# Does Isotretinoin Cause Depression and Suicide?

By J. Douglas Bremner, MD


## KEY WORDS

**prefrontal, depression, isotretinoin, acne, hippocampus, brain**



## ABSTRACT

*Isotretinoin is a retinoid that is approved for the treatment of cystic acne. There has been a growing interest in the possible relationship between isotretinoin use and increased risk of depression and suicide. The issue, however, remains controversial. This review examines the available evidence on this association, including published case reports, studies of challenge-rechallenge, reports to government agencies of isotretinoin-related adverse events involving suicide and depression, and possible biological mechanisms of action. Given the evidence to date, clinicians are advised to counsel their patients about the risk of depression and suicide as possible side effects of isotretinoin use, and to administer self-report questionnaires during treatment to screen for the development of depression. Further epidemiological and neurobiological studies are needed to assess the possible relationship between isotretinoin administration and depression and suicide.* Mental Fitness. *2003;2(4):70-78*


## INTRODUCTION

Isotretinoin (13-*cis*-retinoic acid) is a retinoid that inhibits sebaceous gland function and keratinization, and blocks inflammatory responses. Isotretinoin was approved by the United States Food and Drug Administration (FDA) for the treatment of cystic acne in 1982 and is currently approved for this indication in 80 countries. It has been used by approximately 2 million patients in the US and over 8 million patients worldwide. There has been a growing interest in the possible association between isotretinoin use and depression and suicide. This paper reviews the available evidence on this association, including published case reports, studies of challenge-rechallenge (depression during isotretinoin use that improves with discontinuation and returns after the medication is restarted), epidemiological studies, and reports of adverse events submitted to governmental agencies. In addition, the similarities between vitamin A and isotretinoin are reviewed, as well as the possible biological mechanisms by which isotretinoin may cause depression and suicide. Finally, recommendations for future treatments are offered.

## PHARMACOLOGY AND MECHANISM OF ACTION OF ISOTRETINOIN

Isotretinoin is recommended for use as a second-line agent for the treatment of cystic acne. It is available in 10, 20, and 40 mg tablets. Treatment is initiated at 0.5 mg/kg and increased to 1.0 mg/kg, with a goal of a cumulative dose of >100-120 mg/kg.[1] Following oral administration of 80 mg of isotretinoin, peak plasma levels of the medication occur in 3.2 hours. Terminal elimination half-life ranges from 10 to 20 hours. Isotretinoin leads to an improvement in acne in over 75% of the patients.

The original primary indication of isotretinoin was for cystic acne or acne associated with scarring that did not respond to a 6-month course of treatment with antibiotics. However, more recently some experts have advocated more wide-spread use of isotretinoin and have suggested that it may also be effective in preventing psychological problems related to acne or in reducing the potential for scarring. Currently, the original indication of a second-line treatment for cystic acne is not consistently applied. For example, in one case series less that 10% of the patients treated with isotretinoin had cystic acne; in another case series only 55% of patients treated had either cystic acne or inflammatory acne.[2]

*Dr. Bremner is associate professor of psychiatry and radiology at the Emory University School of Medicine and director of the Emory Center for Positron Emission Tomography.*

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## DEPRESSION AND SUICIDE

Recently there has been considerable interest in the possible relationship between isotretinoin administration and increased risk of depression and suicide. Some authors have contended that there is no evidence for this association,[3] while others have suggested that further inquiry into this area is required.[4]

Depression is a common disorder affecting about 15% of the US population and is associated with substantial morbidity. Diagnosis of depression in the US is based on criteria as established by the American Psychiatric Association outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM–IV*). Drug-induced depression is defined as a depression that occurs in the context of administration of a medication or substance, can likely be attributed to the use of that medication, and resolves with discontinuation of the medication. Some drugs that have been associated with depression include corticosteroids, adrenocorticotropic hormone (ACTH), sedatives, alcohol, L-dopa, cancer drugs, contraceptives, reserpine, propanolol, and interferon.

The number of patients who are identified with depression through typical means is much lower than the number of individuals in the community who are suffering from depression. Only about 20% of individuals with depression seek treatment. Issues of shame, denial, and lack of access to medical services interfere with the ability to seek psychiatric care. About 15% of patients with mood disorders will ultimately commit suicide, and most suicide victims have a history of mood disorders. In the US about 30,000 individuals commit suicide each year, making it the eighth leading cause of death.

