienced depressive symptoms manifested by malaise, crying spells, and forgetfulness within 2 weeks of commencing isotretinoin therapy. Meyskens[49] also noted similar psychologic changes in patients with cancer treated with isotretinoin at a rate of 3 mg/kg/d. The Adverse Drug Reaction Reporting System of the American Academy of Dermatology received reports of 104 suspected adverse reactions to isotretinoin between October 1982 and June 1985, of which 22.1% (23 of 104) represented CNS disorders, which are second in frequency to skin and mucous membrane reactions (29 of 104 [27.9%]).[7] These CNS reactions included headache, depression, dizziness, and personality disorder. Scheinman et al[50] reported

that 1% of patients treated with oral isotretinoin developed psychiatrically diagnosed depressive symptoms of great enough severity to interfere with their normal functioning. In this particular report, the relation between depression and isotretinoin therapy was confirmed by rechallenge. This association was also confirmed by Villalobos et al's patient,[51] who reported the onset of hallucinations and paranoia on day 11 of isotretinoin therapy, which subsided when drug intake was stopped and recurred shortly after resumption of isotretinoin.

Cessation of depressive symptoms does not always occur on withdrawal of the drug. In Italy, Gatti and Serri[52] reported a case of suicide that occurred 2 months after stopping isotretinoin therapy. Bravard et al[53] described case reports of depression in patients with no prior depressive history. One of these patients attempted suicide during the fourth month of isotretinoin therapy, and one committed suicide 3 months after cessation of therapy.[18] Byrne et al[54] described three patients who presented with severe depression requiring active treatment. In all three cases, the patients' moods improved with antidepressant therapy. Despite the recurrence of the patient's acne in one case, follow-up showed no depressive symptoms, as confirmed by a score of 5 on the Hamilton Depression Rating Scale.

ADVERSE DRUG REACTION REPORTS

Although isotretinoin has been associated with severe depression and even suicidal behavior that may remit when the drug is withheld, a definite cause and effect relation has not been established. In fact, it is not surprising that the presence of severe acne itself may predispose teenagers and young adults to depression. Nonetheless, this possible side effect of isotretinoin should be kept in mind whenever the drug is prescribed.[55]

Middelkoop[18] conducted a pharmacoepidemiologic analysis of Accutane and other drugs used to treat acne and reports of suicide, depression, and other psychiatric adverse drug effects. Among the many products available, ethinylestradiol and cyproterone (Dianette), doxycycline, minocycline, oxytetracycline, and tetracycline are five of the most commonly prescribed antiacne treatments. Based on available information, there are more reports of psychiatric adverse events and suicide worldwide attributable to isotretinoin than to the use of the other five acne therapies combined (Table 1, World Health Organization [WHO]). Worldwide, 1830 reports of psychiatric events attributable to the six medications were identified, of which isotretinoin was implicated in 59.8% (1095 of 1830 events). Second to isotretinoin was minocycline, implicated in 14.2% (261 of 1830 events). Suicide and suicidal ideation were reported in association with the use of Accutane in 47 and 56 cases, respectively, with none being reported for the other medications. Of 75 cases of attempted suicide reported, 89.3% (67 of 75) were associated with the use of isotretinoin, 4% (3 of 75) were associated with the use of both Dianette and tetracycline, and 2.6% (2 of 75) were associated with minocycline use. Adverse drug reaction (ADR) data for the United Kingdom (Table 2, Medicines Control Agency) reflect a similar pattern, with 51.9% (135 of 262) of psychiatric ADRs attributed to isotretinoin. In addition, all cases of suicide/suicide attempt/suicide ideation were associated with the use of this medication. The source for these data relies on voluntary reporting and probably represents significant underreporting, because not all serious ADRs are reported.[18]

Table 1. Rate of ADRs reported for 6 acne medications.

