Isotretinoin and the Risk of Depression in Patients With Acne Vulgaris: A Case-Crossover Study

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Objective: To determine whether isotretinoin increases the risk of depression in patients with acne vulgaris.

Method: A case-crossover study was performed among subjects who received ≥ 1 isotretinoin prescription from 1984 through 2003. Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. Cases were defined as those with a first diagnosis or hospitalization for depression (ICD-9 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 acne diagnosis in the 12 months prior to the index date. Those who received an antidepressant in 12 months prior to the index date were excluded. Exposure to isotretinoin in a 5-month risk period immediately prior to the index date was compared to a 5-month control period. Relative risks along with 95% CIs 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% CI = 1.03 to 3.89). After adjusting for potential time-dependent confounders, the relative risk for those exposed to isotretinoin was 2.68 (95% CI = 1.10 to 6.48).

Conclusion: 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.

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Isotretinoin is an effective medication in the treatment of severe recalcitrant nodular acne. Therefore, the expected result of a successful treatment would be improvements in quality of life and decreases in rates of anxiety and depression.[1–5] However, over the past 2 decades, case reports have suggested a controversial association between isotretinoin and depression.[6–10]

Observational studies investigating this association have produced contradictory results. Whereas in some studies no association was found between isotretinoin and depression,[11,12] 1 study found that it increases the use of mental health services.[13] Against this backdrop, the U.S. Food and Drug Administration has received reports of 394 cases of depression and 37 suicides in patients exposed to isotretinoin between 1982 and 2000.[14,15] In the U.S. Adverse Event Reporting System (AERS), isotretinoin is the fifth most common medication linked to depression and the tenth most common linked to suicide reports.[14] Using data mining techniques, Wysowski et al.[14] estimated that 6 suicide reports would be expected to be reported in the AERS by chance compared with the 37 actually reported. In Canada, of the 222 isotretinoin adverse events archived in the Health Canada adverse drug reaction database between 1983 and 2003, 56 (25%) were psychiatric.[16]

These reports have prompted several governments to modify their isotretinoin package labeling to include depression as a possible side effect of the drug. These modifications were first introduced in France in March 1997,[17] the United States in February 1998,[15] and Canada in May 2000.[18] In 2001, a Dear Health Care Professional Letter was sent to Canadian physicians, advising them to closely monitor patients presenting with depression or depressive symptoms during the course of an isotretinoin treatment.[19]

Given the contradictory results in the current literature and the repeated signals reported in adverse drug reaction databases, the association between isotretinoin and depression warrants further investigation. Therefore, the objective of the present study was to determine whether there is an association between isotretinoin and depression in patients with acne vulgaris.

METHOD

Data Sources

Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. All Quebec residents are covered by the RAMQ for medical services. Prior to January 1, 1997, the RAMQ drug plan covered those who were aged 65 years and older as well as welfare recipients and their children. After January 1, 1997, the RAMQ drug plan was changed to also include workers and their spouses/children who do not have access to a private insurance program. The RAMQ drug plan covers approximately 50% of Quebec residents.[20]

The medical and pharmaceutical databases of the RAMQ were linked by a unique patient identification number. The medical claims database includes information on the date and type of services received, and diagnoses are classified according to the *International Classification of Diseases, Ninth Revision* (ICD-9).[21] The pharmaceutical claims database contains information on the date medications were dispensed, formulations, doses, duration of prescriptions, and quantities dispensed. Medications prescribed during hospitalizations are not included in the database. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate for certain diagnoses.[22,23]

The unique patient identification number was also used to link the RAMQ to the Med-Écho administrative databases. Med-Écho contains hospitalization data on all Quebec residents. These data include patient demographic information, physician characteristics, admission diagnosis, and length of stay as well as all services received during the hospitalization. Medical diagnoses recorded in Med-Écho have been shown to be valid and precise.[24]

The study protocol was approved by the CHU Sainte-Justine Ethics Committee and the Commission d'accès à l'information du Québec.

