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Retinoids in the Management of Acne with Depressive Symptoms: A Treatment Conundrum

S. J. Swetha[1*], M. Preethi[2], J. Sharanya[3], Saai Ram Thejas[4] and M. Karthik[5]

[1]Department of Dermatology, RVM Institute of Medical Sciences, Siddipet District, Telangana – 502279, India.
[2]Medipoint Polyclinic, Secunderabad, Telangana – 500015, India.
[3]Department of Psychiatry, RVM Institute of Medical Sciences, Siddipet District, Telangana – 502279, India.
[4]Department of Otorhinolaryngology, RVM Institute of Medical Sciences, Siddipet District, Telangana – 502279, India.
[5]Department of Orthopaedics, RVM Institute of Medical Sciences, Siddipet District, Telangana – 502279, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Isotretinoin (ITT) a first-generation synthetic retinoid derived from Vitamin A for the treatment of Acne Vulgaris (AV). It effectively treats acne by acting on the pathogenetic mechanisms like comedolytic effect, anti-inflammatory effect, sebostatic effect and the inhibitory effect on proliferation of Propionibacterium acnes. The first occurrence of depressive symptoms associated with isotretinoin was seen in 1983 and since then a lot of controversies have emerged regarding the causal relationship between isotretinoin and depression.
Materials and Methods: All patients presenting to the Dermatology Out Patient Department in a Rural Private Hospital in South India with diagnosed Grade III-IV acne non-responsive to Oral Tetracyclines and Topical Clindamycin were taken to be part of the study after obtaining adequate

*Corresponding author: E-mail: shwetalka@gmail.com;

consent. Each patient filled a Hamilton Depression Rating Scale (HDRS) and Dermatology Life Quality Index (DLQI) before the commencement of treatment. Patients with mild depression secondary to acne were considered. They were started on Oral Isotretinoin 10 mg and Topical Adapalene 0.1% for 16 weeks. The same scale was given at the end of 16 weeks for data completion.

Results: The mean DLQI score before the commencement of treatment was 13.34 and it came down to 6.94 at the end of 16 weeks, an improvement of 47.87%. The mean HDRS score before the commencement of treatment was 18.10 and it went up to 19.32 at the end of 16 weeks, a deterioration of 6.74%.

Conclusion: Based on the collected data, it can be said that although Retinoids significantly help in the management of severe Acne, they can possibly have a negative effect on the mood of the individual and worsen the symptoms of Depression slightly. A sort of double-edged sword, it can be left to the Dermatologist to alter the dosage of the Retinoids used and also have proper Psychiatric consultations including Psychotherapy for the patient to achieve success in treatment.

Keywords: Isotretinoin; acne vulgaris; adapalene; hamilton depression rating scale; dermatology life quality index.

1. INTRODUCTION

Acne vulgaris (AV) is a common condition which affects about 85% of adolescent youths and can also progress to adulthood [1,2]. AV can cause permanent scars in 3–7% of patients and has a large impact on physical and mental health [3]. There are numerous methods of treatment available for AV. Some of them are not effective or evidence-based and some even cause injury psychologically and physically to patients [4].

The pathogenesis associated with AV include hormone-mediated sebum overproduction, follicle hyper-keratinization, colonization of pilosebaceous microbe (especially Propionibacterium acnes) and significant immune responses. The exact pathogenesis of acne has not been fully elucidated until now [5]. Genetic factors play an important role in the development of acne, especially in severe cases [6].

The stress induced by the lesions caused by AV precipitates Depression in affected individuals. This, in turn, affects the Quality of Life and is associated with other social and psychological disorders [7].

There are plenty of ways of assessment of the grades of AV proposed and being practiced. Among them is a system where AV is graded from I-IV which we have used in this study [8]. The conventional treatment for AV includes topical therapy (Benzoyl Peroxide, Retinoids, Antibiotics, Salicylic Acid, Azelaic Acid) and systemic therapy (Antibiotics, Retinoids). Mild cases can be treated with topical/oral antibiotics with acidic face washes whereas severe cases need Retinoids, both oral and topical.

The rate of depression after oral isotretinoin is variable and ranges between 1% and 11% [9]. The Hamilton Depression Rating Scale (also known as the Ham-D/HDRS) is the most widely used clinician-administered depression assessment scale. It has 17 questions and assesses the levels of depression on a quantitative scale of 0-55. A score of 0–7 is generally accepted to be within the normal range while a score of 20 or higher is usually required for entry into a clinical trial [10].

The Dermatology Life Quality Index (DLQI) questionnaire is self-explanatory and can be handed to the patient who is asked to fill it in without the need for detailed explanation. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired [11].