Acne medication	Extract period	Number of Psychiatric ADR reports	Estimated patient exposure	Rate of Psychiatric ADRs per million
*Dianette	1980–Mar 1998	55		
*Doxycycline	1965–Mar 1998	213		
*Minocycline	1971–Mar 1998	261		
*Oxytetracycline	1965–Mar 1998	37		
*Tetracycline	1964–Mar 1998	169		
Total Combined		735	300 million	2.5
†Roaccutane	1982–Oct 1997	1095	6 million	182.5

*Data provided by WHO, cut-off date March 1998. ADR, adverse drug reaction.
†Data provided by WHO, cut-off date October 1997.
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Table 2. Number of cases of suicide, suicide attempt and suicide ideation received for acne medications.

Acne medication	Extract period	Suicide	Suicide attempt	Suicide ideation	Total	Estimated patient exposure	ADRs reported per million people
*Dianette	1980–Aug 1998	—	3	—	3		
*Doxycycline	1965–Aug 1998	—	0	—	0		
*Minocycline	1971–Aug 1998	—	2	—	2		
*Oxytetracycline	1965–Aug 1998	—	0	—	0		
*Tetracycline	1964–Aug 1998	—	3	—	3		
Total Combined			8		8	300 Million	0.03
†Roaccutane	1982–May 1998	47	67	56	170	6 Million	28.34

*Data provided by WHO, cut-off date August 1998. ADR, adverse drug reaction.
†Data provided by Roche Laboratories Ltd. Irl., cut-off date May 31st 1998.
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Table 3 shows the number of prescription items dispensed in the United Kingdom from 1982 to 1997. Although it attracted the largest percentage of psychiatric ADRs, isotretinoin had the lowest number of prescriptions issued (12,400 prescriptions). During this period 1,214,600 prescriptions were dispensed for Dianette, of which the indication for 184,200 prescriptions was acne. Dianette was implicated in only 1.9% (5 of 262) of psychiatric ADRs.

Minocycline is used extensively in the treatment of acne vulgaris (8,802,000 prescriptions issued between 1982 and 1997). Between 1970 and 1997, 6.5 million patients[56] were treated with minocycline in the United Kingdom. A total of 45 psychiatric adverse events were received by the Medicines Control Agency between 1973 and 1997. Accutane has a patient exposure of 50,000 in the United Kingdom (8 million worldwide, PharmFocus data), and there have been reports of 135 Accutane-related psychiatric adverse events. Based on these figures, the incidence rates of psychiatric adverse reactions for Accutane and minocycline are 270 and 0.692 per 100,000 people treated, respectively. The five medications studied (with the exception of Accutane) are used to treat conditions other than acne. Because patient exposure data for these medications for which the indication was acne was unobtainable, the frequency of psychiatric reactions attributable to these medications in the population of patients with acne remains unknown. Middelkoop[18] concluded that Accutane is several hundred times more likely to cause depression than the five other acne medications studied.

Table 3. Number of suicide-related cases recorded on Roche database between November 1997 and May 1998.

	Nov 30, 1997	Mar 15, 1998	May 31, 1998
Suicide	26	38	47
Suicide attempt	37	47	67
Suicide ideation	24	37	56
Total	87	122	170

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U.S. FOOD AND DRUG ADMINISTRATION MEETING OF THE DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE ON ACCUTANE-ASSOCIATED PSYCHIATRIC EVENTS ON SEPTEMBER 19, 2000

Several experts from Roche as well as the FDA addressed the issue of Accutane and depression and suicide.

Dr. Russell Ellison (Roche) stated, "We had a signal (psychiatric events) which had yet to be confirmed, and stated that Roche has been very diligent in trying to evaluate and trying to confirm this signal." He and his consultants (Drs. Nelson and Jacobs) opined that there was insufficient evidence to attribute causality to the Accutane psychiatric toxicity reports: "We believe that the evidence from these investigations does not support a causal association between Accutane and psychiatric events, including suicide. That is, the signal has not been confirmed by these investigations."

