Acne, Isotretinoin Treatment and Acute Depression

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Summary
The association between isotretinoin therapy and depressive symptoms in acne patients has generated much recent interest but has not been systematically explored.
A 17-year-old man with acne vulgaris developed symptoms of acute depression two weeks after beginning isotretinoin therapy. The depressive symptoms improved with reduction of isotretinoin dose and treatment with sertraline. Of note, however, is that when the isotretinoin dose was again increased, the depressive symptoms recurred despite clearing of the skin, leading to an unsuccessful suicide attempt. Isotretinoin was finally discontinued and the depression rapidly resolved. Although the effects of hypervitaminosis A may be involved etiologically, the predictive factors of drug-related depression remain unclear. Significant depressive symptoms that develop during the course of treatment need close monitoring and may necessitate both antidepressant therapy and discontinuation of the drug. Given the uncertain causal relationship between isotretinoin and depression, versus the potential psychological benefits of effective acne treatment, systematic studies exploring the impact of isotretinoin on mood are needed.

Key words: acne, isotretinoin, depression, suicide, causal relationship.

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Introduction
Acne is a common condition affecting young patients. A significant proportion of those with moderate to severe acne is treated with systemic isotretinoin, particularly if there are concerns about facial and bodily appearance. Isotretinoin, a retinoid derivative (13-cis-retinoic acid), is a highly effective treatment for cystic acne. While side effects like dry skin, photodermatitis, lethargy and abnormal liver and lipid functions are well known (Wolff et al 1991), its effect on mood is less well documented. Severe depression can develop for the first time following isotretinoin use in a subgroup of patients, as highlighted by the following case.

Concern about depression associated with isotretinoin use from numerous reports has led to much recent publicity linking the risk of depression and other psychiatric effects with isotretinoin. The Antidepressant Drug Reaction Advisory Committee has received at least 12 reports since 1986 of depression related to isotretinoin in Australia (ADRAC 1998). Furthermore, the U.S. Food and Drug Administration has reported about 20 cases where depression resolved when therapy was ceased but recurred when treatment was re-introduced (Ault 1998). Consequently, product information was recently changed, warning that isotretinoin may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide.

Recently a retrospective cohort study of 7516 isotretinoin users from two large population health databases found no increase in relative risk estimates for depression, psychotic symptoms, suicide and attempted suicide (Dick et al 2000). Despite having the largest data set yet published, the study remains inconclusive because of methodological limitations including the retrospective study design, use of a computerised database, inadequate method used for case recognition and lack of psychometric measure. Significant variables like severity of acne, treatment compliance, concomitant medications and comorbid conditions were not adequately controlled. It is also possible that anecdotal case reports may be picking up a small subgroup of patients at risk of developing depression that too few to show significant differences in systematic studies.

Case report
We report the case of a 17-year-old male who...
developed acute depression and suicidal ideation during a course of treatment with isotretinoin for moderately severe facial acne vulgaris. The patient was previously a well-adjusted and active adolescent although he had been self-conscious about the facial acne he suffered for the last five years. He had no premorbid history of any psychiatric problems but there was a family history of post-natal depression. Despite previous topical treatment with adapalene 0.1% gel and azelaic acid 5% cream, and 18 months therapy with antibiotics (doxycycline hydrochloride), he still had moderate inflammatory acne consisting of multiple papules, pustules and comedones. After discontinuing the topical therapy and antibiotics he was immediately commenced on isotretinoin (0.63 mg/kg/day) for the first time following normal routine physical and laboratory examination. About two weeks into treatment he began to develop depressive symptoms over several weeks which included uninterest, insomnia, decreased appetite, lack of motivation and interest, social withdrawal and suicidal ideation. Subsequently, his family reported that after the onset of depression, he had angry outbursts related to alcohol use that had not previously occurred. He also stopped regular attendance to both school and the gym.

His isotretinoin dose was reduced (0.32 mg/kg/day) for two weeks and he was commenced on sertraline 50 mg, which was gradually increased to 150 mg. He responded to sertraline and his symptoms further improved with the support of his general practitioner and a counsellor. However, he also had high expectations of the anti-acne drug and became depressed when the skin cleared. He experienced (a) side effect of isotretinoin had temporarily worsened his facial appearance. As his self-consciousness about his skin may have been aggravating his depression, the higher isotretinoin dosage was resumed to treat his acne and help alleviate any negative psychological impact. After another two weeks, the patient further increased the dose of isotretinoin (1.0 mg/kg/day) to achieve a more rapid and effective response.

