

Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide

Susan S. Jick, DSc; Hilal Maradit Kremers, MD, MSc; Catherine Vasilakis-Scaramozza, MPH

Background: It has been suggested that there is a causal association between isotretinoin therapy and the risk of depression, psychotic symptoms, suicide, and attempted suicide.

Objective: To further investigate the proposed association between isotretinoin therapy and the risk of depression, psychotic symptoms, suicide, and attempted suicide using a formal study design.

Design: Large population-based cohort studies.

Setting: The Canadian Saskatchewan Health Database and the United Kingdom General Practice Research Database.

Patients: Data were analyzed for 7195 isotretinoin users and 13 700 oral antibiotic users with acne from the Canadian Saskatchewan Health Database and for 340 isotretinoin users and 676 oral antibiotic users with acne from the United Kingdom General Practice Research Database. All subjects had computer-recorded histories of between 6 months and 5 years before, and at least 12 months after, their first isotretinoin or antibiotic prescription.

Outcome Measure: Prevalence rates of neurotic and psychotic disorders, suicide, and attempted suicide were compared between isotretinoin and antibiotic users and within isotretinoin users as their own comparison (pretreatment vs posttreatment). The results were expressed as relative risks, calculated using multiple logistic regression analyses.

Results: Relative risk estimates, comparing isotretinoin use and oral antibiotic use with nonexposure to either drug for newly diagnosed depression or psychosis, were approximately 1.0 regardless of the data source. Similarly, relative risk estimates were all around 1.0 when comparing before with after isotretinoin use. The relative risk estimate for suicide and attempted suicide was 0.9 (95% confidence interval, 0.3-2.4) when comparing current isotretinoin exposure with nonexposure.

Conclusion: This study provides no evidence that use of isotretinoin is associated with an increased risk for depression, suicide, or other psychiatric disorders.

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ISOTRETINOIN (13-*cis*-retinoic acid) is the active ingredient of Roaccutane or Accutane (F. Hoffmann–La Roche Ltd, Basel, Switzerland), which is indicated for the treatment of severe recalcitrant nodulocystic acne. Isotretinoin is a retinoid, the 13-*cis* isomer of all-*trans*-retinoic acid (tretinoin) and a derivative of vitamin A. Acne vulgaris affects approximately 80% to 90% of teenagers but also affects individuals in their 20s and 30s.¹

Surveys²⁻⁷ show that approximately 30% to 50% of those aged 12 to 20 years with acne have psychological responses to their disease, which range from mild anxiety to depression, embarrassment, self-consciousness, lowered self-esteem, lack of self-confidence, and perceived social rejection.^{5,8-10} Lack of knowledge, especially about prognosis, may be a source of anxiety for the individual patient.³

Successful acne therapy significantly reduces anxiety and depression in patients with acne.¹¹⁻¹³ However, isolated patients developing depression months after therapy suggest that clearing of a disfiguring disease may make it more difficult for some individuals to accept difficulties previously attributed to appearance alone.^{14,15}

Isotretinoin therapy and alleged adverse psychiatric effects received considerable media attention during the past years. These anecdotal reports created a widespread concern among prescribers and users. In turn, the manufacturer received several inquiries and spontaneous reports from users and prescribers (F. Hoffmann–La Roche Ltd, unpublished safety data, 1999). To explore a possible association between isotretinoin therapy and the risk of depression, psychotic symptoms, suicide, and attempted suicide, we conducted a study using data from the Ca-

From the Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, Mass (Dr Jick and Ms Vasilakis-Scaramozza); and Global Drug Safety, F. Hoffmann–La Roche Ltd, Basel, Switzerland (Dr Kremers).