Study Design

We employed a case-crossover design, first introduced by Maclure[25] in 1991. In the case-crossover design, cases serve as their own controls by assessing exposure at different time intervals. The time intervals in which exposure is assessed are the risk and control periods. The risk period is a time interval immediately prior to the event. The control periods are time intervals that are prior and equal in length to the risk period and provide an expected baseline frequency of exposure for each study subject in the absence of the outcome. Since cases serve as their own controls, time-independent confounders (known and unknown) are automatically adjusted by design. Confounders that change over time must be adjusted for in the analyses.

Case Definition

Cases were selected from a cohort of subjects who received at least 1 isotretinoin prescription between January 1, 1984, and December 31, 2003. Incident cases of depression were defined according to the following algorithm. We identified all subjects with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, major depressive disorder, single episode; 298.0, depressive type psychosis; 300.4, neurotic depression; 309.0, brief depressive reaction; 309.1 prolonged depressive reaction; 311, depressive disorder, not elsewhere classified) during the study period (1984–2003). In addition to having been diagnosed or hospitalized for depression, cases were required to have filled an antidepressant prescription (American Hospital Formulary System code: 28:16.04) in the 30 days following their diagnosis or hospitalization. The index date was defined as the calendar date of the diagnosis or hospitalization for depression.

Furthermore, cases had to be covered by the RAMQ drug plan for at least 12 months prior to the index date. This was deemed necessary to ensure that drug exposure information was available during the time periods of interest. In addition, cases had to have at least 1 diagnosis of acne vulgaris (ICD-9 code: 706.1) at any time in the 12 months prior to the index date. This criterion ensured that cases had acne and thus had an exposure opportunity to receiving isotretinoin. Finally, cases were excluded if they had received an antidepressant prescription in the 12 months prior to the index date. Since the index date was defined as the subjects' first diagnosis or hospitalization for depression in their entire recorded medical history, none had any diagnoses or hospitalizations for depression at any time prior to the index date. That time period ranged from a minimum of 12 months up to 20 years.

Time Windows

The risk period was hypothesized to be a total of 5 months based on data found in the literature.[6,26,27] A 5-month control window was separated from the risk

Figure 1. Case-Crossover Analysis Using 5-Month Risk and Control Periods Separated by a 2-Month Washout Period

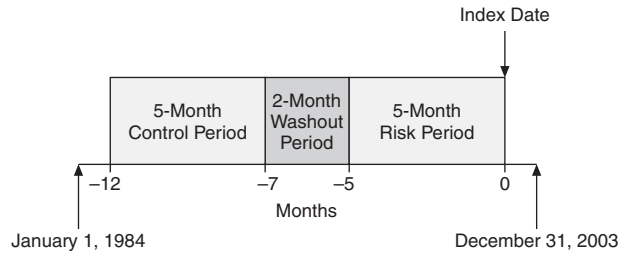

Table 1. Characteristics of Cases (N = 126)

Characteristic	Value
At the index date	
Age, mean (SD), y	28.1 (9.0)
Males, N (%)	47 (37.3)
Welfare recipients, N (%)	88 (70.0)
Urban dwellers, N (%)	106 (84.1)
In the 12 months prior to the index date	
Dermatologic visits, mean (SD)[a]	1.1 (1.3)
Nondermatologic visits, mean (SD)	6.2 (7.1)
At least 1 visit to the emergency department, N (%)	42 (33.3)
At least 1 hospitalization, N (%)	24 (19.1)
Number of different medications other than isotretinoin, mean (SD)	5.5 (4.0)

[a]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the medical doctor (*International Classification of Diseases, Ninth Revision* code: 706.1).

window by a 2-month washout period (Figure 1). A 2-month washout period was chosen because product guidelines suggest initiating a second course of isotretinoin in those who have not responded to the treatment only 8 weeks after the completion of a first course.[28] This recommendation is based on the fact that improvements in patients continue to occur during that time period despite their having terminated the treatment.