## METHODS

The purpose of this review was to examine the evidence for a possible relationship between isotretinoin administration and depression and suicide. A number of sources were used, including published case reports and studies of challenge-rechallenge (ie, patients who became depressed on isotretinoin, remitted with discontinuation, and became depressed again when medication was restarted), as well as epidemiological studies that had examined such a relationship. These data were surveyed using the MEDLINE databases for 1982-2002 (the years during which isotretinoin has been available for clinical use). Reports to the FDA and the World Health Organization (WHO) of adverse events involving depression and suicide relative to other medications and other treatments for acne were also examined, using publicly available information from these sources. Studies of the effects of isotretinoin on mental well-being and psychological health were reviewed. The evidence for a possible mechanism by which isotretinoin could cause depression and suicide was examined by a review of the neurobiological literature of vitamin A (which has a closely similar chemical structure) and isotretinoin.

## CASE REPORTS OF A RELATIONSHIP BETWEEN ISOTRETINOIN AND DEPRESSION AND SUICIDE

There are a number of cases of depression following isotretinoin administration reported in the scientific literature (See Table). Meyskens[5] reported symptoms of depression in patients with cancer treated with isotretinoin. Hazen and colleagues[6] reported that 5 out of 110 (5.5%) patients with acne or related disorders treated with isotretinoin developed symptoms of depression, including depressed mood, crying spells, malaise, or forgetfulness, within 2 weeks of initiation of the medication. One patient had a prior history of depression. Isotretinoin was discontinued in 1 patient because of depression. Bravard, Krug, and Rzeznick[7] reported 3 cases in which isotretinoin administration was associated with the development of depression. Duke and Guenther[8] reported 2 cases of depression associated with isotretinoin administration. In the first case, a 15-year-old girl without a previous psychiatric history developed strange behavior 1 month after initiating treatment with 40 mg a day of isotretinoin, including cutting the hair off of one side of her head, exhibiting personality changes, and leaving home. She also developed sleep disturbances and irritability, became sullen and withdrawn. At that point the medication was stopped because of symptoms of depression. Two days later she threatened to cut her wrists and set fire to her clothes. After several months of being off of the medication her behavior was reported to be normal again. The second case involved a 17-year-old boy who was treated with 80 mg/day of isotretinoin, which was reduced to 40 mg/day after 6 weeks because of side effects. This boy had no prior history of depression. After a month of treatment he developed mood swings, depression, decreased appetite, weight loss, and moved out of his house. His father noticed strange behavior and asked the physician whether this could be related to the medication; at that

## CASE REPORTS OF RELATIONSHIP BETWEEN ISOTRETINOIN ADMINISTRATION AND DEPRESSION

| AUTHOR | NO. CASES | DEPRESSION | SUICIDAL IDEATION | TEMPORAL RELATIONSHIP WITH DRUG ADMINISTRATION | REMISSION WITH DISCONTINUATION | RELAPSE WITH RECHALLENGE | PRIOR/ SUBSEQUENT HISTORY OF DEPRESSION |
|---|---|---|---|---|---|---|---|
| DUKE & GUENTHER,[8] 1993 | 2 | ++ | – | ++ | ++ | NT | –– |
| SCHEINMAN ET AL,[9] 1990 | 7 | +++++++ | + | +++++++ | +++++++ | + | ------- |
| BIGBY & STERN,[27] 1988 | 3 | ++? | + | +++ | +?? | NT | ++- |
| HAZEN ET AL,[6] 1983 | 5 | +++++ | – | +++++ | + | NT | + |
| BRAVARD ET AL,[7] 1993 | 3 | +++ | ? | +++ | ? | NT | ? |
| VILLALOBOS ET AL,[13] 1989 | 1 | ? | – | + | + | + | ? |
| BYRNE ET AL,[10] 1998 | 3 | +++ | ++ | +++ | +++ | NT | --- |
| MIDDELKOOP,[11] 1999 | 1 | + | + | + | NA | NA | – |

+=case positive for this variable; -=case negative for this variable; NT=not tested; ?=unknown. (See text for details.)

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point—3 months after initiation of treatment—the medication was stopped. Three days later, his mood returned to normal, and he has since had no problems with depression.

