

## A prospective Study of the Risk of Depression in Acne Patients Treated with Oral Isotretinoin

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### ABSTRACT

**Background:** depression showed up as potential side effect of isotretinoin in the summary of product characteristics. There have been numerous studies treating this issue yet as a rule not distinguishing any significant depression or suicide risk.

**Aim of the Work:** this study aimed to evaluate the risk of depression in acne patients treated with oral isotretinoin therapy. **Methods:** one hundred patients with moderate to severe acne were enrolled in non-controlled prospective study. The psychological condition was evaluated at the baseline and fourth month by the Hamilton Depression Rating Scale (HDRS) for all patients. Statistical analysis of HDRS scores was performed. **Results:** all patients completed the study. Before the treatment 18% of the patients had suffered from mild depressive symptoms. at end of 4 months The patient's scores remained below the subclinical level for depression except only 2 patients one was mildly depressed turned to moderately depressed after four months treatment with isotretinoin other was mildly depressed and still mildly depressed after four months treatment with isotretinoin. The incidence of depression was 1%. Symptoms of depression which occurred in two patients, in which case coexisting situational factors were found to be the cause. **Conclusion:** our results showed that the oral isotretinoin treatment for acne at the typical therapeutic dose caused significant reduction in depression scores with a depression incidence only 1%. These changes might be related to clinical effect of isotretinoin. Moreover, the treatment of acne improved symptoms of depression for most patients.

**Keywords:** Acne vulgaris, systemic isotretinoin, depression.

### INTRODUCTION

Due to its brilliant anti-acne effect, isotretinoin is the first choice of treatment for severe acne or moderate acne not responding to topical and or oral antibiotic <sup>(1)</sup>. The relationship between isotretinoin treatment for acne and depression stays controversial both clinically and experimentally <sup>(2)</sup>.

#### AIM of the WORK

The aim of the study was to evaluate the risk of depression in acne patients treated with oral isotretinoin therapy.

#### Materials and Methods:

The participants in the study were recruited between September 2017 and September 2018 among attendants of Department of Dermatology and Venereology Outpatient Clinic Damietta Al-Azhar University Hospital. Male and female patients aged  $\geq 12$  years who were suffering from moderate to severe acne was eligible to participate. At the screening assessment, patients completed medical histories were recorded, and routine physical and laboratory examinations were performed.

Before the oral administration of isotretinoin (at baseline), the severity of acne was assessed by grading, clinical photographs, and physical dermatological examination. Grading was performed according to Global Acne Grading scale. Details of any psychiatric history (Psychiatric diagnoses and/or treatment by a psychiatrist or psychologist) were recorded. The psychiatric status of patients was determined by using questions about depression, anxiety and psychological responses to acne. Participants completed the Hamilton Depression Rating Scale (HDRS). All questionnaires were checked by a psychiatrist. HDRS gave a rating of depression and changes in violent behavior of the patient. Scoring was based on the 17-item scale and scores of 0–7 were considered as being normal, 8–13 suggested mild depression, 14–18 moderate depression and scores over 19–23 are indicative of severe depression  $\geq 23$  indicative for very severe depression. Although the HDRS form lists 21 items the scoring was based on the first 17 to assess severity of depression.

Isotretinoin was administered at a mean dose of 0.5 mg/kg per day. All participants and their parents were informed about the possibility of depression and were asked to report any depressive symptoms without delay. Participants or their parents signed written informed consent. Follow-up visits were carried out at one-month intervals until the isotretinoin treatment concluded. During each check-up, acne severity was assessed, and patients were asked about their psychological responses to acne and about any side effects of isotretinoin therapy, including depression, anxiety, and suicidal ideation. At month 4 (the final month of isotretinoin therapy for some patients), participants completed the HDRS questionnaire. Total scores were assessed and again, all questionnaires were checked by a psychiatrist.