Dr. Robert Nelson (Pharmacoepidemiological Analysis; Hoffmann-La Roche, Nutley, NJ) provided

his analysis and opinions: "Suicide attempts and completed suicides. Suicidal ideation is under DSM-IV as a depressive case. There was a total—and this is worldwide total—of 168 reports before the data lock point. 104 were attempts; 64 were completed suicides. My overall conclusions ... given no clear biologic plausibility, no consistent pattern in the data that I reviewed, complex environment of background symptoms, very high background rates of disease, very high background rates of alternative risk factors, I conclude that there is no evidence in these data to support a causal relationship between Accutane administration and psychiatric disorders."

Dr. Mills, an epidemiologist, commented on and criticized Middelkoop's data[18] (slide presented by Liam Grant): "If I remember the slide correctly, ,400,400 prescriptions for one of the antibiotics with no suicides, no suicidal ideation. Now, you tell me that there's a population of a million and a half people anywhere in this country where nobody has any of those problems. It's a classic case of poor reporting. I personally would make absolutely nothing out of the data there for that simple reason, that you're just not getting accurate reporting at all."

Richard Josephson, a lawyer who has represented Roche on regulatory and other matters, pleaded with the Advisory Committee for a scientific review: "In law and in science we have adopted your methodologies. After years of not considering the scientific method in courts, we now have adopted from science the scientific method. If you look just briefly at the scientific method, they ask on the question of the contention of whether Accutane causes psychiatric reactions, the extent to which the theory has been assessed based on scientific valid reasoning and methodology, whether the theory has been subjected to peer review, case reports versus peer-reviewed studies, whether the theory is only based on subjective belief or speculation, whether there is a potential rate of error in this case in the adverse drug reports, and whether the underlying theory or technique has been generally accepted as valid by the scientific community. I merely ask you to consider the fact that you now have a label, which under the scientific method, no one here can conclude that Accutane causes those effects. As you consider what remedial action, if any, is needed or additional action is needed, I only ask that you keep that in mind."

Dr. Alan Byrne (FDA) stated, "Therefore, in relation to isotretinoin, my clinical observations have been that this agent can influence mood in certain individuals. My feeling is that the effects on mood may be very persistent, and obviously anything that can precipitate a depressive illness may be life-threatening, because there is a significant risk of suicide with depressive illness."

Dr. Marilyn Pitts (FDA, Case Review) offered the following comments: "The top 10 adverse events for Accutane include depression, ranked number 6. By contrast, we looked at tetracycline, which is another agent used for less severe acne. We have 8 cases of depression and two deaths, and we looked at Claritin in the Adverse Effect Reporting System database, where we have 10 cases of depression and two deaths.

"In 1998, the FDA's Office of Postmarketing Drug Risk Assessment analyzed spontaneous adverse drug event reports of positive dechallenge–rechallenge cases of depression, mania, psychosis, and suicide attempt. The 2998 case series supported the Accutane labeling change, which included a warning concerning psychiatric disorders. The warning stated that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide.

"In summary, we have 41 Accutane-associated dechallenge–rechallenge cases. Seventy-six percent were without a reported psychiatric history. The median time to onset of symptoms during the first course of Accutane was 30 days, and a median recovery time of 4.5 days. During the second course, or the rechallenge course, the time to onset of symptoms was shorter in the cases that provided the information. Also, after the second course of Accutane, depression persisted in some patients after discontinuation of Accutane and/or medical intervention. There was a possible dose-response to Accutane observed in 6 patients.

"In conclusion, dechallenge–rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event. We have presented 41 cases of positive dechallenge–rechallenge which provide further evidence to support a relationshup between Accutane and depressive symptoms."