SUBJECTS AND METHODS

CANADIAN SASKATCHEWAN HEALTH DATABASE

The province of Saskatchewan provides universal health care coverage to about 1 million people through its Department of Health. An important resource that has come from the publicly funded health coverage is the health database, containing information on all Saskatchewan residents covered by the Department of Health and including prescription drug data, inpatient and outpatient diagnoses, patient demographics, and records of special medical and supportive services. Psychiatric services delivered by physicians outside the program are recorded on the physician services data file. Inpatient and outpatient psychiatric care data are recorded in the hospital data file, the Mental Health Services data file, or both. This data resource has been used for many drug safety studies and has proved accurate and complete.¹⁶⁻²⁰

UNITED KINGDOM GENERAL PRACTICE RESEARCH DATABASE

More than 4 million people in the United Kingdom are enrolled, with selected general practitioners who use office computers provided by Value Added Medical Products and have agreed to provide data for research purposes. The GPRD is administered by the Medicines Control Agency. General practitioners have been trained to record medical information—including demographic data, medical diagnoses, details of hospital stays, and deaths—in a standard, anonymous form. The physicians generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record. Death certificates are available for

review. A modification of the Oxford Medical Information System classification (similar to the *International Classification of Diseases, Eighth Revision [ICD-8]*)²¹ is used to enter medical diagnoses, and a coded drug dictionary based on the United Kingdom's Prescription Pricing Authority dictionary is used for recording prescriptions. The information recorded on drug exposure, diagnoses, and deaths in the GPRD is of high quality and is satisfactory for drug safety studies.²²⁻²⁴

STUDY DESIGN

This study involves 2 separate retrospective cohort studies of oral isotretinoin users identified in the 2 databases previously described. In each study, all recruited subjects had between 6 months and 5 years of computer-recorded history before their first isotretinoin prescription and at least 12 months of computer-recorded history after the last isotretinoin prescription, except where death occurred.

In the first study, we identified a cohort of subjects with acne in whom the condition was diagnosed within the same period (± 6 months) and who fell within the same 10-year age bands as the isotretinoin-treated patients but who were treated with only antibiotic therapies, as shown by prescriptions for tetracycline, erythromycin, clindamycin, minocycline, or doxycycline, received within 30 days following the acne diagnosis.

Subjects were considered to be "currently exposed" from the first prescription for isotretinoin or oral antibiotic for treatment of acne through 3 months after receiving the last study drug prescription. (A prescription length, in both databases, was generally 1 month long.) *Recent users* were defined as receiving their last study drug prescription 4 to 6 months previously. All other time after receipt of the study drug was considered "nonexposed

nadian Saskatchewan Health Database and from the United Kingdom General Practice Research Database (GPRD) to determine the rates and relative risks (RRs) of psychotic and neurotic disorders, suicide, and attempted suicide among users of oral isotretinoin compared with nonusers with antibiotic-treated acne.

RESULTS

CANADIAN SASKATCHEWAN HEALTH DATABASE

There were 7195 isotretinoin users in the Saskatchewan data resource from 1983 to 1997; 53% were male, and 79% were aged 10 to 29 years. There were 13700 antibiotic users; 43% were male, and 75% were aged 10 to 29 years (**Table 1**).

Most users filled 3 to 6 prescriptions for isotretinoin (62%), and 18% filled 7 or more prescriptions. Of all prescriptions for isotretinoin, 86% were for the 40-mg preparation; 66% of isotretinoin prescriptions were prescribed by dermatologists (compared with 13% of antibiotics) and 29% by general practitioners (compared with 78% of antibiotics). Most patients with acne treated with

antibiotics received tetracycline (64%), followed by erythromycin (22%), minocycline (10%), and doxycycline (5%) (percentages total >100 because of rounding). Among these, 26% filled 3 to 6 prescriptions, and 17% filled 7 or more.

Analysis 1

There were 1777 patients with depression or psychosis. Most experienced anxiety disorders (61%). Twenty-nine percent had mood disorders, 6% had affective disorders, and 3% had nonaffective disorders (percentages total <100 because of rounding). There was no material difference in exposure across the different categories of psychiatric illness.

