Update on Isotretinoin, Depression, and Suicide: Appropriate Monitoring is Key

Data have failed to show a direct relationship between isotretinoin use and depression or suicide, but the cumulative evidence suggests patients with severe acne require careful monitoring.

By Joshua Zeichner, MD

The controversial alleged association between isotretinoin and depression and/or suicide has dogged the dermatology community for more than a decade. Despite several studies that failed to show a negative correlation, a few inconclusive studies and reports suggesting a risk for depression plus several high-profile instances of suicide by patients taking isotretinoin raised concern about the drug among both physicians and patients.

A warning regarding risk for depression and suicidal ideation was added to the isotretinoin label in 1998, and prescribers have been advised to caution patients about possible depression associated with use of the drug. Yet a causal relationship between isotretinoin use and depression or suicide had not been definitively established. Specialists have noted that acne itself, rather than isotretinoin use, is associated with depression, anxiety, and diminished quality of life (QoL). In fact, a new study shows a correlation between acne severity and depression and that acne treatment improves QoL. Furthermore, a new, large study has failed to identify a link between isotretinoin use and suicide and found that the attempted suicide risk in severe acne patients actually was lower during treatment compared to after treatment. Following is a review of the latest data on isotretinoin, suicide, and depression, a look at updated AAD guidelines regarding isotretinoin, and implications for clinical care.

Recent Findings
Conventional dosing of isotretinoin ranges from 0.5 to 1.0mg/kg per day to reach a total cumulative dose of 120 to 150mg/kg, usually obtained in 16-32 weeks. To minimize the risk of adverse events (including skin dryness and irritation, chelitis, etc.), low-dose isotretinoin (ranging from 0.25 to 5mg/kg/day) has been widely adopted. A recent comparative study

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Take-Home Tips. Accumulating evidence suggests that severe acne is associated with significant psychological and quality of life influences that may have more impact on suicide risk more so than isotretinoin does. All patients with severe acne require comprehensive monitoring, including by family members and other physicians.
found no statistical difference in efficacy between patients treated with traditional isotretinoin doses (0.5-1.0mg/kg/day) and those treated with low isotretinoin doses (0.25-0.4mg/kg/day). However, there was higher patient satisfaction in the low dose group. Moreover, both continuous dosing regimens were significantly more effective than an intermittent dosing regimen (0.5-0.7mg/kg/day for one week every four weeks).12

An Australian retrospective review of more than 1,700 patients treated with isotretinoin for acne confirmed a lower rate of adverse events (AEs) with lower doses. Among patients receiving 10-20mg isotretinoin daily, there were no serious AEs reported. The most common side effects reported among all isotretinoin-treated patients were cheilitis (dose-dependent), eczema, and mood changes. Each AE occurred significantly less frequently among those patients receiving a dose less than 0.25mg/kg/day compared to more than 0.75mg/kg/day (Table 1). Most mood change was preceded by tiredness and was self-reported as mild in most cases. In total, 13 patients discontinued isotretinoin therapy due to mood changes.

A recent Swedish study assessed risk for suicide associated with isotretinoin therapy and failed to identify a causal relationship. The investigators evaluated 5,756 patients ranging in age from 15 to 49 years who received isotretinoin for severe acne and evaluated attempted suicide risk before, during, and after treatment.10 In total, 128 patients were admitted to the hospital for attempted suicide. However, analysis showed that the incidence of suicide was raised before initiation of therapy. In the year before treatment, the risk of attempted suicide began to rise in severe acne patients. Moreover, the risk of attempted suicide was even higher in the six month period after isotretinoin therapy was completed. Only after three years post-isotretinoin therapy did the attempted suicide risk reflect that of the general population. The authors concluded that collectively, these observations do not support a causal relationship between isotretinoin and depression.