Although there is a lot of material and research available about the association of Isotretinoin to Depression, it is very much unclear how these two are complexly intertwined with each other. Whilst Isotretinoin is a must in the management of severe Acne, it should be kept in mind that excess use of the same can cause Depression, Anxiety and low mood as side effects in the patients who are already depressed because of the diagnosis itself. In this study, we aim to try and find an association between the three entities and hope to set a paradigm for future practitioners to refer.

2. MATERIALS AND METHODS

2.1 Study Group

All patients presenting to the Dermatology Out Patient Department in a Rural Private Hospital in South India.

2.2 Inclusion Criteria

- Age group of 18-30.
- Grade III-IV acne non-responsive to Oral Tetracyclines and Topical Clindamycin.
- Mild depression as diagnosed by the HDRS.
- Patients willing to be part of the study and a 16-week follow-up.

2.3 Exclusion Criteria

- Depression secondary to other causes.
- Severe form of Depression requiring pharmacological management.
- Pregnancy and Lactation.

2.4 Sample Size

One-hundred and five (105).

2.5 Statistical Analysis

All statistics were performed using the SPSS Statistics 19 for Windows (IBM Corp., Armonk, NY, USA). Samples were compared by a Paired T-test. A P-value of <0.05 was considered statistically significant. The confidence interval was set at 95%.

All the enrolled patients first filled out both the HDRS [Image 2] and DLQI [Table 3] (translated to the local language by the Practitioner as and when needed). It was verified thoroughly by both the Dermatologist and the Psychiatrist that they were having a mild form of Depression secondary to the diagnosis and lesions of Acne. They were then started on Medical Management (Oral Isotretinoin 10 mg once per day with Topical application of 0.1% Adapaleneat night) and Psychotherapy for 16 weeks [Images 3 and 4]. At the end of this period, the HDRS and DLQI were filled out again.

3. OBSERVATIONS AND RESULTS

A total of 105 patients were taken to be part of our study with 79 females and 26 males [Image 1].

The mean DLQI score before the commencement of treatment was 13.34 and it came down to 6.94 at the end of 16 weeks, an improvement of 47.87% [Tables 1 and 2]. The mean HDRS score before the commencement of treatment was 18.10 and it went up to 19.32 at the end of 16 weeks, a deterioration of 6.74%.

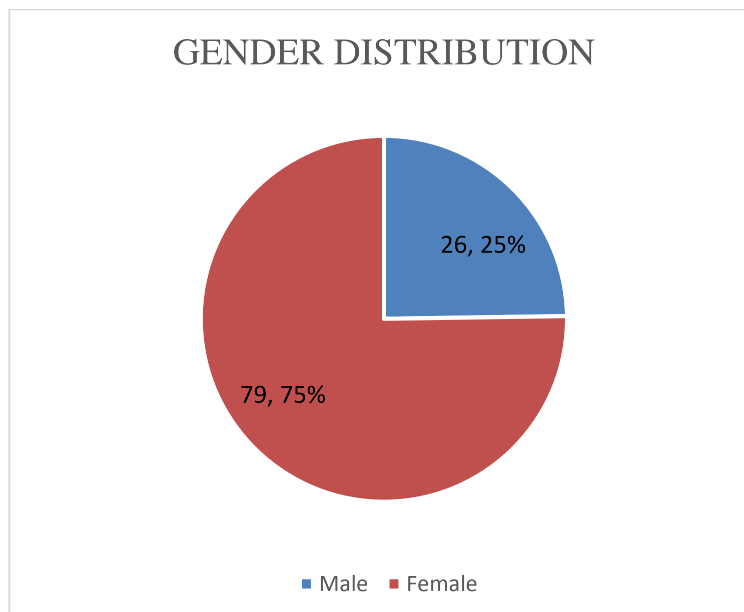

Image 1. Gender distribution

Table 1. Paired samples correlations before and after treatment for DLQI

	Paired Differences					t	Sig.	Correlation
	Mean	Standard Deviation	Standard Error Mean	95% confidence interval of the difference				
				Lower	Upper			
Before vs After	6.40	2.42	0.24	5.93	6.87	27.18	0.001	0.84

Table 2. Paired samples statisticsbefore and after treatment for DLQI

	Mean	N	Standard deviation	Standard error of mean
Before	13.34	105	4.47	0.43
After	6.94	105	3.76	0.37

Table 3. The dermatology quality life index

OBSERVATION	RESULT				
	Very much (3)	A lot (2)	A little (1)	Not at all (0)	Not relevant (0)
How itchy, sore, painful or stinging has your skin been?					
How embarrassed or self-conscious have you been because of your skin?					
How much has your skin interfered withyou going shopping or looking after your home or garden?					
How much has your skin influenced theclothes you wear?					
How much has your skin affected anysocial or leisure activities?					
How much has your skin made it difficultfor you to do any sport?					
How much has your skin been aproblem at work or studying?					
How much has your skin createdproblems with your partner or any of your close friends orrelatives?					
How much has your skin caused anysexual difficulties?					
How much of a problem has thetreatment for your skin been, for example by making yourhome messy, or by taking up time?					