Dr. Wysowski (FDA, Postmarketing Experience Suicide and Depression) provided the following analysis: "Over the 18-year period of marketing, the FDA received reports of 37 US patients who committed suicide, 24 on Accutane and 13 after stopping the drug. Twenty-two percent of suicide cases were reported to have a psychiatric history. About 57% had other possible contributing factors for depression. In addition to the suicides, the FDA received reports of 110 US Accutane users hospitalized for depression, suicidal ideation, and suicide attempt, 85 on Accutane and 25 after stopping the drug.

"About a third of patients had positive dechallenges with psychiatric treatment, and nearly a third experienced persistent depression after drug discontinuation. One person had a positive rechallenge, while three others were rechallenged and were able to continue on Accutane with alcohol abstinence, dose lowering, and continued use of an antidepressant.

"As of May 2000, the FDA received reports of 284 US Accutane users with nonhospitalized depression. Forty-five percent were received in 1998 after depression and suicide were added as a warning to the labeling. About half of the nonhospitalized patients reported accompanying side effects such as dry mucous membranes, headaches, hair loss, and joint and muscle pain. About 50% of reports were from consumers and relatives, a higher proportion compared with most reports for most drugs.

"The top 10 adverse events reported for Accutane include depression, which ranks number 6. Of course, the degree of underreporting is unknown and may be quite substantial.

"There are several pieces of evidence supportive of a possible association between Accutane and depression and suicide. These include the relatively large number of reports of serious depression, more than for most drugs in the FDA's database, the temporal association between use of Accutane and onset of depression, positive dechallenges in individuals who felt better once Accutane was discontinued and psychiatric care was obtained, and positive rechallenges in individuals who experienced symptoms again after restarting the drug.

"So, in summary, the FDA has received reports of suicide and serious depression in US Accutane-treated patients. The case reports are suggestive of an association with Accutane but do not allow definitive determination as to whether Accutane causes depression and suicide in treated patients."

Dr. Kathryn O'Connell (FDA, Biological Plausibility and Risk Management) stated, "The first item that I mentioned was we ask ourselves, do we see psychiatric adverse events? Have they been reported with distinct substances that bind to the same physiologic receptor? Dr. Byrne and several other people have already referred to the fact that it is known that high-dose vitamin A, hypervitaminosis A, has been associated with psychiatric adverse events. If you look in the published cases about time to offset, the most useful data—actually, the paper has already been referred to, I think, by Dr. Byrne and perhaps by the sponsor as well that was published by Scheinman et al[50] in 1990. I want to emphasize that this was not a trial done to examine the psychiatric adverse events of Accutane. This was just 700 patients—I believe it was a National Institutes of Health trial that had received Accutane for various indications. It wasn't even all acne. Seven patients in that group had enough psychiatric problems to come to attention. Let's put it that way. But of those 7 patients that they reported in this paper, it's notable that the symptoms in all 7 of them resolved within 1 week of stopping Accutane, and 1 of the patients was rechallenged and did have a positive rechallenge.

"For Accutane, the central nervous system, interestingly, ranks second only to psychiatric in the highest percentage of serious adverse events—serious adverse events—in the Hoffmann-LaRoche postmarketing database for Accutane. So, I think it's clear that Accutane affects the central nervous system.

"We don't know a mechanism for the psychiatric adverse events observed with any of the retinoids . . ."

Dr. Miller recommended improvements in asking Accutane patients appropriate question to evaluate them from a psychiatric point of view: "What would help me and make my practice much easier would be to have a specific form that would be dealt with each patient that would include the pregnancy contraceptive issues, that would include the appropriate questions that I would ask from a psychiatric standpoint, because I don't know what those questions are, but those questions that the psychiatrists feel are appropriate. And upon completion of that form, I would then be able to write a prescription for a patient. But the fulfillment of the recommendations would be the sine qua non for my writing the prescription for Accutane. I think this would help."

The second question before the committee dealt with what kinds of future studies are both desirable and feasible (i.e., would further studies help clarify the relationship between Accutane use and psychiatric events?). The response was positive; interventions in the form of basic science studies and retrospective epidemiologic studies were suggested.

