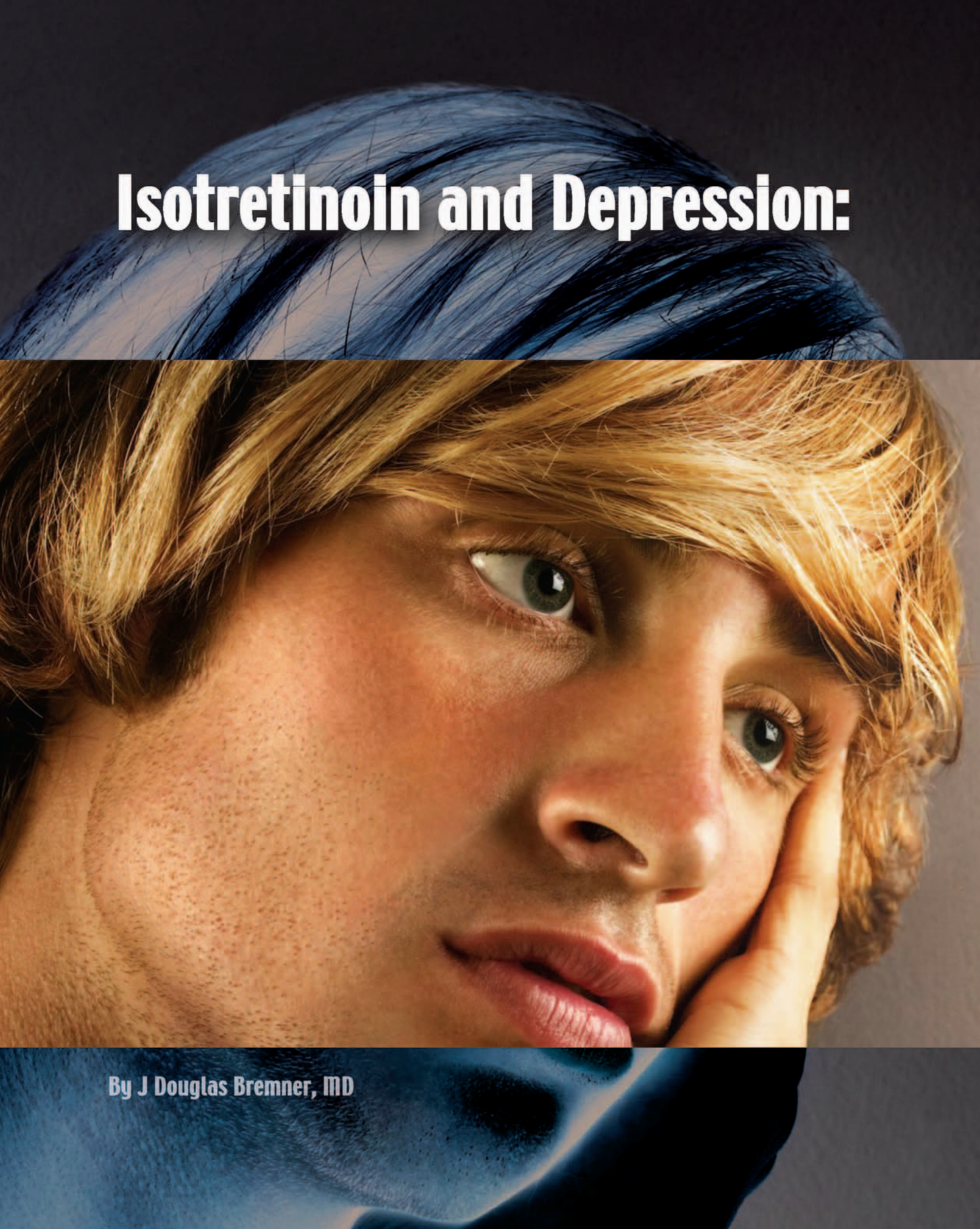
Isotretinoin and Depression:



By J Douglas Bremner, MD

Is There A Causal Link?

One of the most hotly debated issues in dermatology today is isotretinoin and its potential ability to cause depression and suicide. As many dermatologists know, isotretinoin (13-cis-retinoic acid, Accutane) is currently approved by the Food and Drug Administration (FDA) for the treatment of cystic acne and is prescribed to millions of patients worldwide.[1-3] It is a retinoid that inhibits sebaceous gland function, keratinization, and inflammatory responses. Because of its teratogenic effects, isotretinoin was originally approved only for severe acne, but today, only about eight percent of patients treated with isotretinoin have severe acne.[3] Therefore, in light of the controversy concerning the possible link between isotretinoin and depression, this review outlines evidence that isotretinoin (and other retinoids) regulate brain function and can contribute to behavioral changes, including depression and suicide.