**STATISTICAL ANALYSIS**

Data were collected, summarized and reported on data collection sheets. Data was re-entered into computer Microsoft Excel sheets with appropriate tabulation and graphical presentation. IBM SPSS software package version 20.0. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Tests of significance (Chi square, Wilcoxon signed ranks test, Mann-Whitney's test, Monte Carlo correction, Pearson coefficient and Simple correlation coefficient) were used. Data were presented and suitable

analysis was done according to the type of data. P-values less than 0.05 (5%) was considered to be statistically significant.

**RESULTS**

**Baseline data**

A total of 100 patients were included in the study, of whom 35 (35%) were male and 65 (65%) were female. The mean age of the patients was 22.47 ± 5.64 years (range: 16-35 years). At baseline, 85 patients (85%) patients were found to suffer from moderate acne, (15%) with severe acne. The duration of the condition ranged from 1 to 10 years with mean of 3.7. All patients received 0.5-1.00 mg/kg/day of isotretinoin for a period not less than 16 weeks. According to the Hamilton Depression Rating Scale (HDRS) at baseline they were 82 patients (82%) were normal and 18 patients (18%) were mildly depressed. All patients completed the study.

**After 4 months treatment data**

At end of 4 months treatment of daily dose (0.5-1 gm. / kg) isotretinoin 87 patients (87%) were complete cured (asymptomatic with no visible lesions) and 13 patients (13%) were partially cured. When HDRS repeated at end of 4 months 98 patients (98%) turned to normal and only 1 patient were (1%) mildly depressed and another 1 patient (1%) were moderately depressed (table 1). A statistically significant difference was observed between acne patients HDRS scores at baseline and at end of 4 month treatment with isotretinoin. The mean score significantly decreased at end of 4 month treatment with isotretinoin (**Table 2**).

**Table 1:** distribution of the studied cases according to depression (n=100)

Depression	Baseline		At the end 4 months		MHp
	No.	%	No.	%	
Normal	82	82.0	98	98.0	<0.001*
Mild	18	18.0	1	1.0	
Moderate	0	0.0	1	1.0	

**Table 2:** descriptive analysis of the studied cases according to HDRS (n=100)

HDRS	Baseline	At the end 4 months	Z	P
Min. – Max.	5.0 – 13.0	3.0 – 15.0		
Mean ± SD.	6.96 ± 1.68	5.87 ± 1.35	5.885*	<0.001*
Median	7.0	6.0		

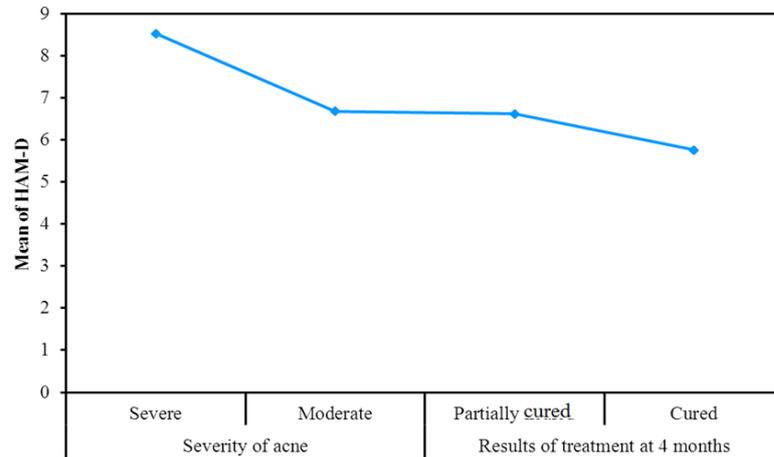
**Factors affect final HDRS results**

- Severity of acne at baseline

A statistically significant difference was observed between severity of acne and HDRS scores at baseline before starting isotretinoin. At baseline the mean score of patient with moderate acne is lower than mean score of patient with severe acne.