The Swedish investigators concluded that isotretinoin should not automatically be withheld from a patient with severe acne and a history of depression. In the study, the incidence of suicide was already increased in severe acne patients before isotretinoin therapy initiation. They interestingly found that patients who had attempted suicide before treatment made fewer attempts during treatment compared to those who had not made previous attempts. These findings lend support to the argument that acne itself increases an individual’s risk for suicide. Moreover, other investigators have shown that isotretinoin treatment for severe acne actually alleviates depressive symptoms and improves acne-related QoL.10,14

Data supporting the theory that acne confers its own mental health risks was gathered in a recent Norwegian questionnaire-based study. Approximately 3,700 patients between 18-19 years old were surveyed on the effect of acne on their mental and social functioning. The investigators found that substantial acne was associated with a higher risk of suicidal ideation and mental health problems. Additionally, these patients had a lower level of social functioning, particularly a low attachment to friends, not thriving in school, and an impairment of romantic relationships.15

**Clinical Implications**

As noted above, ample data document an association between acne and depression and decreased QoL. Findings from the currently available studies show that patients with severe acne are at increased risk of suicide even before initiating isotretinoin and that this risk continues after completion of isotretinoin therapy. Severe acne itself may correlate with increased depression and suicide risk, and treatment with isotretinoin may improve symptoms of depression from poor quality of life as a result of severe acne. While a causal relationship cannot be established between isotretinoin and depression, all severe acne patients should be carefully monitored for suicidal behavior before, during, and after treatment.

So why is continued monitoring after treatment so

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**Table 1: Incidence of AEs Reported with Isotretinoin**

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Low Dose (&lt;0.25 mg/kg/day)</th>
<th>High Dose (&gt;0.75 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheilitis</td>
<td>78%</td>
<td>47%</td>
<td>96%</td>
</tr>
<tr>
<td>Eczema</td>
<td>12%</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>Tiredness</td>
<td>12%</td>
<td>5%</td>
<td>18%</td>
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important? Why was the risk of attempted suicide highest in the six month period after completion of isotretinoin in the Swedish study? Perhaps this, too, relates to QoL. Response to isotretinoin therapy can be dramatic and rapid. However, the social benefits of clear skin may not be as quickly evident. Patients who have unrealistic expectations of treatment outcomes—including associated social and QoL improvements—may be particularly prone to psychological distress if those expectations aren’t met. Consider, too, that severe acne is associated with risk of scarring, which can be disfiguring. While treatment with isotretinoin helps prevent the formation of new scars, it does not improve existing scars. Therefore, patients whose acne responds to oral isotretinoin may still suffer psychological sequelae from scarring even after acne improves. Fortunately, in an era of fractionated laser therapies, there is hope for improvement of these scars.

### The Take Away

The true relationship between severe acne, isotretinon therapy, and depression is still to be elucidated. Despite newer data, prescribers cannot dismiss the association between isotretinoin and depression, given that the drug may modulate serotonin signaling in the brain. Regardless of the type of treatment selected, physicians must assess and monitor the psychological health of all acne patients, especially those with severe acne. Continued monitoring beyond the active treatment period is essential.

This past November, the AAD updated its position on isotretinoin, noting in part:

- “A correlation between isotretinoin use and depression/anxiety symptoms has been suggested but an evidence-based causal relationship has not been established. Other studies give evidence that treatment of acne with isotretinoin was accompanied by improvement of both depressive and anxiety symptoms, as well as improved quality of life of patients with acne.”

- “The Association concludes that the prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the issues related to isotretinoin use, including IBD or psychiatric disturbance, and educate their patients about these and other potential risks. Physicians also should monitor their patients for any indication of IBD and depressive symptoms.”

In light of these findings and recommendations, clinicians must focus on careful monitoring of patients with severe acne, especially those treated with isotretinoin. Physicians should monitor their patients for any indication of IBD and depressive symptoms. Physicians also should monitor their patients for any indication of IBD and depressive symptoms. Physicians also should monitor their patients for any indication of IBD and depressive symptoms.

**Dr. Zeichner has no relevant conflicts of interest.**

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**References:**