Vitamin A

Isotretinoin is identical to the predominant physiological form of retinoic acid (RA) (the physiologically active form of vitamin A), all-trans retinoic acid, differing only in molecular geometry having its double bond at C13 in cis conformation (Fig. 1). Although isotretinoin only weakly binds to the retinoic acid receptors, it converts to the active form of retinoic acid in tissues.[4,5]

High doses of vitamin A have long been known to have effects on mood and behavior. Early explorers who ate polar bear liver often developed depression and psychosis.[6-8] There are multiple reports of behavioral changes with vitamin A overdoses and toxicity related to taking high dose vitamin supplements, including aggression, personality changes, depressed mood, poor concentration, tearfulness, psychosis, and guilty rumination, which resolve with discontinuation.[6,8-24] Large doses of vitamin A can have a number of other neurological and mental effects that are also seen in isotretinoin toxicity, including nausea, vomiting, weakness, fatigue, irritability, drowsiness, loss of appetite, ataxia, decreased interest, headache, and diplopia (double vision). Several case reports found benign intracranial hypertension, or pseudotumor cerebri, characterized by headache, papilledema, and normal CT/MRI and CSF, in children and adults exposed to high levels of vitamin A.[7,10,17,20,22,23,25-27] Given the chemical similarity of vitamin A and isotretinoin, these behavioral findings provide further evidence that retinoids may promote affective disorders.

For isotretinoin to effect depression and suicide, it must be acting through the brain. The high rate of neurological side effects in treated patients supports the idea that isotretinoin does act on the brain. Headache is the second most common side effect of isotretinoin behind dry skin.[28] Pseudotumor cerebri is another side effect of isotretinoin.[21,25,27] Nearly half of all babies exposed to isotretinoin in utero will develop some cognitive changes.

Developing Symptoms

A number of cases of depression occurring in response to isotretinoin treatment have been reported, some involving re-occurrence with re-treatment.[29-40] Hull and Demkiw-Bartel[40] studied 124 patients treated with isotretinoin and found evidence of depression in four percent that persisted throughout the course of treatment. Hazen et al[32] reported that six out of 110 patients with acne or related disorders treated with isotretinoin developed symptoms of depression, including depressed mood, crying spells, malaise, or forgetfulness within two weeks of initiation of the medication. Scheinman et al[36]

Science supports a possible link between isotretinoin and depression. Further studies can better elucidate the connection and uncover safe ways to administer this agent.