A statistically significant difference was observed between HDRS scores and results of treatment acne patients with isotretinoin at end of 4 months. At the end of month 4 the mean score of cured patients was lower than the mean score of partially cured patients (Fig.1).

- **Result of treatment acne patient by systemic isotretinoin after 4 months**



**Figure 1:** relation between depression represented by HDRS scores and acne course during 4 month treatment of isotretinoin (n=100).

## DISCUSSION

Recent reviews of the medical literature (3-13) had not sufficiently discovered proof to build up a causal link between isotretinoin use and depression, except for two studies (14,15) have suggested that isotretinoin had a causal link with depression. The present study aimed to measure risk of depression in acne patient treated with oral isotretinoin. The mean age of the patients who participated in this study was  $22.47 \pm 5.64$  SD with median 21 age years. Most were in their early 20s. According to an FDA report, the age range of the 37 patients that committed suicide was 13–32 years and the median age 17 years (16). Therefore, with regard to age of participants, our study sample was regarded as being appropriate for investigating the relationship between oral isotretinoin therapy and psychiatric symptoms like depression or suicide.

According to a statistical expert opinion, the sample size of (100 patients) was considered to be representative in relation to other studies had similar sample size (100 patients) (17-21) or lower numbers of patients (22-24). To test cognitive, affective, and somatic symptoms of depression, we used the Hamilton Depression Rating Scale (HDRS), with 17 item

version. The HDRS had also been used in other studies (4,20,26) with good results. Regarding the optimal time for assessment depressive changes in acne patients treated with isotretinoin **Bremner and his colleagues** suggested that depression usually develops 1-2 months or sometimes around 2-4 months after treatment (15). In the present study the depression scores significantly decrease after 4 months except only one patient. This finding is similar to other studies (23,26,27).

In the current prospective study oral isotretinoin treatment for acne at the typical therapeutic dose caused a significant reduction in depression scores with a depression incidence only 1%. These changes might be related to improvement of acne lesions as a result of treatment by systemic isotretinoin. Moreover some patients might be more prone to depression regardless of acne or other conditions. The results are similar to other controlled studies (28, 29) and uncontrolled studies (22-26,27,30-32).

In the present study, 87% of patients were completely cured and therefore very satisfied with their appearance. 13% of patients were still had acne described as partially cured

category. At the end of month 4 the mean score of HRDS of cured patients was lower than the mean score of partially cured patients. This result is in line with studies of many authors (29,33,34). In the present study, moderate depression was developed in a single patient (1%). The 21-yr.-old female's score increased from 13 (mild depression) to 15 (moderate depression) at month 4 of treatment. The psychiatric evaluation identified lack of interest, feeling guilty about the past, difficulty going to sleep, waking up early in the morning, mild disturbance of menstruation, preoccupation with health and slowed-down thinking and speech. There were no somatic symptoms, agitation, or suicidal thoughts. A diagnosis of moderate depression was made with these findings. Although the patient used isotretinoin for four months at this stage, she was very worried about the acne lesions continuing and new lesions appearing. She believed that her hopelessness was due to not experiencing the improvement in her acne lesions she had expected, and she therefore wanted to continue the treatment. The treatment was continued and all lesions had healed completely by the end of the seventh month. The depression score also decreased to 7 at the end of the treatment.

Mild depression was still presented in a single patient (1%). The 27-yr.-old female's score decreased from 13 (mild depression) to 8 (mild depression) at month 4 of treatment which mean that the depression risk was lower than the baseline. The psychiatric evaluation productivity decreased, agitation, difficulty going to sleep, waking during night, waking up early in the morning. There were no symptoms depressed mood, somatic symptoms or suicidal thoughts. A diagnosis of mild depression was made with these findings, the patient was very happy for the end result of 4 month treatment with isotretinoin as almost all acne lesions was disappeared and patient clinically cured. Depressive symptoms thought to be caused by coexisting psychosocial stressors unrelated to acne.

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