Scheinman and colleagues[9] reported on 7 cases of depression associated with isotretinoin administration. These patients were part of a larger clinical trial of isotretinoin in 700 patients treated for cystic acne and other skin disorders. Diagnosis of depression was made based on patient self-reports and was confirmed by a psychiatrist in 3 patients; in the other 4 patients the symptoms resolved with discontinuation of medication before there was a chance for a psychiatric interview. In 5 out of 7 patients the symptoms of depression developed during the first course of treatment with the medication; the other patients had 1 or 2 prior courses of treatment with isotretinoin. Patients reported symptoms of depression following administration of isotretinoin including fatigue, irritability, sadness, decreased concentration, crying spells, loss of motivation, forgetfulness, and loss of pleasure. One patient had suicidal ideation. Symptoms resolved in all cases after discontinuation of medication within 2-7 days. One of the patients was rechallenged with isotretinoin and experienced a recurrence of symptoms 3 months after re-initiation of treatment. Three of the patients had headaches which resolved with discontinuation.

Byrne and colleagues[10] reported on 3 cases of depression associated with isotretinoin use. The first patient had several months of symptoms of depressed mood, irritability, aggression, agitation, decreased sleep, decreased appetite, reduced concentration, anhedonia, and early morning awakening. These symptoms eventually led to the breakup of her marriage. There was no prior history or family history of depression. During initial evaluation the Hamilton

Rating Scale for Depression (HAM-D) score was 26, consistent with clinically significant depression. Five weeks after isotretinoin was discontinued and antidepressant treatment was begun, the HAM-D score fell to 9. The second patient attempted suicide while on isotretinoin. He had several months' history of depressed mood, loss of interest, apathy, insomnia, anergia, anhedonia, and irritability, with feelings of guilt. There was also deterioration in work and social function. There was no family or personal history of depression. The initial HAM-D score was 31. After discontinuation of isotretinoin and administration of an antidepressant there was an improvement in mood over 4 weeks. The third patient was treated with isotretinoin and developed depression, tearfulness, suicidal ideation, feelings of worthlessness and agitation, anergia and anhedonia, irritability and anger. HAM-D score was 29. There was no prior history of depression or family history of depression. The patient also had symptoms of headache. Following discontinuation of isotretinoin and treatment with antidepressants the patient had a reduction of symptoms within two weeks and a follow-up HAM-D score of 8.

Middelkoop[11] reported a case of isotretinoin administration associated with depression, withdrawn behavior and social impairment, decreased appetite and interest in things, fatigue, and changes in personality and behavior. After 4 months of treatment the patient committed suicide. There was no prior history of depression or family history of depression.

Hull and Demkiw-Bartel[12] studied 124 patients treated with isotretinoin and found evidence of depression that persisted throughout the course of treatment in 4% of these patients.

Isotretinoin administration has also been associated with psychosis. Villalobos, Ellis, & Snodgrass[13] reported a case of isotretinoin administration associated with hallucinations, paranoia, and incoherence. The behavior stopped with discontinuation and restarted with readministration of the medication. After discontinuation of medication the symptoms improved over a 1-month period. The authors concluded that isotretinoin may be associated with an increased risk of psychosis and/or manic depression.

Other authors have documented individual cases of clinical depression after administration of isotretinoin that remitted with discontinuation. In some patients depression has remitted with discontinuation of treatment.[8,9,14,15] Other medications used for acne have not been associated with a similar incidence of depression.