SUBMISSION OF ADVERSE DRUG REACTION REPORTS

ADR reports often paint an incomplete picture, because the cases that are filed each year represent only a fraction of actual cases. According to the U.K. Medicines Control Agency, only 10% to 15% of serious ADRs are ever reported. An FDA MedWatch Continuing Education article[57] describes significant underreporting in the United States. Estimates are

cited that rarely more than 10% of serious ADRs and 2% to 4% of nonserious reactions are reported to the British spontaneous reporting program. A similar estimate is that the FDA receives direct reports of less than 10% of suspected serious ADRs. This means that cases spontaneously reported to any surveillance program, which comprise the numerator of a rate, generally represent only a small portion of the number that have actually occurred. The effect of underreporting can be somewhat lessened if submitted reports, irrespective of number, are of high quality.

Under FDA regulations, a pharmaceutic company must submit all ADR reports to the FDA periodically (at least annually) or on an expedited basis within 15 days of receipt. On January 5, 1998, the FDA sent a warning letter to Hoffman-La Roche (Nutley, NJ) for failing to submit a number of adverse drug experience reports that were both serious and unexpected within 15 working days as required by regulations [21 CFR 314.80 (c)(1)] as recently as October 1997 (with some dating back to 1989).[58] The letter documented, among others, two ADR reports on Accutane that were received by the manufacturers on September 4, 1991 and July 24, 1991. Both reports were not received by the FDA until October 8, 1997 (FDA/T. Middelkoop, personal communication, 1999). In one case (Tigason; Produits Roche, Neuilly sur Seine, France), the company reported the adverse drug event almost 11 years after receiving the information. Thus, although regulations require it, the companies sometimes do not report on a timely basis, if at all.[18]

REVISED LABEL WARNING

In February 25, 1998, the FDA issued a Talk Paper declaring new safety information regarding isotretinoin as a result of adverse event reports the agency received. The revised information leaflet now reads: "Psychiatric disorders: Accutane may cause depression, psychosis and, rarely, suicide ideation, suicide attempt and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary . . . Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy." Earlier information leaflets read: "Depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstitution of therapy." Thus, the FDA has spoken: Accutane is linked to depression, psychosis, and suicide.

Almost 1 year before this revision, the French product label was altered on March 3, 1997, to include "suicide attempt" as a side effect of isotretinoin therapy, and it now reads: "On rare occasions, neuropsychologic problems have been recorded (behavioral difficulties, depression, convulsions, and suicide attempts)" (French Product License, 1997). This revision was introduced in France after a prospective national inquiry (1993–1994) in which Roche and more than 2000 state dermatologists participated. This inquiry followed the presentation of a paper that reported on a suicide associated with isotretinoin therapy.[53] The result of this inquiry was presented at the Third Forum of the National and Provincial Journal of Dermatology in Montpellier (March 14–17, 1996) but was never published. It was almost 1 year later before this warning was introduced in any other country. According to *The Star-Ledger* (November 16, 1998), "Roche never informed the FDA of this new label change, who did not learn of the French label warning until this summer [1998]." Revised warnings have now been introduced in Ireland (May 1998) and the United Kingdom (April 1998). Many have asked why French physicians and their parents were given a stronger and more explicit warning than their counterparts in the United States, United Kingdom, and Ireland.