We compared current and recent isotretinoin use and, separately, antibiotic use with nonexposed time in relation to the risk of newly diagnosed depression and psychosis and then separately for the risk of suicide and attempted suicide (**Table 2** and **Table 3**). For newly diagnosed depression or psychosis, the RR estimate for current isotretinoin use compared with the nonexposed period was 1.0. The RR estimates for recent isotretinoin use, current antibiotic use, and recent antibiotic use in

time." Person-time was accrued from enrollment into the study until a person became a case, or until the end of follow-up (12 months after completion of the last study drug prescription). Rates of neurotic and psychotic disorders and suicide or attempted suicide were compared between isotretinoin users and antibiotic users.

We controlled for a *history of psychiatric disorder*, defined as a recorded code for any psychiatric diagnosis (including depression, psychosis, and attempted suicide) before receipt of the first study drug by stratifying each analysis according to psychiatric history. This enabled us to analyze the risk for newly diagnosed psychotic and neurotic disorders.

In the second analysis, we evaluated isotretinoin users only by comparing the rates of newly diagnosed neurotic and psychotic disorders in the 6 months following receipt of an isotretinoin prescription to outcome rates in the 6 months before receipt of the first isotretinoin prescription. This choice of comparison enabled us to control for acne severity and other patient characteristics.

For cases of suicide or attempted suicide, we controlled for a history of psychiatric disorder, as defined previously.

OUTCOMES

Study outcomes (depression, psychoses, suicide, and attempted suicide) were defined as follows.

Canadian Saskatchewan Health Database

1. *Neurotic and psychotic disorders*: Any outpatient or hospital diagnosis of neurotic or psychotic disorder (*International Classification of Diseases, Ninth Revision [ICD-9]*,²⁵ codes 296-301) recorded in the patient's automated medical record after study enrollment.

2. *Suicide or attempted suicide*: All subjects with a code of suicide or attempted suicide (*International Classification of Diseases, Ninth Revision [ICD-9]*, E code from the accident field) occurring after study enrollment.

United Kingdom General Practice Research Database

1. *Neurotic and psychotic disorders*: Any outpatient or hospital diagnosis of neurotic or psychotic disorder (*International Classification of Diseases, Eighth Revision [ICD-8]*, codes 306-311) recorded in the patient's automated medical record.

2. *Suicide*: All subjects with a diagnosis of suicide (Oxford Medical Information System code 3009D) recorded in the medical record.

3. *Attempted suicide*: All subjects with an inpatient or outpatient code for attempted suicide (Oxford Medical Information System codes 3009C, 3009BN, 3009BT, 3009BP, 9779DL, 9779NA, and 9779L) in their medical record.

All subjects with these defined outcomes were considered cases for this study. For simplicity, we shall hereafter refer to cases of neurotic and psychotic disorders as *cases of depression or psychosis*.

DATA ANALYSIS

We calculated incidence rates of suicide or attempted suicide and prevalence rates of newly diagnosed depression or psychosis using person-time as the denominators and the number of cases of each outcome (all events) as the numerators, stratified by exposure, age, and sex. Relative risks comparing the various exposures to the nonexposed period were calculated using multiple logistic regression models in SAS statistical software, version 6.12 (SAS Institute Inc, Cary, NC). Results are presented as point estimates with 95% confidence intervals (CIs).

patients with acne were 0.9, 1.3, and 0.9, respectively. There was no difference between the exposure groups.

We found an RR estimate for suicide and attempted suicide of 0.9 for current isotretinoin use compared with nonexposed time. The RR estimates were 1.1, 0.8, and 0.5 for recent isotretinoin use, current antibiotic use, and recent antibiotic use, respectively (Table 3), compared with nonexposed time, with wide CIs in all instances. Increasing age was independently related to an increased risk for suicide or attempted suicide, and the RR for females compared with males was 1.2. The independent RR for history of depression or psychosis when entered in the model was 8.0. When the risk for suicide or attempted suicide was evaluated in those with no psychiatric history, the RR estimates did not change materially.