4. DISCUSSION

Treatment with oral isotretinoin has been linked to adverse psychiatric effects suchas low mood, depression, and suicidal ideation; however, a concrete causal link hasyet to be proven [12,13]. Thus, various studies have taken shape in the understanding, diagnosis and adequate management of the condition.

Most studies have not yet evidently proved for or against the use of Retinoids in Acne. The results are almost always hinging on the borderline. One such study found a link of Isotretinoin to an overall improvement in psychologicalwellbeing, even in patients suffering with stable mental illness. However, they also found that a small minority of patients were susceptible to severe mood deterioration, particularly in conjunction with severe physical side effects [14].

Currently, the main open questions concern the establishingof effective but safe dosing regimens and the possibilityof identifying subpopulations prone to depressivedisorders in response to treatment with isotretinoin orother retinoids [15].

1 DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*
- 0 |__| Absent.
- 1 |__| These feeling states indicated only on questioning.
- 2 |__| These feeling states spontaneously reported verbally.
- 3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT
- 0 |__| Absent.
- 1 |__| Self reproach, feels he/she has let people down.
- 2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
- 3 |__| Present illness is a punishment. Delusions of guilt.
- 4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 SUICIDE
- 0 |__| Absent.
- 1 |__| Feels life is not worth living.
- 2 |__| Wishes he/she were dead or any thoughts of possible death to self.
- 3 |__| Ideas or gestures of suicide.
- 4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT
- 0 |__| No difficulty falling asleep.
- 1 |__| Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
- 2 |__| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT
- 0 |__| No difficulty.
- 1 |__| Patient complains of being restless and disturbed during the night.
- 2 |__| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING
- 0 |__| No difficulty.
- 1 |__| Waking in early hours of the morning but goes back to sleep.
- 2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES
- 0 |__| No difficulty.
- 1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
- 2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
- 3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
- 4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
- 0 |__| Normal speech and thought.
- 1 |__| Slight retardation during the interview.
- 2 |__| Obvious retardation during the interview.
- 3 |__| Interview difficult.
- 4 |__| Complete stupor.

9 AGITATION
- 0 |__| None.
- 1 |__| Fidgetiness.
- 2 |__| Playing with hands, hair, etc.
- 3 |__| Moving about, can't sit still.
- 4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC
- 0 |__| No difficulty.
- 1 |__| Subjective tension and irritability.
- 2 |__| Worrying about minor matters.
- 3 |__| Apprehensive attitude apparent in face or speech.
- 4 |__| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
<u>gastro-intestinal</u> – dry mouth, wind, indigestion, diarrhea, cramps, belching
<u>cardio-vascular</u> – palpitations, headaches
<u>respiratory</u> – hyperventilation, sighing
<u>urinary frequency</u>
<u>sweating</u>
- 0 |__| Absent.
- 1 |__| Mild.
- 2 |__| Moderate.
- 3 |__| Severe.
- 4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL
- 0 |__| None.
- 1 |__| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
- 2 |__| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS
- 0 |__| None.
- 1 |__| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
- 2 |__| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)
- 0 |__| Absent.
- 1 |__| Mild.
- 2 |__| Severe.

15 HYPOCHONDRIASIS
- 0 |__| Not present.
- 1 |__| Self-absorption (bodily).
- 2 |__| Preoccupation with health.
- 3 |__| Frequent complaints, requests for help, etc.
- 4 |__| Hypochondriacal delusions.

16 LOSS OF WEIGHT *(RATE EITHER a OR b)*

a) According to the patient:	b) According to weekly measurements:
0 |__| No weight loss.	0 |__| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |__| Greater than 1 lb weight loss in week.
2 |__| Definite (according to patient) weight loss.	2 |__| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |__| Not assessed.

17 INSIGHT
- 0 |__| Acknowledges being depressed and ill.
- 1 |__| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2 |__| Denies being ill at all.