## EPIDEMIOLOGICAL STUDIES OF ISOTRETINOIN AND DEPRESSION AND SUICIDE

Jick and colleagues[3] studied 7,195 patients treated with isotretinoin and 13,700 oral antibiotic users with acne from the Saskatchewan Health Database, and 340 isotretinoin and 676 antibiotic users from the United Kingdom General Practice Research Database. Prevalence of suicide, attempted suicide, and "neurotic and psychotic disorders" based on computer-recorded histories at 0.5 to 5 years before and more than 5 years after medication use were compared between the groups. The authors reported no increase in relative risk of newly diagnosed depression or psychosis (1.0) or suicide/attempted suicide (0.9; 95% confidence interval, 0.3-2.4) with isotretinoin administration. The relative risk for depression and psychosis with isotretinoin exposure in the first 6 months after initiation of treatment compared to the 6 months before treatment was reported as 1.2 (0.9-1.7) in the Saskatchewan data base and 1.3 (0.2-5.7) in the UK database. The authors concluded that there is not an increased risk of depression and suicidality with isotretinoin administration. There are several limitations to this study that are worthy of comment. Psychiatric diagnoses were recorded in the database only when patients were hospitalized or were evaluated by a psychiatrist for depression. However, many patients do not seek psychiatric treatment for depression and will not be identified in such a database. Also, at the time depression and suicidality were not identified as possible side effects of the medication, which may have further contributed to the underreporting or underrecognition of these symptoms. The best way to identify depression and suicidality in a population treated with the medication is through a systematic assessment of depressive symptoms with standardized measures administered by a psychiatrist or other trained mental health professional. The authors also reported relative risks as high as 1.8 for depression with isotretinoin (that is close to a 2-fold increase in risk), which would probably have been statistically significant with a larger sample.

## REPORTING OF ADVERSE EVENTS TO GOVERNMENT AGENCIES

Another potential source of information about the possible relationship between isotretinoin and depression and suicide is from the reports of drug-related adverse events that are submitted to

government agencies such as the FDA and the WHO. Such reports of drug-related adverse events are likely to underestimate the true frequency of these events. However, if the number of reports of adverse events is above a certain minimal frequency, it does provide evidence of a potential relationship that may stimulate further investigations. Also, one can compare the frequency of reporting of adverse events for a particular medication relative to other medications used for the treatment of the same disorder.

A review of the adverse drug reactions (ADR) reported to the WHO, the UK Medicines Control Agency (MCA), and the manufacturer Roche was reported by Middelkoop.[11] Among patients treated for acne, isotretinoin was found to be associated with a much greater number of psychiatric adverse events and suicides than antibiotics, accounting for 60% of all acne treatment-related adverse events in spite of the fact that antibiotics are prescribed more commonly than isotretinoin (eg, in the UK, 12,400 prescriptions for isotretinoin versus 147,237,000 prescriptions for tetracycline). The authors found 47 cases of suicide and 56 reports of suicidal ideation.



Wysowski, Pitts, and Beitz[4] published a review of cases of isotretinoin-related depression and suicide that had been reported to the FDA in between 1982 and 2000. During that time period, the FDA received a total of 431 ADRs: 37 reports of isotretinoin-treated patients who had committed suicide; 110 reports of isotretinoin-treated patients who had been hospitalized for depression, suicidal ideation, or suicide attempts; and 284 reports of patients with depression who had not been hospitalized. The cases also showed evidence of a temporal relationship between administration of isotretinoin and the development of depression. In addition, with removal and readministration of the drug, there was a remission of depression followed by an increase in depressive symptoms. The authors noted that there were several factors to suggest a relationship between isotretinoin and depression.

ADRs reported to the WHO in the 1982-1990 time period included 1,095 cases related to psychiatric symptoms, including 34 suicide attempts/completions and 69 total deaths related to isotretinoin..[4] Psychiatric symptoms reported included depression, amnesia, anxiety, mood swings, insomnia and suicide.

Since isotretinoin's introduction in 1982, depression has been the sixth most common side effect of isotretinoin reported to the FDA.[16] Isotretinoin ranked fourth in the top 10 of all drugs in the FDA database that were associated with risk of depression as a side effect.

