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Does Isotretinoin Increase the Risk of Depression?

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Commentary on: Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study

Azoulay L, Blais L, Koren G, LeLorier J, Bérard A
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Question: In patients with acne vulgaris, does treatment with isotretinoin increase the risk of depression?

Design: A case-crossover study was performed among subjects who received 1 or more isotretinoin prescriptions from 1984 through 2003.

Setting: Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Echo) administrative databases.

Patients: Cases were defined as those with a first diagnosis or hospitalization for depression (*International Classification of Diseases, Ninth Revision* codes 296.2, 298.0, 300.4, 309.0, 309.1, and 311) during the study period (1984-2003) and those who filled a prescription for an antidepressant in the 30 days following their diagnosis or hospitalization. The index date was the calendar date of the diagnosis or hospitalization for depression. Cases were covered by the RAMQ drug plan and had 1 or more acne diagnoses in the 12 months prior to the index date. Those who received an antidepressant in the 12 months prior to the index date were excluded.

Intervention: Exposure to isotretinoin in a 5-month risk period immediately prior to the index date was compared with a 5-month control period.

Outcome: Relative risks along with 95% confidence intervals were estimated using conditional logistic regression.

Results: Of the 30 496 subjects in the initial cohort, 126 (0.4%) cases met inclusion criteria. The crude relative risk for those exposed to isotretinoin was 2.00 (95% confidence interval, 1.03 to 3.89). After adjusting for potential time-dependent confounders, the relative risk for those exposed to isotretinoin was 2.68 (95% confidence interval, 1.10 to 6.48).

Conclusions: This is the first controlled study to find a statistically significant association between isotretinoin and depression. Because depression could have serious consequences, close monitoring of isotretinoin users is indicated.

Comment

The case-crossover method is one that is not commonly used, and its use in studying skin disease is rare. Since each patient serves as his or her own control, the method adjusts for all time-independent confounders. It is important to understand what was done in this study to generate the estimated crude and adjusted relative risks.

The risk period was defined as the 5 months preceding the first diagnosis of depression. The definition of depression was quite strict (ie, patients had to be diagnosed by a physician or have been hospitalized for depression *and* they had to have filled a prescription for an antidepressant). Five months was chosen as the risk period because it is the recommended and most commonly used period of treatment for a single course of isotretinoin. The control period was defined as a 5-month period that started 12 months prior to the first diagnosis of depression (thus, it is the same duration as the risk period and is separated from the risk period by a 2-month washout period [see Figure 1 in the article by Azoulay et al]). Evaluable data were available for 126 of 30 496 patients (ie, there were 126 patients with depression who had risk periods matched with control periods). Patients who were exposed to isotretinoin in both the risk and control period (n=15) and not exposed to isotretinoin in either period (n=72) were not counted. Twenty-six patients were exposed to isotretinoin in the risk period and not in the control period, whereas 13 patients were exposed in the control period and not in the risk period, yielding a crude relative risk of 2 (26/13).

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The authors included the following potential confounders in their adjustment model: dermatologic visits (to adjust for acne severity); nondermatologic visits, hospitalizations, and emergency department visits (to adjust for general health); and total number of prescriptions other than isotretinoin (to adjust for other comorbidities). Adjusting for these factors produced an adjusted relative risk of 2.68, with a 95% confidence interval of 1.10 to 6.48.

The authors do not provide a control event rate for depression, and therefore risk difference and number

Table 1. Number Needed to Harm for a Relative Risk of 2.7 With Varying Control Event Rates

Rate of Depression in the Control Group	Control Event Rate	Risk Difference	No. Needed to Harm
1 in 100	0.01	0.017	59
1 in 200	0.005	0.009	118
1 in 500	0.002	0.0034	295
1 in 1000	0.001	0.0017	588
1 in 2000	0.0005	0.0009	1177

Table 2. Population-Based Studies of Isotretinoin and Depression

Source	Study Design	Outcome	Relative Risk (95% Confidence Interval)
Azoulay et al, 2008	Case-crossover study	Depression	2.7 (1.1 to 6.5)
Jick et al, ³ 2000	Case-control study	Depression, suicide, or attempted suicide	1.0 (0.7 to 1.3) ^a
			1.2 (0.9 to 1.7) ^b
			1.8 (0.4 to 5.2) ^c
			1.3 (0.2 to 5.7) ^d
Hersom et al, ⁴ 2003	Prescription sequence symmetry analysis	Depression	1.0 (0.9 to 1.02)

^aCurrent isotretinoin use vs current antibiotic use (Saskatchewan Health Data).

^bBefore isotretinoin use vs current isotretinoin use (Saskatchewan Health Data).

^cIsotretinoin use vs current antibiotic use (UK General Practice Research Database).