Potential Confounders

By design, the case-crossover method adjusts for time-independent confounders, such as gender. However, the following potential time-dependent confounders were recorded in each time window and adjusted for in the models: dermatologic visits, nondermatologic visits, ≥ 1 hospitalization, ≥ 1 emergency department visit, and comorbidity. Dermatologic visits were defined as consulting a dermatologist and/or being diagnosed with acne vulgaris (ICD-9 code: 706.1). Comorbidity was assessed by using the total number of different types of medications prescribed other than isotretinoin. The number of different types of medications taken by a person has been shown to be a very good predictor of health care utilization, similar in its reliability to ones used in other comorbidity measures.[29]

Table 2. Two-by-Two Table of Cases Exposed in the Risk and Control Periods[a]

	Control Period	
Risk Period	Exposed	Not Exposed
Exposed	15	26
Not exposed	13	72

[a]Crude relative risk = 26/13 = 2.0.

Statistical Analyses

Descriptive statistics were used to describe the characteristics of the cases. Relative risks along with 95% CIs were estimated by using conditional logistic regression with the individual case as the stratifying variable. In a first analysis, exposure to isotretinoin was entered as a dichotomous variable in the models (exposed at least once during each specific time window, yes or no). Isotretinoin is typically prescribed for 30-day intervals. In a second analysis, we determined whether there was a dose response of isotretinoin on the incidence of depression. The cumulative dose in milligrams of isotretinoin dispensed was calculated in each time window and entered as quartiles in the models. Crude and adjusted models were calculated for all situations. Analyses were 2 sided and $p \leq .05$ was considered significant. SAS version 8.2 (SAS Institute, Inc.; Cary, N.C.) was used to conduct the analyses.

RESULTS

Of the 30,496 subjects in the initial cohort, 126 (0.4%) cases met the inclusion criteria. This corresponded to 126 risk periods matched to 126 control periods. The mean age of cases was 28.1 (SD = 9.0) years, close to 40% were males, and most were urban dwellers (Table 1).

Most cases were diagnosed with neurotic depression (65%), followed by brief depressive reaction (15%), depressive disorder (9%), major depressive disorder (6%), depressive type psychosis (3%), and prolonged depressive reaction (2%). The most frequently prescribed antidepressants were selective serotonin reuptake inhibitors (48%), tricyclics (37%), new antidepressants (13%), and monoamine oxidase inhibitors (2%). Depression was diagnosed by psychiatrists (49%), general practitioners (47%), and other physicians (4%) (data not shown).

Isotretinoin and Depression

The numbers of cases exposed to isotretinoin in the 5-month risk and control periods were 41 (32.5%) and 28 (22.2%), respectively. Twenty-six cases were exposed in the risk and not the control period, versus 13 exposed in the control and not the risk period (crude relative risk = 26/13 = 2.0) (Table 2). The adjusted relative risk of isotretinoin associated with depression was 2.68 (95% CI = 1.10 to 6.48) (Table 3).

Table 3. Risk of Depression Associated With Exposure to Isotretinoin Using 5-Month Risk and Control Periods

Risk Factor	Crude Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
Exposure to isotretinoin	2.00 (1.03 to 3.89)	2.68 (1.10 to 6.48)
Nondermatologic visits	1.21 (1.10 to 1.34)	1.13 (1.01 to 1.25)
Dermatologic visits[b]	1.09 (0.90 to 1.30)	0.81 (0.62 to 1.05)
At least 1 hospitalization	2.44 (1.13 to 5.31)	1.73 (0.65 to 4.58)
At least 1 emergency department visit	1.81 (0.98 to 3.34)	0.94 (0.43 to 2.04)
Number of different medications other than isotretinoin	1.40 (1.20 to 1.63)	1.34 (1.11 to 1.61)

[a]Adjusted for the covariates in the table.
[b]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the medical doctor (*International Classification of Diseases, Ninth Revision* code: 706.1).

Table 4. Risk of Depression Associated With Isotretinoin Cumulative Dose Using 5-Month Risk and Control Periods

Risk Factor	Crude Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
Cumulative dose of isotretinoin		
0 mg	Reference (1.00)	Reference (1.00)
300–1199 mg	0.52 (0.05 to 5.42)	0.79 (0.05 to 13.86)
1200–2399 mg	3.09 (1.04 to 9.15)	3.24 (0.89 to 11.79)
2400–4799 mg	2.55 (0.81 to 8.01)	3.13 (0.84 to 11.64)
≥ 4800 mg	1.46 (0.53 to 4.00)	2.14 (0.62 to 7.43)
Nondermatologic visits	1.21 (1.10 to 1.34)	1.13 (1.01 to 1.26)
Dermatologic visits[b]	1.09 (0.90 to 1.30)	0.82 (0.62 to 1.07)
At least 1 hospitalization	2.44 (1.13 to 5.31)	1.69 (0.63 to 4.53)
At least 1 emergency department visit	1.81 (0.98 to 3.34)	0.92 (0.42 to 2.02)
Number of different medications other than isotretinoin	1.40 (1.20 to 1.63)	1.33 (1.10 to 1.60)