## POSITIVE BEHAVIORAL EFFECTS OF ACNE REMITTANCE WITH ISOTRETINOIN

It has been suggested that acne is associated with psychological discomfort in many patients and that successful treatment is likely to lead to a resolution of these acne-related psychological disturbances[17]. Some authors have reported problems with feelings of impairment in general well-being or self image[18,19] and feelings of anxiety in patients with cystic acne,[20,21] while others have not found such an association[22]. It should be noted, however, that these studies have not involved specific assessments of psychiatric symptoms. Also, feelings of dissatisfaction with improvements in customer satisfaction with successful treatment of acne should not be confused with clinical depression that improves with successful treatment of acne (see discussion below). Rubinow and colleagues[23] studied 72 patients with cystic acne before and after treatment with isotretinoin. The authors reported no cases of isotretinoin-induced depression, and, in fact, reported improvements in anxiety and depression with treatment. Mood and anxiety was assessed by self reports with a variety of instruments including Profile of Mood States, Hopkins Symptom Checklist, and National Institutes of Mental Health (NIMH) Mental Health Mood Scale, as well as self-esteem measured with the Rosenberg Self-Esteem Questionnaire. About half of the subjects were interviewed before and after treatment, although it is unclear whether this was a psychiatric interview. At baseline, cystic acne patients had higher scores on the Hopkins Scale (5 factors), no difference in self esteem, and lower depression scores. Treatment resulted in no change in most of the factors of the Hopkins Checklist, except for an anxiety factor. When patients who had the greatest response were assessed, there were significant improvements in scales of anxiety and depression. However, the authors noted that this finding is limited by the multiple comparisons of different scales used in assessing the effect of isotretinoin. The authors reported the best results in individual interviews and anecdotal reports of greater life satisfaction. The study was limited by the use of self-report assessments of mood and anxiety without clinician-administered assessments of these factors or use of structured diagnostic interviews administered by a clinician (eg, the Structured Clinical Interview for *DSM-IV* [SCID]). Also, as the authors point out, the findings do not support the idea that acne per se is associated with true psychiatric distress, apart from bodily complaints such as discomfort, embarrassment,

pain, and distress that are to be expected with cystic acne. Although there was mild improvement in assessments of anxiety and depression with treatment, the multiple comparisons employed in this study, as noted by the author, as well as the lack of a clear abnormality at baseline, make this finding less convincing. The primary outcome of this study appears to be an improvement in patient satisfaction with isotretinoin use, without clear evidence of changes in psychiatric symptomatology.

Kellett and Gawkrodger[24] assessed baseline anxiety and depression as well as other factors such as self-esteem in patients with acne before and after treatment with isotretinoin. The authors found elevated levels of anxiety and depression as measured with the Hospital Anxiety and Depression Scale relative to historical controls. The authors also reported increased levels of shame and lower self-esteem. Isotretinoin treatment did not result in a significant change in measures of anxiety or depression, although there were improvements in measures of shame and embarrassment. This study was limited by the use of self-report measures of anxiety and depression, and the lack of clinician assessments of psychiatric symptoms or diagnosis based on structured interview. The study also used historical controls and did not recruit a specific control group.

Another study[25] examined over 100 patients with acne who were treated with isotretinoin. The authors measured depression with the Beck Depression Inventory, a self-report measure, before and after treatment with isotretinoin. The authors found no significant change in self-reported depression. One of the limitations of the study is the use of a self-report measure of depression. Baseline levels of depression were also lower than historical values for normal individuals.

## Relationship Between Isotretinoin and Vitamin A

Isotretinoin and vitamin A share a similar chemical structure, which suggests that they may have similar mechanisms of action in the brain. The brain has retinoid receptors (described below) which trap both isotretinoin and vitamin A. Many of the adverse side effects of isotretinoin are similar to those of patients taking high doses of vitamin A.

Potential side effects of isotretinoin include pseudotumor cerebri (benign intracranial hypertension), decreased night vision, corneal opacities, inflammatory bowel disease, elevation in plasma triglycerides and cholesterol, skeletal hyperostosis, and hepatotoxicity. The most common adverse reaction is cheilitis, followed by conjunctivitis. Other symptoms include musculoskeletal symptoms, peeling palms and soles, skin infections, urogenital symptoms, headache, fatigue, and increased susceptibility to sunburn. Usage of isotretinoin during pregnancy has been associated with an increased risk for birth defects.