Total score: |__|__|

Image 2. The hamilton depression scale

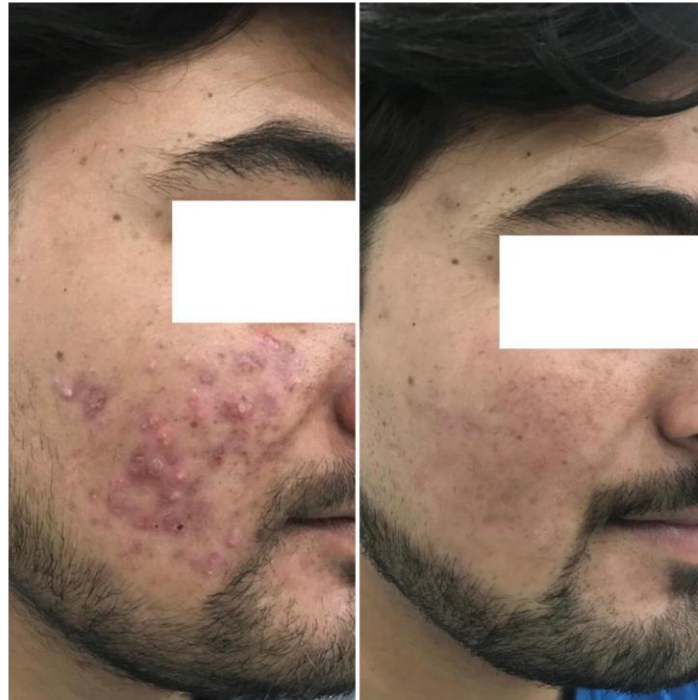

Image 3. Sample image of a male patient before and after treatment for 16 weeks

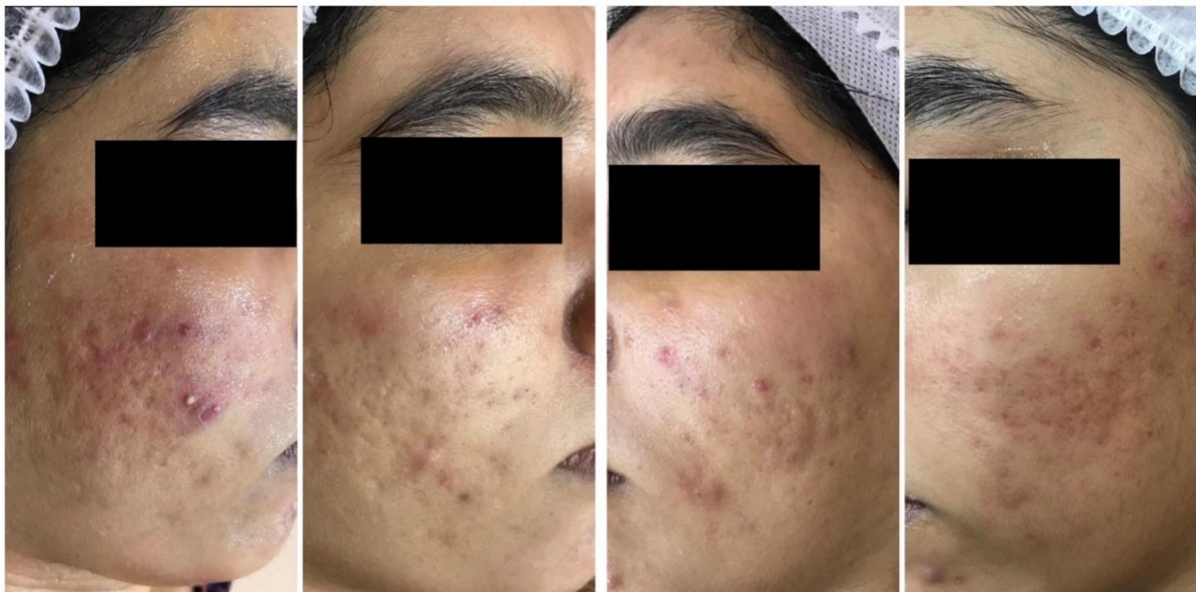

Image 4. Sample image of a female patient before and after treatment for 16 weeks

Patients with untreated acne are at risk for depression,suicide and other psychiatric or psychosomatic conditions [16]. Therefore, psychiatric or psychosomatic comorbidityshould be diagnosed before and not just duringisotretinoin treatment. It is important to observe suchpatients before and during the treatment in orderto record their mood changes and to identify whether adetailed investigation of psychosomatic problems or apsychiatric examination is needed.

Isotretinoin has proven its efficacy in reducing the severity of acne.Although it has shown improvement in anxiety, it causesdepression in small number of patients [17].

In the absence of a concrete treatment regimen, it would be wise to note that the management

has to be catered to purely on the basis of the symptoms presented and the past history of the affected individual. Since Retinoids (both oral and topical) are the cornerstone in the treatment of Grade III-IV Acne and there are no substitutes, it becomes important to understand the Pharmacology of the drug and monitor the side effects closely.

Thus, inter-departmental activity becomes important in understanding both the cutaneous and psychological manifestations.

5. CONCLUSION

Isotretinoin in the management of Grade III-IV AV is very effective as evidenced by the fact that the DLQI improved by 47.87% after the treatment regimen. The drawback of the treatment was seen in the HDRS which deteriorated by 6.74%. In conclusion, we would like to state that although the benefits outweigh the side effects it should be looked at closely on a person-to-person basis before the treatment is started. Inter Department association can be a useful tool and both Dermatologists and Psychiatrists can work together in dealing with the problem. Psychotherapy is a viable option in the management of these mild depressive symptoms.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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