[a]Adjusted for the covariates in the table.
[b]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the medical doctor (*International Classification of Diseases, Ninth Revision* code: 706.1).

To assess whether our results could be explained by surveillance bias due to increased physician awareness of isotretinoin's possible psychiatric effects, we stratified the cases according to the calendar date of Canadian label change addressing isotretinoin's possible psychiatric risks. There were no statistically significant differences in the relative risks of cases diagnosed or hospitalized for depression after the label change (after May 2000) than cases diagnosed or hospitalized for depression before the label change (before May 2000) (data not shown).

Cumulative Dose

Although the point estimates were large, none of the cumulative doses of isotretinoin in the adjusted model reached statistical significance (Table 4).

DISCUSSION

To our knowledge, the present controlled study is the first to detect an association between isotretinoin and depression in patients with acne vulgaris. The risk of depression in subjects with no previous history of the condition increases close to threefold after being exposed to isotretinoin. Because depression could have serious consequences, our results advocate for close monitoring of patients undergoing isotretinoin therapy. This may be done by administering psychiatric assessments prior to and during therapy.

To date, Jick et al.[11] have conducted the largest population-based study investigating the association between isotretinoin and depression, psychotic symptoms, and suicide. They used data collected between 1983 and 1997 in the Canadian Saskatchewan Health Database and the United Kingdom General Practice Research Database. In their primary analysis, the authors compared a cohort of patients with acne treated with isotretinoin to another cohort treated with systemic antibiotics. No association was found between isotretinoin and depression, psychotic symptoms, or suicide. Unlike the study conducted by Jick et al.,[11] it was not possible for us to determine whether there is an association between isotretinoin and suicide, given that we had access only to inpatient and outpatient medical visits. However, with regard to depression, there are several reasons why our results differ from that study. First, we used a strict case definition in which cases were required to have both a diagnosis or hospitalization for depression and an antidepressant. This led to the inclusion of 126 cases. Despite this small sample size, the associations obtained were large enough to be statistically significant. In contrast, Jick et al.[11]

identified cases of depression using diagnostic codes alone, and thus it is possible that some cases were misclassified as noncases, which could have biased the relative risks toward the null. Second, we identified incident cases of depression. The cases identified in the present study had no diagnoses or hospitalizations for depression for a minimum of 12 months up to 20 years prior to the index date. In contrast, Jick et al.[11] adjusted for previous psychiatric history using data recorded 6 months up to 5 years before the first isotretinoin prescription. Therefore, it is likely that some residual confounding occurred, which would have once again biased the relative risks toward the null. Finally, 1 of the strengths of the case-crossover design is that cases serve as their own controls. As such, known and unknown time-independent confounders are automatically adjusted by design.

In claims data, the length of the risk and control periods necessitates knowledge of the duration of exposure required to alter the risk for an outcome, to become noticed by the physician, and then to be recorded in the administrative database.[30] Depression has been reported as early as 1 day and up to 4 months after initiating an isotretinoin treatment.[6,26,27,31] Therefore, the maximum induction time was hypothesized to be 4 months. Furthermore, patients undergoing isotretinoin treatment are typically seen by their treating physicians at 1-month intervals. Therefore, if depressive symptoms do appear, physicians would be expected to diagnose them at one of the follow-up visits. For these reasons, the risk period was set to be 5 months in length. This time window also concords with the recommended duration of an isotretinoin treatment.[32,33]

Dose-Response Relationship

Although the point estimates relating cumulative dose of isotretinoin to depression were large, none reached statistical significance. This is likely due to the small number of cases in each cumulative dose stratum. Studies with greater sample sizes would be needed to determine the exact dose-response relationship between isotretinoin and depression.