Analysis 2

In the analyses restricted to isotretinoin users only, we compared rates of depression or psychosis in the 6 months after the start of isotretinoin therapy with rates in the 6 months before isotretinoin use. For newly diagnosed depression and psychosis (Table 2), we found an RR estimate for current isotretinoin use of 1.2 compared with

Table 1. Age and Sex Distribution of Isotretinoin and Antibiotic Users With Acne (Saskatchewan Health Data)*

Age Group, y	Isotretinoin Users			Antibiotic Users		
	Males	Females	Total	Males	Females	Total
<20	2200	1152	3352	3520	3384	6904
20-29	1175	1157	2332	1240	2124	3364
30-39	295	814	1109	480	1328	1808
≥40	161	241	402	695	929	1624
Total	3831	3364	7195	5935	7765	13 700

*Data were obtained using the Canadian Saskatchewan Health Database.

the nonexposed period (6 months before use). The RR estimate for recent isotretinoin use was 1.0.

UNITED KINGDOM GENERAL PRACTICE RESEARCH DATABASE

Analysis 1

There were 340 isotretinoin users in the GPRD study population who received 660 prescriptions; 58% were male, and

Table 2. Independent Relative Risk Estimates for Newly Diagnosed Depression or Psychosis by Exposure Status, Age, and Sex (Saskatchewan Health Data)*

Variable	No. of Cases/ Person-years	Adjusted Relative Risk Estimate	95% Confidence Interval
Isotretinoin and Antibiotic Users With Acne			
Exposure status			
Nonexposed†	225/11 655	1.0	...
Current isotretinoin use	61/3469	1.0	0.7-1.3
Current acne with antibiotic use	214/9324	1.3	1.0-1.5
Recent isotretinoin use	25/1455	0.9	0.6-1.4
Recent acne with antibiotic use	70/4303	0.9	0.7-1.1
Age, y			
<20†	180/14 172	1.0	...
20-29	199/9491	1.7	1.4-2.0
30-39	140/4122	2.5	2.0-3.2
≥40	76/2421	2.4	1.8-3.1
Sex			
Male†	223/1438	1.0	...
Female	372/15 468	1.4	1.2-1.7
Isotretinoin Users Only: Before and After Isotretinoin Use			
Exposure status			
Nonexposed (before isotretinoin use)†	65/3160	1.0	...
Current isotretinoin use	93/3516	1.2	0.9-1.7
Recent isotretinoin use	34/1588	1.0	0.6-1.5
Age, y			
<20†	54/3977	1.0	...
20-29	66/2743	1.7	1.2-2.5
30-39	58/1141	3.4	2.3-5.0
≥40	14/402	2.4	1.3-4.2
Sex			
Male†	84/4673	1.0	...
Female	108/3591	1.3	0.7-1.8

*Data were obtained using the Canadian Saskatchewan Health Database. Ellipses indicate data not applicable.
†Reference group.

78% were aged 10 to 29 years (**Table 4**). In the United Kingdom, the 20-mg formulation of isotretinoin was the most widely used (75%) compared with the 5-mg formulation. Of all users, 81% received 1 to 2 prescriptions for isotretinoin, 16% received 3 to 5 prescriptions, and 3% received 6 or more prescriptions. We identified 676 patients with acne treated with an oral antibiotic; 59% were male, and 78% were aged 10 to 29 years. Sixteen percent received 1 to 2 prescriptions for an antibiotic, 32% received 3 to 6 prescriptions, and 53% received 7 or more prescriptions (percentages total >100 because of rounding). The demographics were similar to those of the Saskatchewan study population.

