# NO ASSOCIATION FOUND BETWEEN PATIENTS RECEIVING ISOTRETINOIN FOR ACNE AND THE DEVELOPMENT OF DEPRESSION IN A CANADIAN PROSPECTIVE COHORT

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## ABSTRACT

### Background
There has been concern that the use of isotretinoin to treat acne may lead to depression. To date, research has not conclusively determined if this concern is warranted when contemplating the use of isotretinoin.

### Objective
This study investigated the impact of isotretinoin use for patients with acne on mood status. The hypothesis was that an association exists between the use of isotretinoin and the development of depression, aside from acne severity.

### Methods
We studied the relationship between isotretinoin and depression using a prospective, controlled, cohort design. The study was conducted in a community dermatology clinic. The exposed cohort consisted of consenting patients who were initiating isotretinoin treatment for acne. Patients were either treated with isotretinoin (Acutane®) therapy (study group) (N=100) or by oral (N=41) or topical acne therapy (control group) (N=59). The Center for Epidemiologic Studies Depression scale and the Zung Depression Status Inventory were used to assess depression both at baseline and after 2 months of prescribed use of isotretinoin or a control medication (topical or oral antibiotics).

### Results
There was no correlation between isotretinoin use and the development of depression, based on either the Centre for Epidemiologic Studies Depression scale (Fisher's exact test, P=0.497) or Zung Depression Status Inventory (ANOVA; F=1.4, P=0.2).

### Conclusion
Isotretinoin does not appear to be associated with the development of depression. Thus, denying patients with significant acne an effective medication for fear of developing depression may not be indicated at this point in time.

**Key Words:** *Isotretinoin, depression, acne*

Acne, a common dermatological condition that can occur in virtually 100% of adolescents, accounts for approximately 3% of all dermatological visits.[1,2] The psychological impact of acne is similar to that of patients with chronic diseases of other organ systems, such as arthritis, back pain, diabetes, epilepsy, and disabling asthma.[3] Depression, anxiety, personality changes, diminished self-image and esteem, feelings of social isolation, and the inability to form

relationships, have all been associated with acne[4]. Acne poses a great psychological challenge on people of all ages.[4] Management of patients with acne includes: empathy, education and medical treatment.[5] Isotretinoin is a third line therapy that can limit or prevent scarring and decrease the length of the condition resulting in the most significant psychosocial outcomes.[6]

Isotretinoin (Acutane® or 13-cis-retinoic acid) has been used to treat severe acne unresponsive to conventional treatments for over 2 decades.[7] In the mid 1980's, post-marketing reports of depression resulted in labeling changes, listing depression as a possible adverse reaction to isotretinoin. In 1996, two cases of suicide associated with isotretinoin use lead to a more detailed investigation by the FDA. Hoffman-La Roche estimates that approximately 8 million patients use isotretinoin worldwide, with 3.2 million users in the U.S. Although research has been done looking at a causal relationship between isotretinoin and depression and possible suicide, the evidence so far differs among studies.[8-10]

Ng and associates have reviewed the literature and performed a prospective study of isotretinoin use and depression.[11,12] Although their research identified no correlation between isotretinoin dose and depression, five isotretinoin patients were removed from the study because of worsening mood (215 patients total). Chia et al found similar results when they examined isotretinoin patients treated for moderate to severe acne in the adolescent population.[13] Most recent reviewers have concluded that there is no clear evidence of an association.[14,15] Nevertheless, brain-imaging studies have identified isotretinoin-associated changes in brain functioning that may be related to depression.[16]

One of the challenges in interpreting studies of the association between isotretinoin use and depression is that severe acne is itself associated with depression, and individuals taking isotretinoin have more severe acne than those receiving alternative treatments. Thus, we attempted to investigate the impact of isotretinoin on mood status, taking into account acne severity. We evaluated changes in depression ratings in a sample of patients before and during treatment with isotretinoin. We hope the results will assist clinicians with risk-benefit decision-making in the treatment of acne. To the best of our knowledge this is the first prospective controlled study of this kind in North America.

## METHODS

### *Study Design and Setting*

The relationship between isotretinoin and depression was studied using a prospective cohort design. Depression was defined by research based rating scales. The traditional format of the prospective cohort design was modified slightly for this project as persons with depressive symptoms at baseline were not excluded. Since treatment of acne may improve depressive symptoms by such mechanisms as improved self-esteem, data from subjects with depressive symptoms at baseline were included in the study. The study was conducted in a community dermatology practice and was approved by the Ethics Committee at the University of Calgary.