FOOD AND DRUG ADMINISTRATION'S BATTLE WITH ACCUTANE

During the 1980s and early 1990s, FDA officials debated on options to control and prevent the occurrence of Accutane-exposed pregnancies, including removal of the product from the market. *The Columbus Dispatch* (July 14, 1996) documented David Grahams' (Section Chief of the FDA's Epidemiology Branch) investigation of the situation and detailed several documents and memos that showed the FDA battling itself and Hoffman-LaRoche. Such documents revealed that between approximately 1.2 million people were treated with Accutane between 1982 and 1987. This includes 560,000 women, of whom 427,000 were between the ages of 12 and 44 years, and more than 90% did not have severe cystic acne. In a 1990 memo, Graham wrote: "The magnitude of injury and death has been great and permanent with 11,000 to 13,000 Accutane-related abortions and 900 to 1100 Accutane-related birth defects. There is no alternative to immediate withdrawal." This analysis by Graham provides

strong evidence that the overwhelming use of Accutane is not for severe acne.

INDICATIONS FOR USE: FAILURE TO COMPLY

The package insert–approved indication for Accutane states that "Accutane is indicated for the treatment of severe recalcitrant nodular acne...Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy including systemic antibiotics." Despite the plethora of serious side effects associated with Accutane therapy and the high number of exposed pregnancies that occur every year because of poor compliance with prescription guidelines, there is evidence of prescription for mild to moderate acne, which is not listed in the manufacturer's indication for use (for severe recalcitrant, nodular acne). Published accounts document high rates of use in patients with nonsevere acne, and many authors endorse its use in mild and moderate acne, claiming an excellent safety profile. Clearly, teenagers with acne benefit from improvement of their disease. To ignore the serious reports of depression and other psychiatric toxicities is to continue to place this population at risk, however.

SUMMARY AND RECOMMENDATIONS

Although the future may hold interesting possibilities for therapeutic uses of the retinoids, the present ambiguity about therapeutic use versus potential hazardous side effects of these retinoids shows that a greater level of scrutiny needs to be given to adverse reactions. Given the increasing reports of depression and suicide associated with Accutane, special care must be exercised in prescription and in monitoring.

An FDA memo of February 1998 stated that for most cases of suicide, suicide attempt, or suicide ideation associated with Accutane that could be evaluated, there was no antecedent history of depression and that the patients were not noted or known to be depressed before their suicide. As a result of underreporting, the actual number of suicides could be 10 times greater than the number of reports.

Clearly, the numbers provided by Roche, the FDA, and Middelkoop[18] differ and vary greatly. Any study, any case evaluation, or any reporting system can be faulted, criticized, and subject to bias and misinterpretation.

Although a definite causal relation between Accutane use and depression has not been established, the large body of literature and high number of adverse drug reports describing this association establish literature precedence and biologic plausibility. Other criteria that are used to assess causality in an exposure–disease relation and are supported by the existing data are temporality of the exposure to the disease and reversibility of disease with withdrawal of exposure. The link between retinoids and schizophrenia is also biologically plausible.

Absolute scientific proof is not necessary to recognize a signal and act on it. Indeed, the mechanism of action of Accutane in treating acne is unknown. In fact, the FDA rarely has more than a signal before significant warning changes and drug withdrawal sometimes occurs. There is sufficient evidence to be concerned and to take some corrective steps. Opponents claim that the teenage population is at high risk for suicide. All the more reason to be cautious when prescribing Accutane, a drug that is suspected of causing psychiatric toxicity even though causality has not been proven.

Clearly, for patients with severe acne, Accutane has an important place in therapy. The drug is overwhelmingly prescribed for minor and moderate conditions, however, despite existing warnings to the contrary in the package insert.

Patient registries, independent epidemiologic studies, and scientific research documenting the pathophysiologic basis of Accutane psychiatric toxicity are needed. A consumer education campaign via FDA consumer alerts encouraging prescribers to limit prescriptions in patients with nonsevere acne and to use whatever consent forms are developed can help to inform the public and prescribers and thus limit the toxicity. Clear patient package information describing and informing of the psychiatric risks is important so that the patient and family can make a decision to accept the risk, and if so, to be vigilant for signs of toxicity so that the drug can be stopped and the patient monitored. The psychiatric toxicities could easily be added to the existing informed consent form designed to warn of pregnancy risks.

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