However, three months into treatment his mood deteriorated and the depressive symptoms relapsed, despite significant improvement of his skin status and being compliant with sertraline. He was not enjoying his casual work and felt increasingly frustrated and hopeless. Consequently, he planned and attempted suicide by ingesting a substantial overdose of pseudoephedrine and diazepam, medications that belonged to his parents. Fortunately his family found him and he was treated at the local emergency department.

Following discharge to the care of his general practitioner, he was referred to a consultant psychiatrist who confirmed the diagnosis of severe major depressive disorder associated with isotretinoin treatment (Hamilton Depression 17-item scale score of 28). The patient was maintained on sertraline at 150 mg but isotretinoin was ceased. Altogether he had taken 7200 mg (144 mg/kg) of isotretinoin. At the time of discontinuation of isotretinoin, his skin was clear and he did not wean subsequently. Over the next two weeks his mood, sleep, appetite, energy levels and motivation improved rapidly and he no longer suicidal. After six weeks, he reported no depressive symptoms and had returned to normal functioning, working full-time and attending the gym regularly.

**Discussion**

Data from the current literature on the possible association between isotretinoin and depression is mostly limited to brief anecdotal case reports published in non-psychiatric journals (Scheinman et al. 1990; Guttman et al. 1991; Feck et al. 1991; Branson et al. 1991; Haiden et al. 1983). One study reported spontaneous depression in 1 out of 730 patients participating in a clinical trial with isotretinoin, which was unrelated to dosage (range of 0.5 to 1.3 mg/kg/day) or period of exposure (Scheinman et al. 1990). The depressive symptoms resolved rapidly within two to seven days after cessation of isotretinoin. The authors suggested that depression is a rare idiosyncratic adverse effect that may develop during isotretinoin therapy in predisposed patients.

Another report raised concern about the severity of such drug-related depressive illness particularly among younger patients, quoting cases of reported suicides involving mainly patients aged under 18 (Byrne et al. 1987). Anecdotally other authors have also suggested that total discontinuation of the drug may be a necessary condition for sustained recovery from depression (Aylward et al 1993; Scheinman et al. 1990). Challenging spores, irritability, malaise and headache can be produced by bupropion intracranial hypertensive related to hypervitaminosis A associated with use in combination with retinoids (Scheinman et al. 1990; Byrne and Hiattko 1993). The similarities to these neuropsychiatric symptoms and the drug challenge/elution data imply possible mechanisms involved in isotretinoin-induced depression.

Clinical should assess the risk factors and past history of depression prior to prescribing isotretinoin, although the predictive factors of drug-related major depression remain uncertain. Any depressive symptoms that develop during the course of treatment need close monitoring and may require prompt psychiatric assessment. Significant depression may necessitate both discontinuation of the drug and further evaluation for antidepressant therapy. Resolution of depression associated with isotretinoin appears to be rapid and complete with appropriate treatment.
On the other hand, severe acne, especially in adolescents and young adults, is frequently associated with depression, anxiety, low self-esteem, body image problems, self-consciousness, lack of self-confidence, social withdrawal and psychological distress (Gupta and Gupta 1998; Koo 1995). Hence effective acne treatment is likely to result in a positive psychological outcome (Kellett and Gawley. 1998; Rubinow 1987; Macdonald-Hull et al, 1991) and better quality of life. However, in the above case, the depression worsened despite clearing of the acne. Another aspect relates to possible unrealistic expectations following treatment that the clearing of the disfiguring skin condition would lead to resolution of personal and social inadequacies (Gatti and Scull 1991; Feck et al. 1991). Such unfulfilled hopes may heighten the sense of failure previously attributed to the acne and precipitate depression.

Given the uncertain causal relationship between isotretinoin and depression versus the potential psychological benefits of effective acne treatment, carefully designed systematic studies exploring the impact of isotretinoin on mood are needed. A prospective study comparing the effect on depressive symptoms and quality of life in patients treated with isotretinoin versus those treated with antibiotic or topical therapies is currently being conducted to further clarify these issues (Ng et al. unpublished data).

References