### *Subjects*

A total of 200 subjects were involved in this study. The exposed cohort consisted of consenting patients who were initiating isotretinoin treatment for acne (N=100). The study setting, a community dermatology practice, allowed access to a representative sample of such subjects. Eligible criteria for the study included: being 1) 14 years old, or older, 2) mentally competent to provide informed consent, 3) not currently under pharmacological treatment with antidepressants, 4) not anticipating a change in residence during the period of study, and 5) able to provide at least two options for follow-up contact. The control group consisted of dermatology patients with acne initiating treatment with topical creams (N=59) or oral antibiotics (N=41). All subjects provided written, informed consent. Parental consent was obtained for subjects under the age of 16.

A major methodological concern in observational studies of pharmacological adverse events is the issue of confounding. Such studies are vulnerable to confounding due to the reason for drug treatment (confounding by indication) or for reasons related to illness severity or extraneous variables. The first issue, confounding by indication, was dealt with by restricting subject selection to those with acne; the remaining variables (severity of acne and extraneous depression risk factors) were measured and dealt

with at the stage of data analysis. Since isotretinoin is commonly used to treat acne that is unresponsive to other treatments, there may be residual confounding by illness severity. For this reason, a measure of acne severity was included in the data collection.

The analysis included an evaluation of possible confounding by acne severity, and statistical adjustment as necessary. We decided against the use of matching (partial restriction) since control of confounding for easily measurable factors (e.g. demographics) can be achieved using other methods and potential gains in precision resulting from matching are likely to be outweighed by diminished recruitment as a result of the inconvenience that matching would create.

### *Measures*

Depression

Using the Zung Depression Status Inventory and the Center for Epidemiologic Studies Depression Scale (CES-D), we assessed the patients' depression scores both prior to starting treatment and after 2 months of prescribed use of isotretinoin. The Zung scale is a valid, reliable and internally consistent measure of depressive symptom severity; whereas, the CES-D has been designed to identify episodes of clinically significant depression in the general population. For a review of psychometric properties of these instruments, please see reviews by McDowell.[17,18] We view these two scales as being complementary since the Zung provides a valid measure of change in symptom levels, and the CES-D will complement this by indicating the frequency with which episodes of probable clinical significance emerge.

Potential Confounding Variables

The most important confounders other than acne severity were considered to be: 1) demographic variables 2) social support 3) stress and recent life events 4) self esteem 5) past and family history of depression 6) chronic medical conditions 7) perceived health 8) medication use, and 9) drug and alcohol use. A questionnaire was developed to collect this data. The instruments chosen were both brief and acceptable for administration over the telephone. Social support (Medical Outcomes Study Social Support Scale), stress, recent life events, and self esteem were evaluated using modules from the questionnaire used by Statistics Canada in the Canadian Community Health Study. The chronic conditions, perceived health, and medication items were adapted from those employed in the Canadian National Population Health Survey, and have been used in a variety of telephone surveys in Alberta, Canada.

### *Data Collection and Management*

To avoid an intrusion of privacy when potential research subjects were approached the consent forms were handed out by existing staff in the dermatology practice. This was accomplished by hiring a current part-time employee of the practice on an hourly basis for subject recruitment and data collection. Each potential subject was given time to read the consent form and to ask questions about the study. Consenting subjects were administered the baseline questionnaire and baseline depression ratings. All data collection procedures were identical for both control and exposure groups.

The baseline questionnaire was completed in pen and paper format. The data was subsequently entered into an electronic database within one week of the data collection. Double entry was used to minimize errors. The principal investigator examined the database weekly to look for errors and suspected errors by looking for out of bounds values, missing values and improbable combinations of values. The follow-up interview was conducted by telephone, within 25 to 35 days of the start of acne treatment. In addition to the depression rating scales, the self-esteem and social support sections were re-administered.

### *Data Analysis*

Once data entry was complete, a careful check of the database for missing values and possible errors occurred. Any errors identified were corrected, where possible, by returning to the original pen and paper forms or if possible, by re-contacting the study subject. The primary analysis consisted of two components: First, a comparison of changes in mean Zung scale ratings over time; second, a comparison of changes in nominal depression status, as determined by the CES-D. When the distribution of data was represented by a bell-shaped curve, means were reported as a measure of central tendency. Medians were used when distributions were not normally distributed.

Confounding Variables

To act as a confounder, a variable must be associated both with exposure (isotretinoin) and outcome (depression). The association between potential confounders and other study variables was therefore explored in a series of preliminary tables, which were then used to select those variables for which statistical adjustment for confounding was required. Statistical adjustment consisted of stratified analysis and linear regression.