As there was only one case of suicide or attempted suicide in the GPRD, no conclusions could be drawn on relative rates of either. The one case of suicide was nonexposed. Isotretinoin use yielded an RR estimate for newly diagnosed depression or psychosis of 1.8 compared with the nonexposed period. The RR estimates were 1.8, 1.5, and 1.7 for recent isotretinoin use, current antibiotic use, and recent antibiotic use, respectively (**Table 5**).

Analysis 2

In the analyses restricted to isotretinoin users only, the RR estimates for newly diagnosed depression or psychosis were 1.3 and 1.1 for current and recent isotretinoin use, respectively, compared with nonuse (during the 6 months before isotretinoin receipt).

COMMENT

There was no evidence, from either resource, that use of isotretinoin is associated with an increased risk for newly diagnosed depression, other psychiatric disorders, or suicidal behavior. Relative risk estimates comparing isotretinoin and oral antibiotic use with nonexposed time, for these outcomes, were all close to 1.0 regardless of the data source.

Table 3. Independent Relative Risk Estimates for Suicide or Attempted Suicide in Isotretinoin Users and in Patients With Acne Treated With Antibiotics by Exposure Status, Sex, and History of Depression or Psychosis (Saskatchewan Health Data)*

Variable	All Subjects		Subjects With No Psychiatric History	
	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)
Exposure status				
Nonexposed†	17/13 894	1.0	8/12 136	1.0
Current isotretinoin use	4/4003	0.9 (0.3-2.4)	4/3553	1.3 (0.3-4.6)
Current acne with antibiotic use	11/11 051	0.8 (0.4-1.7)	3/9617	0.5 (0.1-1.6)
Recent isotretinoin use	2/1678	1.1 (0.2-3.7)	1/1499	1.0 (0.1-5.7)
Recent acne with antibiotic use	3/5133	0.5 (0.1-1.4)	2/4433	0.7 (0.1-2.7)
Sex				
Male†	14/16 510	1.0	8/15 101	1.0
Female	24/19 247	1.2 (0.6-2.5)	10/16 136	1.4 (0.5-3.8)
Previous depression or psychosis				
No†	18/31 237	1.0
Yes	20/4520	8.0 (4.1-15.5)

*Data were obtained using the Canadian Saskatchewan Health Database. Ellipses indicate data not applicable.
†Reference group.

Table 4. Age and Sex Distribution of Isotretinoin and Antibiotic Users With Acne (GPRD Data)*

Age Group, y	Isotretinoin Users			Antibiotic Users		
	Males	Females	Total	Males	Females	Total
<20	99	40	139	198	80	278
20-29	71	55	126	142	110	252
30-39	17	30	47	34	58	92
≥40	11	17	28	22	32	54
Total	198	142	340	396	280	676

*Data were obtained using data from the United Kingdom General Practice Research Database (GPRD).

In the larger, Saskatchewan database, the RR estimate for newly diagnosed depression or psychosis was 1.0 (95% CI, 0.7-1.3) for current isotretinoin exposure compared with the nonexposed period. The same analysis in the GPRD yielded an RR estimate of 1.8 (95% CI, 0.4-5.2). For suicide and attempted suicide in the Saskatchewan database, the RR estimate was 0.9 (95% CI, 0.3-2.4) when comparing current isotretinoin exposure with the nonexposed period. There was only one suicide attempt in the GPRD, and that person was nonexposed.

In both databases, the results of the newly diagnosed depression or psychosis analysis, restricted to isotretinoin users only before and after use, yielded RR estimates around 1.0 for use of isotretinoin compared with the nonexposed period. We also looked at all diagnoses of depression or psychosis and suicide attempt, including preexisting conditions and newly diagnosed disorders, and found no association between isotretinoin use and the outcomes.

To our knowledge, this is the first population-based study of the psychiatric and suicide risk associated with isotretinoin exposure, and the largest to date.^{5,12} We conducted the study using computerized databases that allowed for the assessment of large, well-documented cohorts of isotretinoin- and oral antibiotic-treated patients with acne.