^dBefore isotretinoin use vs current isotretinoin use (UK General Practice Research Database).

needed to harm (NNH) were not provided or calculable. Estimates for the annual incidence of depression average about 3% (ie, 3 per 100 patient-years), with a range from 1.6% to 7.5%.^{1,2} Using this estimate and the relative risk provided by this study would yield an NNH estimate for depression of 20. This NNH estimate is not realistic when compared with the experience with isotretinoin over 20 years of use.

The mean age of the patients in this study was 28 years, and 40% were male. The 5-month incidence of depression as defined in this study in a control population of patients with acne is unknown. The NNH can be estimated over a range of possible controlled event rates (**Table 1**).

The results of this study are in contrast to the 2 other population-based studies of the incidence of depression in patients receiving isotretinoin.^{3,4} One study found no statistically significant increase in relative risk of depression with isotretinoin use.³ The adjusted relative risk estimates were 1.0 for patients with current isotretinoin use compared with nonexposed patients with acne and 1.2 among isotretinoin users only, before and after isotretinoin use. In the same study, similar results were found when using the same methodology on a smaller data set from the United Kingdom (**Table 2**).³

Table 3. Critical Appraisal of Studies of Harm

Criteria	Azoulay et al, 2008	Jick et al, ³ 2000	Hersom et al, ⁴ 2003
Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?	Yes	?	?
Were treatment exposures and clinical outcomes measured the same ways in both groups (eg, was the assessment of outcomes either objective [eg, death] or blinded to exposure)?	Yes	Yes	Yes
Was the follow-up of study patients complete and long enough?	Yes	Yes	Yes
Do the results satisfy some "diagnostic tests for causation"?	NA	NA	NA
Is it clear that the exposure preceded the onset of the outcome?	Yes	Yes	NA
Is there a dose-response gradient?	No	No	No
Is there positive evidence from a "dechallenge-rechallenge" study?	Yes ^a	Yes ^a	Yes ^a
Is the association consistent from study to study?	No	No	No
Does the association make biological sense?	?	?	?

Abbreviations: NA, not applicable; ?, unknown.

^aSee Wysowski et al.⁵

There are important and noteworthy differences between these 2 studies. The diagnosis of depression in the study by Jick et al³ was based solely on *International Classification of Diseases* codes for depressive disorders. Second, the risk was expressed as events per patient-years of exposure, not per standard course of isotretinoin therapy. What result would have been obtained using per course of therapy is not known.

The second population-based study used prescription sequence analysis to determine the relative risk of depression after isotretinoin exposure based on whether prescriptions for antidepressive medication were more frequent after rather than before isotretinoin was prescribed.⁴ The result indicated that the relative risk of depression after isotretinoin prescriptions was 1.0 (Table 2). Similar results were obtained from examining the prescription sequence analysis for minocycline.⁴

The diagnosis of depression in the study by Hersom et al⁴ was based solely on the patient receiving a prescription for an antidepressive medication. As in the study by Azoulay et al, the incidence rate of depression in a control population of patients with acne was not provided so that the risk difference and NNH were not provided or calculable.

What is one to conclude given the conflicting data currently available? First, the studies should be critically appraised (**Table 3**).⁶ All of the studies can be criticized for underestimating the incidence of depression because of reliance on diagnostic codes and/or prescriptions for antidepressive medications and criteria that excludes patients with inadequate data. Underestimation of patients with depression may be a particular problem for the study by Azoulay et al. Since the relative risk estimate was based on a very small subset of patients who filled very strict criteria for depression and completeness of data, the results may not be generalizable to a general population of patients treated with isotretinoin. The study by Jick et al³ had wide confidence levels and did not exclude a relative risk of 1.2 for depression and 4.7 for having attempted or committed suicide. Hoffman and Laroche (sole producer of isotretinoin at the time the studies were performed) sponsored both of the earlier studies.

Case-control studies are level 3 evidence at best and are most convincing when they have results of similar magnitude and direction.⁶ When studies yield results that vary significantly in the magnitude and the direction of the point estimate, firm conclusions cannot be drawn. That isotretinoin increases the risk of depression has neither been proven nor disproved. Since the consequence of depression in young patients with acne can be quite severe (significant morbidity and death), it is prudent to advise patients starting or wanting to start isotretinoin therapy that the possibility of an association with depression has been raised and to provide some estimate of the magnitude of the risk.

Bottom Line: Relative risk estimates for depression after isotretinoin exposure vary from 0.9 to 2.7, with wide confidence intervals in some studies. Firm conclusions regarding the risk of depression associated with isotretinoin cannot be drawn. It is prudent to advise patients starting or wanting to start isotretinoin that the possibility of an association with depression has been raised and to provide some estimate of the possible magnitude of the risk.

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