Acne has been associated with depression, suicidal ideation, and suicide in patients.[34,35] Acne is thus an important confounder of the isotretinoin-depression association. The presence of acne was intrinsically controlled by requiring cases to have at least 1 acne diagnosis in the 12 months prior to the index date. Due to the retrospective nature of the study and lack of clinical data, it was not possible to directly adjust for acne severity. However, the possibility of confounding by acne severity is unlikely for the following 4 reasons. First, all cases had at least 1 acne diagnosis in the 12 months prior to their index date. This indicates that cases received medical attention for their acne and were thus likely to have received an antiacne medication. Receiving an antiacne treatment should, at the very least, stabilize the severity of one's acne, and it is therefore unlikely that it may have worsened during the study period. Second, although there is a correlation between acne and depression, previous studies found no correlation between acne severity and depression,[36,37] thus putting into question whether severity is a true confounder. Third, isotretinoin is a highly effective medication whose utilization is associated with drastic reductions in acne lesions. In theory, the clearing of acne lesions should be associated with improvements in depressive symptoms and quality of life. Fourth, there is evidence that isotretinoin is being prescribed to patients with mild or moderate acne[38] or as a first-line treatment.[28,39] Thus, not all patients receiving isotretinoin have severe nodular acne. We nonetheless attempted to control for acne severity by adjusting our models for dermatologic visits in the risk and control periods, although such analyses would have been subject to some residual confounding.

The present study has limitations inherent in the use of administrative databases. Variables such as smoking, alcohol consumption, and illicit drug use are not available in administrative databases. Although these variables are likely to be associated with depression, it is unclear how they would be related to the use of isotretinoin. Furthermore, these variables are unlikely to have changed over a 12-month period. Given their time-independent nature, they would be automatically adjusted by design in a case-crossover study. Administrative databases report only on medications dispensed, and therefore it is unknown whether medications are actually taken by patients. However, given that isotretinoin is typically prescribed for 30-day intervals, renewals between successive prescriptions are indicative of patient adherence.[39] One major advantage of administrative databases is that they are not prone to recall bias. As such, they provide accurate information on the number, types, and dosages of medications dispensed over a specific time period. Coding errors may be present in administrative databases. If that were the case, nondifferential misclassification of the outcome would result, biasing the relative risks toward the null. If coding errors did occur in our data, then the point estimates obtained would actually be underestimates of the true relative risk.

The population investigated in the present study comprised subjects of low to moderate socioeconomic status. It is known that individuals of lower socioeconomic status are at a greater risk of depression than individuals of higher socioeconomic status.[40] Since we did not have access to medications used by subjects insured by private drug insurance programs, it was not possible to determine whether socioeconomic status was an effect measure modifier of the isotretinoin-depression association. However, several studies have pointed to a possible biological association between isotretinoin and depression.

Isotretinoin and vitamin A share similar chemical structures, and thus many side effects of isotretinoin are similar to vitamin A when taken in large doses.[41] Hypervitaminosis A has been shown to induce irritability and depressive symptoms.[42–44] One study found that exposure to retinoic acid results in hippocampal cell loss in mice.[45] In humans, hippocampal volume has been shown to be inversely related to depression,[46] a finding that indirectly supports the hypothesis that isotretinoin may cause cell loss in this region of the brain. Another study found that daily intake of 1 mg/kg of isotretinoin for 6 weeks in young male mice (similar doses used in humans) was associated with depression-like behavior.[47] Recently, Bremner et al.[48] assessed brain function in patients with acne treated with isotretinoin and antibiotics. They found that isotretinoin decreased metabolism in the orbitofrontal cortex, a region of the brain known to be involved in depression. This effect was not observed in patients treated with antibiotics. More research is needed to elucidate the exact mechanisms through which isotretinoin may induce depression.

Depression is likely to be a rare side effect of isotretinoin therapy. The present study supports close monitoring of patients during the treatment for possible signs of such symptoms. Current guidelines should possibly be modified to include psychiatric assessments of patients prior to and during isotretinoin therapy.

Drug name: isotretinoin (Claravis, Amnesteem, and others).

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