Adverse reactions are common with isotretinoin. At least 90% of patients treated reported at least one adverse event[26]. Bigby and Stern[27] reviewed adverse reactions to isotretinoin reported to the Adverse Drug Reaction Reporting System between 1982 and 1985. They reported 104 side effects which included (in decreasing frequency)the following: skin reactions (dryness); central nervous system complaints; musculoskeletal system complaints; pregnancy-related side effects; eye complaints; hematopoietic, gastrointestinal, cardiorespiratory, and genitourinary side effects. Most common adverse reaction was headache in 11 patients which was associated with pseudotumor cerebri in 4 of the patients. Of the patients who had adverse events related to pregnancy, outcomes included spontaneous abortions or stillbirths of malformed fetuses, planned abortions, delivery of apparently normal children, and delivery of children with apparent respiratory and cardiac defects. Not all patients took isotretinoin throughout pregnancy, and the degree of adverse effects on pregnancy appeared to be related to the duration of treatment and timing relative to gestational period. One patient who had remitted depression treated with antidepressants had a relapse of depression with isotretinoin and isotretinoin was discontinued; 1 patient with a history of bipolar disorder treated with lithium had a depressive episode with suicidal ideation which was resolved 3 months after discontinuation of isotretinoin; and 1 patient reported insomnia, loss of libido and impotence, with no follow-up information available. The authors concluded that the most serious potential adverse event was teratogenicity. Review of these cases suggests that neurological consequences are an important potential negative outcome of isotretinoin use. Given the currently accepted model of depression representing a neurological disorder, this suggests a possible mechanism for isotretinoin-induced alterations in neurological function representing a potential mechanism for isotretinoin-induced depression. Also, the cases of depression, although not described in detail, and in two thirds of the cases occurring in patients with preexisting affective disorder, could have nevertheless represented cases of isotretinoin-induced mood disorders.

Vitamin A is a fat-soluble vitamin stored in high concentrations in the liver and is a retinoid with close similarities in chemical structure to isotretinoin.[28] Large doses of vitamin A can have a number of toxic effects which include both medical and psychiatric consequences. Medical side effects include fatigue, decreased interest in things, headache, musculoskeletal symptoms (bone or join pain) with occasional bone abnormalities, diplopia, alopecia, dry mucous membranes, desquamation, gastrointestinal symptoms (anorexia and weight loss), and liver damage.[29,30]

It has long been known that vitamin A toxicity is associated with mental changes. Arctic people know that the liver of certain animals (eg, the polar bear) is poisonous. Polar bear liver has a very high concentration of vitamin A, and feeding it to laboratory rats results in vitamin A toxicity.[31,32] Arctic explorers who fed on polar bear liver developed symptoms of confusion and psychosis. Restak reported a case of vitamin A toxicity with the development of aggression, personality changes, and depression, which resolved with discontinuation.[32] McCance-Katz and Price[15] reported a case of chronic vitamin A intoxication associated with a 1-year history of depressed mood, poor concentration, tearfulness, and guilty rumination. The patient had no prior history or family history of depression. He also had fatigue and fears of cancer. The HAM-D score was 29, indicating severe depression. Four weeks after discontinuation of vitamin A the HAM-D score dropped to 6, and he was completely normal 2 months after treatment. The authors concluded that this was a case of vitamin A-induced major depression. Fishbane and colleagues[33] reported 2 cases of vitamin A toxicity from a vitamin supplement. They found typical symptoms of toxicity as well as neurological effects of drowsiness and inability to grasp objects in one patient. The second patient had psychotic symptoms (seeing insects crawling over his body) and bizarre behavior (trying to cut off his son's hair because he thought insects had infested his body). There was no prior history of psychiatric disorders. Symptoms resolved after discontinuation of vitamin A.



## POSSIBLE NEUROBIOLOGICAL MECHANISMS MEDIATING THE EFFECTS OF ISOTRETINOIN ON DEPRESSION

In order for isotretinoin to cause neuropsychiatric symptoms it must cross into the brain and have central effects. The neurobiological consequences of isotretinoin use have not been extensively studied. Most research has involved animal models of the developing brain; to date there have been no studies with the adult brain. The brain contains retinoid receptors which bind retinoids, including vitamin A and isotretinoin. The developing eye is rich in retinoic acid. In animal models high doses of retinoic acid have been associated with alterations in the developing eye.[34] Retinoic acid is synthesized from retinaldehyde by several dehydrogenases. High levels of class-1 aldehyde dehydrogenase are found in the basal forebrain, in axons and terminals of the dopaminergic neurons of the mesostriatal and mesolimbic system, forming a retinoic acid-generating projection from ventral tegmentum to corpus striatum and nucleus accumbens.[35,36,37] Mesolimbic dopaminergic systems have been studied extensively and are known to play a key role in reward and motivation; alterations in this system have been hypothesized to play a role in dysregulation of mood and emotion.