Zung Analysis

Since two ratings were obtained, a paired analysis was conducted. This was accomplished by the generation of a change score consisting of the difference between the follow-up rating and the baseline rating. A positive score therefore, indicated an increased level of depression. An ANOVA was used to evaluate the null hypothesis that the means of the two distributions of difference scores were equivalent. Wilcox signed-rank test and Wilcox ranked-sum test were used to compare Zung scores at baseline and follow-up since these distributions were not normally distributed.

CES-D Analysis

Each subject was classified as exceeding or not exceeding the traditional CES-D cut-point for clinically significant depression (>15) both at baseline and at follow-up. The proportion newly exceeding the cut-point during follow-up (incidence) was calculated in each treatment group. A Fischer's exact test was used to test for a statistical difference between these groups.

## RESULTS

### *Descriptive Variables*

The demographic and clinical characteristics of the study groups are displayed based on categorical and non-categorical variable status and are presented in Table 1. The median age of individuals in this study was twenty-two years. Our population contained more females (67%, N=134) than males (33%, N=66). With respect to relationship status, the majority of patients in the study were either married (30%, N=60) or single (68%, N=135). Of the others: two reported that they were living with partner (1%), one was separated (0.5%), and two were divorced (1%). With respect to level of education, 3% (N=6) had less than a grade nine education, 27% (N=54) were between grade 9 and 12 with no diploma, 12% (N=25) had a high school diploma, 12% (N=25) had a trade certificate or diploma, 8% (N=17) had other non-university certificate, 16% (N=32) had some university training with no degree, and 21% (N=41) had university degrees. Most of the patient's in our study were employed (71%, N=143).

Individuals studied were asked to rate their health. The majority of patients felt their general health was very good to excellent (91%, N=182); 7.5% (N=15) rated their health as good; 2% (N=3) rated their health as fair; and no one reported poor health. Dermatologist-rated acne severity was recorded on a scale of mild, moderate or severe. The majority of patients in our study had either mild (38%, N=76), or moderate (53%, N=106) acne. Only 9% (N=18) of patients had severe acne. This reflected the prescribing in the clinical dermatology practice used in this study. Patients receiving isotretinoin therapy represented the group with severest acne in the study. One hundred and twenty-six (63%) patients reported having no chronic medical co-morbid conditions, while seventy-four (37%) had at least one other chronic condition. Four patients (2%) reported having a past history of depression. A family history of depression was reported in 3% (N=6) of patients. There was no evidence that past history of depression had influenced prescribing: two of four participants with a past history of depression were treated with isotretinoin and two were treated with topical medications. No individuals in the study reported heavy alcohol consumption (i.e. greater than 12 drinks per week). Only two individuals in the study reported using illicit drugs in the preceding month.

The total stress scores, self-esteem scores, and recent life stress ratings did not change during the course of the study. There was no change in total stress scores between baseline and follow-up. The average total stress score was 46.2 (CI=46.1-47.4) at baseline and 46.7 (CI=45.5-46.8) at follow-up. The average total self-esteem score was unchanged at follow-up (12.0; CI=11.7-12.3) from baseline (12.4; CI=12.0-12.7). Recent life stress did not differ between baseline and follow-up. The average recent life stress was 18.8 (CI=18.5 to 19.0) at baseline and 18.8 at follow-up (CI=18.7 –to 19.0).

**TABLE 1** Demographic and Clinical Characteristics of Study Groups

| **Categorical Variables** | **Isotretinoin (n=100) N (%)** | **Control Group (n=100)** | |
|---|---|---|---|
| | | **Oral (n=41) N (%)** | **Topical (n=59) N (%)** |
| Female Sex | 59 (59.0) | 27 (65.9) | 48 (81.3) |
| Unmarried* | 75 (75.0) | 31 (75.6) | 32 (54.2) |
| < High School | 28 (28.0) | 15 (36.6) | 17 (28.8) |
| Not Working | 27 (27.0) | 11 (26.8) | 18 (31.0)** |
| Perceived Health*** | 11 (11.0) | 1 (2.4) | 6 (10.2) |
| Medical conditions | 34 (34.0) | 18 (43.9) | 24 (40.7) |
| Acne Moderate/Severe | 96 (96.0) | 24 (58.5) | 4 (6.8) |
| **Non-Categorical Variables Not Normally Distributed** | **Isotretinoin Median ( 95% CI)** | **Oral Median ( 95% CI)** | **Topical Median ( 95% CI)** |
| Age | 21.5 | 26.0 | 20 |
| Baseline Zung (Index) | 30 | 31.25 | 31.25 |
| Baseline CES-D | 2 | 3 | 3 |
| Self Esteem | 12 | 12 | 12 |
| Ongoing Stressors | 46 | 48 | 47 |
| Recent Life Events | 18 | 18 | 18 |