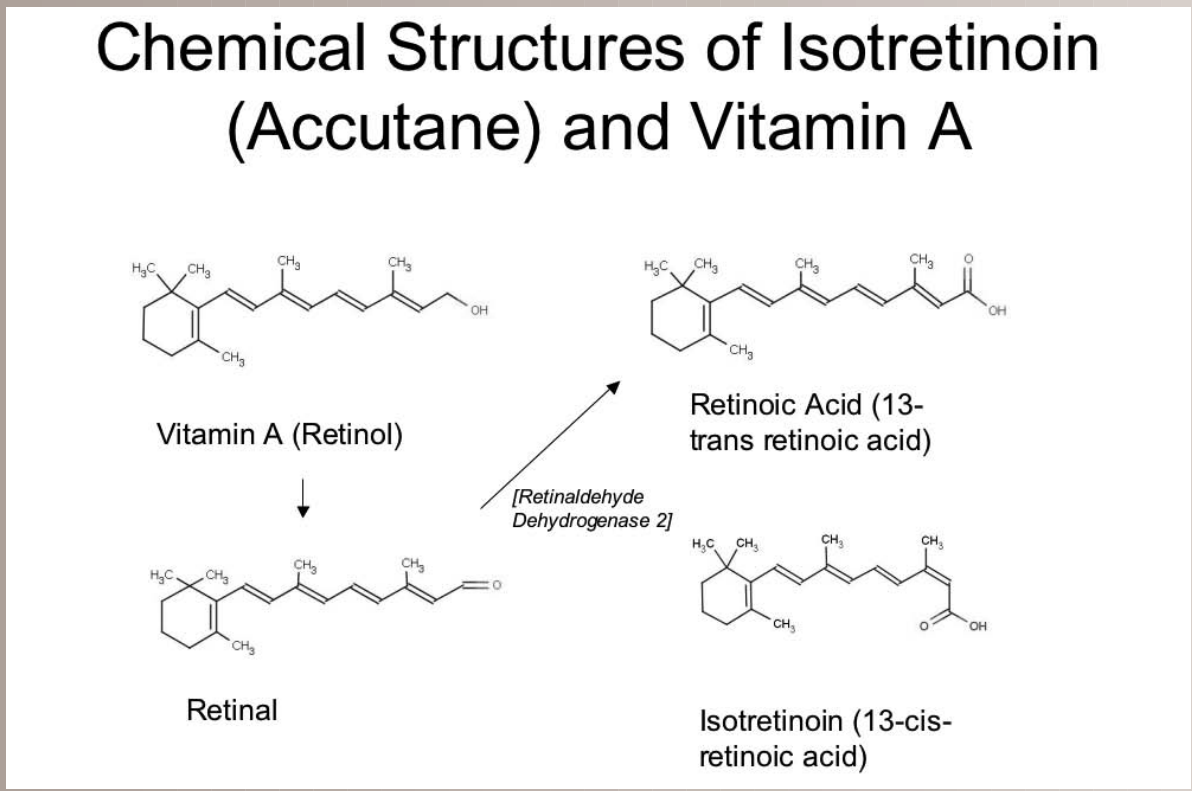


Fig 1. Chemical structure of isotretinoin and related retinoids. Beta carotene, present in orange vegetables, is cleaved after ingestion to form two retinol molecules; retinol is also ingested through consumption of meat and other foods. After ingestion, retinol is converted to retinal, and stored in the liver. 13-trans-retinoic acid is the active form of Vitamin A; a slight conformational shift of a carbon-carbon bond yields 13-cis-retinoic acid (isotretinoin), which is present naturally at low levels in the body.

reported on seven cases of depression associated with isotretinoin administration from a clinical trial of 700 patients. Symptoms resolved in all cases after discontinuation of medication within two to seven days. One of the patients was rechallenged with isotretinoin and experienced a recurrence of symptoms three months after re-initiation of treatment. Villalobos, Ellis, and Snodgrass[34] reported a case of isotretinoin administration associated with hallucinations, paranoia, and incoherence. The behavior stopped with discontinuation and re-started with re-administration of the medication. With discontinuation, symptoms improved over a one-month period. Other authors have found that family members noted depression and other behavioral changes (impulsivity, decreased performance in school or work) more than patients.[29]

There are other examples of drugs causing depression, including corticosteroids, adrenocorticotropic hormone (ACTH), adrenal steroids, sedatives, alcohol, L-dopa, cancer drugs, contraceptives, reserpine, propanolol, and interferon.

Telling Reports

Adverse events related to depression and suicide with isotretinoin treatment reported to the World Health Organization and the FDA are higher than other treatments of acne such as antibiotics. Such reports of drug-related adverse events are likely to underestimate the true frequency of these events by 10 to 100 fold. However, 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. For instance, since isotretinoin's introduction in 1982, depression has been the sixth most common side effect of isotretinoin reported to the FDA.[41] 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. Between 1982 and 2000 the FDA received a total of 431 ADRs: 37

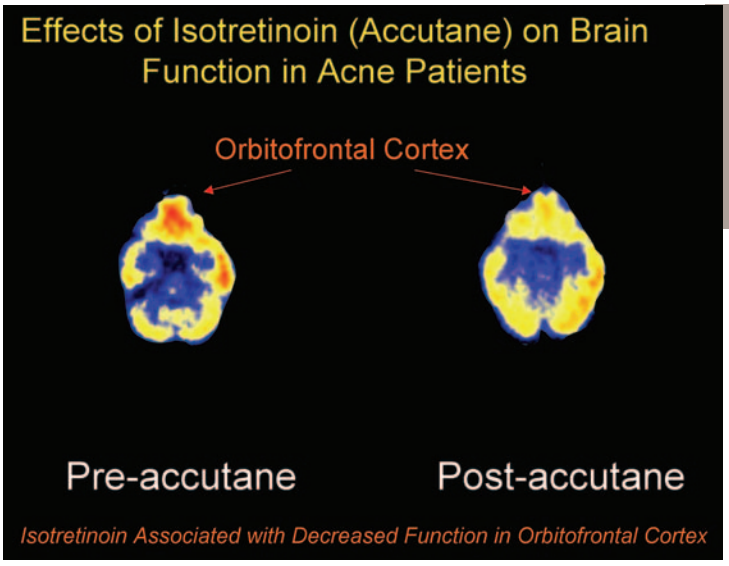


Fig. 2. Effects of isotretinoin on brain function in an acne patient. There was a visible decrease in orbitofrontal brain function after four months of treatment. This patient developed headache and subtle behavioral changes but no clinical depression.