Studies have shown that depression is associated with changes in brain structure and function, and in order for isotretinoin to lead to depression it should act on similar brain regions as are implicated in depression. A number of studies have used positron emission tomography (PET) assessment of brain function, measured with blood flow or metabolism, to show that depression is associated with decreased function in the prefrontal cortex.[38-40] In one study, Bremner and colleagues[40] used positron emission tomography (PET) to measure brain function during experimentally-induced depressive relapse, in order to map out brain correlates of depression. The investigators developed a technique to induce rapid return of depression in patients taking fluoxetine, a selective serotonin reuptake inhibitor, by using a special drink and a diet low in tryptophan, precursor for the brain chemical messenger serotonin. Brain metabolism decreased in orbitofrontal and dorsolateral prefrontal cortex (middle frontal gyrus) and thalamus on the depletion day in patients with depressive relapse, but not in patients without depressive relapse. Studies have also shown both a reduction of volume of orbitofrontal cortex measured with magnetic resonance imaging (MRI) and a loss of neurons in post-mortem brain of depressed patients in this area.[41-43] Other studies have shown a loss of volume in the hippocampus, a brain area involved in learning and memory, in depression.[44-46]

## DISCUSSION AND RECOMMENDATIONS

Several factors have been discussed in evaluating a possible relationship between isotretinoin and depression, including: (1) a temporal relationship

between administration of the drug and depression; (2) a dose response relationship between drug administration and symptoms; (3) a plausible biological mechanism for action; (4) a class effect, so that similar compounds have similar effects; (5) the absence of alternative explanations of the effect; (6) dechallenge, or abatement of symptoms with discontinuation of the medication; (7) rechallenge, or recurrence of symptoms with reinstitution of treatment. There are multiple case reports showing a temporal relationship with the drug administration. Some authors have argued that this could be a coincidence, given the high prevalence of depression. However, there is a higher prevalence of depression with isotretinoin than antibiotics, and isotretinoin ranks high in reporting for adverse events involving depression relative to other medications. Also, because of the way adverse events of depression associated with isotretinoin use are reported, the prevalence is likely to be at least 10 times greater than what is currently reported. A possible dose-response relationship is difficult to assess with the case report literature. However, anecdotal observations that thin and fit individuals are more susceptible suggest that greater brain uptake in these individuals increases risks. There does seem to be a plausible biological mechanism by which isotretinoin could lead to depression and suicide. Retinoid receptors that can bind isotretinoin exist in the brain, high doses of retinoids affect brain development in areas of the brain implicated in depression, and studies of vitamin A toxicity indicate that retinoids can have behavioral and mood effects in humans. The class effect is shown by similarities in side effects of vitamin A toxicity and isotretinoin use (eg, psychosis and confusion in patients with vitamin A toxicity).

Some of the published literature comments on the idea that isotretinoin decreases depression because it improves psychological well-being with improvement on acne. The published literature does not provide strong evidence for an increase in clinical depression in acne patients. There does seem to be good evidence for a relationship between unhappiness and acne, which should not to be confused with clinical depression, which requires a patient to have a certain number of symptoms, functional impairment, and time course for diagnosis. Clinical depression cannot be diagnosed with self-report measures; it requires diagnosis by a clinician, preferably using a structured interviews. The published literature does not support the conclusion that isotretinoin leads to an improvement in clinical depression, although there is an improvement in patient satisfaction.

Based on what we know today about the relationship between isotretinoin and depression, it is appropriate to outline some recommendations for how to proceed in the future. Patients and their families should be counseled about the possibility of developing depression on isotretinoin, and should be provided educational information about the possible symptoms of depression, so that they can recognize it if it should develop. All clinicians should consider the use of self-report questionnaires about depression on a periodic basis during the course of isotretinoin treatment. If patients have an increase in score on these self-report assessments, further clinical evaluation should be performed. If clinicians do not feel comfortable assessing patients for depression themselves, they should be referred to a mental health professional. However, assessment of depression by the primary physician is more efficient and cost-effective, and should be employed when possible; there are a number of training opportunities available now for providing assessment and treatment of depression in the primary care setting. Finally, although we would like to be able to predict who is more susceptible to the development of depression, we do not have enough information to say that particular individuals, for example those with a family history of depression, are at increased risk from isotretinoin-induced depression. Further study is needed to determine the characteristics of these individuals. MF



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