We identified more than 7000 oral isotretinoin users and twice that number of oral antibiotic users with acne in the Saskatchewan files. The sample size was sufficient to generate reliable prevalence and RR estimates for depression and psychotic disorders, since the prevalence of these disorders in the general population exceeds 1%. Although suicidal ideation is not uncommon in patients with acne, attempted and completed suicides are rare.²⁶⁻²⁸ Our population size was not large enough to generate stable estimates for suicide and attempted suicide, as demonstrated by the small number of events and large CIs for the RR estimates (37 cases of suicide or attempted suicide), although there is no suggestion of an association for current isotretinoin use compared with a nonexposed period (RR, 0.9).

The use of computerized databases for conducting studies with psychiatric outcomes has several potential limitations. Previous validation studies^{20,29} of the Saskatchewan databases demonstrated excellent agreement of personal and demographic characteristics across

Table 5. Independent Relative Risk Estimates for Newly Diagnosed Depression or Psychosis by Exposure Status, Age, and Sex (GPRD Data)*

Variable	No. of Cases/ Person- years	Adjusted Relative Risk Estimate	95% Confidence Interval
Isotretinoin and Antibiotic Users With Acne			
Exposure status			
Nonexposed†	27/1349	1.0	...
Current isotretinoin use	3/88	1.8	0.4-5.2
Current acne with antibiotic use	32/1284	1.5	0.9-2.5
Recent isotretinoin use	2/59	1.8	0.3-6.1
Recent acne with antibiotic use	11/347	1.7	0.8-3.4
Age, y			
<20†	17/1176	1.0	...
20-29	33/1349	1.8	1.0-3.3
30-39	17/401	2.6	1.3-5.2
≥40	8/201	2.3	0.9-5.3
Sex			
Male†	32/2025	1.0	...
Female	43/1102	2.2	1.4-3.5
Isotretinoin Users Only: Before and After Isotretinoin Use			
Exposure status			
Nonexposed (before isotretinoin use)†	4/148	1.0	...
Current isotretinoin use	3/88	1.3	0.2-5.7
Recent isotretinoin use	2/63	1.1	0.2-5.7
Age, y			
<20	2/131	1.0	...
20-29	5/110	2.7	0.6-19.1
30-39	1/35	1.5	0.1-16.6
≥40	1/24	2.3	0.1-24.7
Sex			
Male†	4/185	1.0	...
Female	5/115	1.8	0.5-7.5

*Data were obtained using data from the United Kingdom General Practice Research Database (GPRD). Ellipses indicate data not applicable. †Reference group.

different data files but relatively low agreement for non-specific and mild psychiatric diagnoses such as depressive disorders.

Some psychiatric outcomes may have been misclassified, since isotretinoin users are likely to see their physicians more frequently than antibiotic users, resulting in more frequent diagnoses of psychiatric disorders and hence in an overestimate of the RR. However, if such a differential misclassification did occur, then the risk during isotretinoin exposure is actually lower than detected in this study, and we found no increased risk of depression or psychoses or suicide or attempted suicide in isotretinoin users compared with antibiotic users.

Several of our findings strengthen the external validity of the study. First, the results were consistent between the 2 data sources used. Furthermore, the results were consistent with previously described findings on the epidemiological characteristics of psychiatric disorders,

particularly depressive disorders: women were more likely than men to experience psychiatric disorders in all age groups, and the prevalence of disease increased with increasing age.³⁰⁻³³ Prominent effects of medical history on suicide risk (RR, 8.0) and comorbidity for alcohol and other drug abuse were also consistent with the published literature,^{34,35} providing reassurance that these data are valid for conducting research in this area.

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Reprints: Susan S. Jick, DSc, Boston Collaborative Drug Surveillance Program, 11 Muzzey St, Lexington, MA 02421 (e-mail: sjick@bu.edu).

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