reports of isotretinoin-treated patients who had committed suicide; 110 reports of isotretinoin-treated patients who had been hospitalized for depression or suicidal ideation; and 284 reports of patients with depression who had not been hospitalized. ADRs reported to the WHO in the 1982-1998 time period included 1,095 cases related to psychiatric symptoms, including 114 suicide attempts/completions related to isotretinoin.[33]

Arguments against a relationship between isotretinoin and depression are made based on the reported lack of association in a database of isotretinoin and antibiotic users in Canada and the UK.[42] However, limitations of this study have been previously reviewed, including the retrospective nature of the study, lack of standardized diagnosis, and small sample size.[41] It has also been argued that acne is associated with psychological discomfort and that successful treatment leads to a resolution of acne-related psychological disturbances. Studies have reported improvement in feelings of general well-being or self image, or feelings of anxiety in patients with cystic acne following isotretinoin administration, although findings were more directly related to improvement in measures of patient satisfaction, rather than clinical symptoms of depression.[43-49] Feelings of dissatisfaction versus improvements in customer satisfaction with successful treatment of acne should not be confused with clinical depression that improves with successful treatment of acne. More recently, a study of 104 adolescents reported no significant increase in depression in patients treated with isotretinoin compared to conventionally treated patients. However, this study was not adequately powered to assess a difference (see below), the treatment was not randomized or controlled, and the gender distribution was different in the different treatment groups (which is significant because depression is more common in women).[50]

Another argument made against an association between isotretinoin and depression is that depression and suicide are so common, especially in young people, that it is impossible to differentiate depression and suicide from that which occurs by chance.[49] Although suicide is often cited as the third most common cause of death in teenagers, suicide is half as common in teenagers as in people in any other age group, other than elementary school. Also, although depression affects 15 percent of people at some time in their lives (known as prevalence), what is more important is the number of people who will develop depression for the first time during the four-month course of isotretinoin treatment, known as the incidence. The 12 month incidence of depression is only 1.6 percent,[51] making the four month incidence 0.5 percent. Taking the mean number of 3.5 percent from the three studies of isotretinoin and depression with larger sample sizes means that three percent of people will develop depression while on isotretinoin that is caused by the drug alone. Multiplying that by the eight million patients who have taken isotretinoin over the past 20 years, that would be 200,000 patients, much more than those affected by Vioxx.

A report derived from a two-day meeting at the FDA in 2000 outlined the necessary evidence to establish cause and effect between isotretinoin and depression. One required area was a biologically plausible mechanism by which isotretinoin could cause depression and suicide. The consensus was that isotretinoin must effect depression by acting through the brain, however little was known at the time about the effects of isotretinoin on the adult brain.

The Importance of RA

Doctors and researchers now know much more about the effects of retinoids on the adult brain. Retinoids are a family of compounds derived from vitamin A that are necessary for the function of many tissues in the developing and adult vertebrate. The majority of these functions are performed by the vitamin A metabolite retinoic acid (RA), which binds to RA receptors and regulates gene expression.[52] The RA receptors (RARs) are members of the nuclear receptor superfamily that includes the receptors for estrogen, androgen, mineralocorticoids, glucocorticoids and thyroid hormone. All of these recep-

tors function in a similar manner; they sit on the DNA in the nucleus of the cell, and when bound to the hormone, cause gene transcription. They also share a role in modulating mood.

The role of RA in regulating CNS development has been extensively investigated.[53,54] But until recently, the idea that RA may also influence neuronal function in the adult brain was not considered. Several studies, however, have shown that RA signaling occurs in the brain of the adult, suggesting that the adult brain, like the embryo, may be sensitive to exposure to excess RA. RA signaling occurs in the hippocampus, a brain area involved in learning and memory that has also been implicated in depression. The hippocampus is one of the few regions of the adult brain in which new neurons are constantly born. Since RA regulates neuronal differentiation, it should be no surprise that RA also influences this process in the adult brain. In fact, exposure to isotretinoin leads to an inhibition of new nerve growth in the hippocampus.[55] The retinoids are also involved in regulation of dopaminergic function, which has been implicated in depression.[56] Dopamine mesocortical pathways provide dopamine for the orbitofrontal cortex and other parts of the prefrontal cortex, and may putatively be influenced by RA. Deficits in hippocampal function lead to a downstream effect on orbitofrontal function.[57,58] Clinically, many patients on isotretinoin exhibit signs of behavioral disinhibition and affective lability that is consistent with orbitofrontal dysfunction. Therefore retinoids may mediate dysregulation in hippocampal-orbitofrontal function that contributes to symptoms of depression.