* never married, widowed, separated or divorced
** missing data on one subject
*** less than very good or excellent

***Measures of Depression***

The median baseline Zung Index score was 30 (inter-quartile range 28.75 - 32.5) and at follow-up was 31.5 (inter-quartile range 30.0 - 32.5). There was no significant difference between Zung scores at baseline and follow-up (Z = -0.692, P = 0.4892) according to the Wilcox signed-rank test. The Zung index scores at follow-up in the patients with a past history of depression were very similar to those without a past history: 32.5 and 31.25, respectively (Wilcoxon rank-sum test (Z = 0.55, p = 0.58). Among patients with a past history of depression, the median Zung index score at follow-up was 29.4 in those treated with isotretinoin and 30.6 in those treated with topical medications. Based on a CES-D score of greater than 15 indicating depression, two patients who were not depressed at the beginning of the study had a score signifying depression at follow-up; both were in the isotretinoin group. The one patient who was depressed at the beginning of the study was not depressed on follow-up. Compared to controls, the occurrence of depression in two patients who were treated with isotretinoin was not significant (Fisher's exact test, P=0.497). Both of these patients were female and had moderate to severe acne. Neither of the patients with incident depression had reported a past history of depression at baseline.

The mean difference in Zung scores between follow-up and baseline was zero (CI= -0.6 to 0.6). In none of the treatment groups did the mean change in Zung score exceed one and there were no significant differences between groups (one way ANOVA; d.f. = 1, F=1.4, P=0.24). Since the only important difference between treatment groups and therefore, the main potential confounder, was acne severity we used linear

regression to adjust this comparison for acne severity. No significant effect of treatment group was found in this model (t=1.3, P=0.2).

## DISCUSSION

Our results provide no evidence of an association between isotretinoin use and depression. These results confirm recent reports in the literature outside of the North American population.[15] Other recent research, has found that depressive symptoms improved (based upon CES-D scores) when acne was treated either with isotretinoin or more conservative treatments.[13] CES-D scores indicating a possible depression occurred in two percent (N=2) of patients treated with isotretinoin in our study. There were no such cases in the control group, so it remains possible that depression is an uncommon side effect. No evidence was found to challenge the null hypothesis of no association.

### *Limitations*

Although a single interviewer was used to collect the study data, the use of in-person interviews versus the follow-up telephone interview may have affected our results. The CES-D was used as a measure of depression, but a psychiatrist did not perform an examination on patients to confirm this diagnosis. Our study groups were not randomized and overall the study numbers were relatively low. Since the incidence of depression was not likely to be that high even if there was a link between isotretinoin and depression, the study may not have been powerful enough to reveal any differences. To the best of our knowledge, the individuals who showed a significant change in their CES-D scores in the study continued with the treatment. However, we do not have further follow-up testing to see if their depression scores changed as their acne improved. If our study size was larger and thus may have revealed a significant association between isotretinoin use and depression, these depressed individuals could have been followed after discontinuation of the medication and then re-challenged (providing patient safety was not at risk) to attempt to establish a causal relationship. Since the usual course of Acutane therapy could last as long as six months, a longer follow-up group in our study would have been useful to confirm time course of treatment was not a factor in effecting our results. Although not feasible for this study, it may have helped confirm the CES-D measurements with clinical interviews to identify individuals who did not score above 15, who still may have been experiencing a major depressive episode. Measurements of psychosocial factors (e.g. recent life stress) were all based on perceived stress. One might argue that more detailed measures of stress, with a clear definition of its' meaning, should have been considered. To verify these findings, it would be useful to conduct a larger study. However, as isotretinoin use was not found to be associated with any of the psychosocial depression risk factors we evaluated, these factors were not important confounders. In the majority of cases, isotretinoin is given to patients with severe acne and therefore, one could argue that our two cohorts were inherently different and therefore, it may not have been fully possible to control confounding by acne severity using any method other than randomization.

## CONCLUSION

This study did not find a correlation between isotretinoin use and the development of depression. Thus, suggesting that denying patients with significant acne such an effective medication for fear of developing a major depressive episode may not be indicated at this point in time. Although, it should be noted that depression did occur in 2% of treated subjects. This re-emphasizes the need for physicians who are prescribing isotretinoin to regularly screen their patients for depression. The results seem consistent with current practice, where depression is regarded as a possible clinical event in the course of treatment, but not necessarily an event that is causally related to isotretinoin exposure. The results also suggest that the occurrence of depression is not a common or usual occurrence in association with this treatment. To the best of our knowledge this is the first prospective study to analyze this association within North America.

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