The neural circuitry of depression, as established through brain imaging studies, has a high degree of overlap with the neural circuitry of RA. Induction of depressive relapse resulted in decreased function in the orbitofrontal cortex.[59,60,51] The pathway between the hippocampus and orbitofrontal cortex was proposed to be impaired in depression, this impairment occurring through loss of dopamine or stress. The possible importance of RA in regulating neural plasticity as well as dopamine signaling suggests that RA may influence this particular pathway.

However, until recently the effects of isotretinoin on the human adult brain were unknown. In a preliminary study, 28 subjects completed four months of treatment with 13-cis RA or antibiotic with PET FDG imaging of brain metabolism and assessment of depression with the Hamilton Depression Scale (Ham-D) before and after treatment. Thirteen subjects were treated with 13-cis RA and 15 with antibiotics. All subjects suffered from acne. Administration of isotretinoin (but not antibiotic) was associated with decreased brain metabolism in orbitofrontal cortex after four months of treatment. This effect was seen for both absolute metabolism and for the ratio of orbitofrontal to whole brain metabolism. There were no differences in other brain regions after correcting for whole brain metabolism by examining differences in regional to whole brain ratios.[61]

Five patients treated with isotretinoin had symptoms of headache. These patients also had subtle changes in irritability and/or mood as assessed by self, family, or the research staff. These subjects all had decreases in brain metabolism with isotretinoin administration. (A representative subject is shown in Fig. 2.) One subject in the isotretinoin group and one in the antibiotic group had a clinically significant increase in depression as measured by the Ham-D score (greater than nine point increase); however there were no significant increases in Ham-D scores in the groups as a whole or differences between groups. There were no correlations between the Ham-D and brain function.

In summary, there are a number of lines of evidence, including both preclinical and clinical, suggesting that isotretinoin is associated with behavioral changes including symptoms of depression. The retinoids (which include isotretinoin) have been shown in animal studies to affect brain regions involved in mood and implicated in depression, including the hippocampus and striatum, as well as neurotransmitter systems such as dopamine, that have been hypothesized to mediate symptoms of depression. An initial PET study showed that the orbitofrontal cortex is sensitive to isotretinoin in human subjects, which may be part of a hippocampal-orbitofrontal circuit involved in depression. An interesting finding from the brain imaging studies in isotretinoin treated subjects was that patients with headaches were more likely to have decreased orbitofrontal function with isotretinoin. Wysoski and Swartz 28 recently reported an association between headache and depression in patients treated with isotretinoin, suggesting some overlap in the mechanism by which isotretinoin may lead to these symptoms.

Future Studies

Future animal studies need to focus on the effects of isotretinoin on the orbitofrontal cortex. Studies are also required to assess the effects of clinical administration of isotretinoin on the human brain and behavior, including double-blind, placebo-controlled, and randomized trials, to assess the effects of isotretinoin on symptoms of depression and mood lability. The FDA recommended such studies after a two-day meeting on the topic in 2000, but in 2002, the acting director advised against such a study, as it would be too difficult to adequately blind because of the dry skin side effects of isotretinoin. However, topical retinol, which dries the skin, can be given as a control treatment and results in minimal absorption into the bloodstream, thus effectively blinding the subjects to condition. Another argument against

performing epidemiological research has been that depression is very common in the general public, and it would require tens of thousands of patients to show any effect of isotretinoin on depression. However, in the four month period of an isotretinoin trial, only about 0.5 percent of patients would spontaneously develop depression, indicating that about three percent of patients may develop depression from isotretinoin alone. Therefore a trial involving about 1,000 subjects would be sufficient to detect an effect. Furthermore, given the likely effects of isotretinoin on prefrontal cortical function, behavioral symptoms in addition to depression should be investigated, including impulsivity and aggression.

These studies can be performed in a properly controlled and cost-effective way and are essential to understanding the potential involvement of retinoids in the pathophysiology of depression, as well as in developing strategies to provide a safe and effective route of isotretinoin administration in the treatment of skin disorders.

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