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ORIGINAL ARTICLE

Prospective Study

Isotretinoin was not associated with depression or anxiety: A twelve-week study

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Abstract

AIM: To investigate the frequency and severity of depression and/or anxiety in isotretinoin (ITT)-treated subjects and in a non-ITT control group.

METHODS: Sixty consecutively-admitted non-psychiatric outpatients with acne were assigned to either ITT at a fixed dose of 30 mg/d (n = 36) or "other treatment" group (OT; n = 24). The Zung depression or anxiety scales (with cut-off points), two locally developed scales for depression (GeDepr) and anxiety (Ansilet) (without cut-off points) and clinical global impression scales of acne severity were administered at baseline and at weeks 6 and 12 of treatment. Data was analyzed with the chi-squared test and covariance analysis.

RESULTS: Gender distribution, age, marital status and education level did not differ between both treatment groups. The frequency of depression, as defined by the Zung scale cut-off points was similar in the ITT and in the non-ITT groups: Weeks 6 and 12: 8.3% in both groups, P = 0.9. The frequency of anxiety was similar in the groups as well: Week 6: ITT = 8.3%; OT = 0.0%, P > 0.05; week 12: ITT = 11.1%, OT = 4.2%, P > 0.05. The scores in both scales' sets did not differ between the treatment groups at any evaluation time point (P

> 0.05). Five ITT-treated subjects (13.8%) and two from the OT-treated group (8.3%) developed clinically significant anxiety and/or depression during treatment (*P* > 0.05).

CONCLUSION: Our study confirms the safety of ITT regarding psychological side effects in regular dermatological patients. Susceptible subjects may exist but their identification requires additional strategies.

Key words: Isotretinoin; Short-term; Psychopathology; Depression; Anxiety; Other treatments

Core tip: Isotretinoin (ITT) is frequently used for acne therapy, particularly in young people, but concerns exist regarding the risk of depression and suicide attempts. We conducted a 12-wk prospective study administering a fixed ITT dose in non-psychiatric acne patients an in a non-ITT control group. We used categorical and continuous scales for the assessment of depression and anxiety. The frequency and severity of psychopathology was similar in both treatment groups, stressing the safety of ITT in typical dermatological patients. However, 13.8% ITT subjects and 8.3% of the non-ITT developed clinically significant anxiety and/or depression. Hence, susceptible subjects exist, who deserve further investigation and assistance.

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INTRODUCTION

Isotretinoin (ITT) is a vitamin A-related compound widely used in the treatment of severe cystic acne vulgaris[1]. It is less frequently used to treat squamous-cell carcinoma, brain or pancreatic cancer and severe ichtyosis[2].

The safety of ITT on mental functioning has been a concern since its introduction into clinical practice. For example, as early as in 1983, clinically significant depression was reported in a case series[3].

The association between ITT treatment and psychopathology, particularly with depressive symptoms, comes from accumulated evidence of case reports, temporal association, challenge-re-challenge tests, dose response/class effect studies, and biological plausibility[4]. As a matter of fact, ITT was among the top five drugs with the most frequent spontaneous reports of depression in a recent survey conducted in the United Kingdom[5]. Collectively, these results have been criticized for not discriminating between the worsening of pre-existing psychopathology and the development of *de novo* psychopathology[4].

The frequency of depression during ITT administration observed in group studies ranges from 1% to 11%[4]. The low frequency of depression obtained in some studies has been associated with protocols based on self-reports of psychological symptoms. Research has shown that patients tend to underestimate the magnitude of depression in comparison to their family controls[6]. Besides, numerous negative studies lacked standardized diagnostic protocols and/or control groups[4].

Current research trends suggest that the risk of ITT-related depression maybe particularly relevant in a minority of patients who are also susceptible to other ITT neural side effects, such as headache[4,7]. Besides, subjects with bipolar, anxiety or obsessive-compulsive disorders may be at risk of clinical worsening during ITT administration[4,8]. By contrast, numerous practitioners and research studies report that ITT may rather improve the psychological status in patients with severe acne[4]. These results are not in contradiction with the finding of a specific minority of subjects with increased susceptibility to ITT-related psychological side effects.

In this longitudinal 12-wk study, we evaluated depression and anxiety symptoms in acne patients receiving either ITT or antibiotics by using not only the well-known Zung scales for depression/anxiety but also a set of instruments developed and previously validated at Los Andes University, Mérida, Venezuela.

MATERIALS AND METHODS

This is a naturalistic, longitudinal, open-labeled study conducted in a non-probabilistic sample from February 2013 to June 2013 at the Dermatology Department of Los Andes University Hospital in Mérida, Venezuela. It was approved by the Ethics Committee and by the Institutional Review Board of the Department of Psychiatry, Los Andes University Medical School, Mérida, Venezuela. No formal trial registration system exists in this country.

Subjects and treatments

Consecutively admitted patients consulting for acne were invited to participate in the study and filled an informed consent of voluntary participation. Treatments were assigned by a dermatologist (YC) according to disease severity and patient's income. The participating subjects were assigned either to the ITT-group (30-40 mg/d) or to the OT-group that consisted in the administration of a combination of oral or topic antibiotics and the antibacterial agent benzoil peroxide. Exclusion criteria were previous administration or intolerance to ITT, < 18 years of age, and/or explicit refusal to participate in the study.

Evaluation

Acne severity was assessed by the dermatologist at

Table 1 Demographic features

Isotretinoine (n = 36)		Other treatments (n = 24)	
Gender [n (%)][1]			
Females	Males	Females	Males
16 (44.4)	20 (55.6)	11 (45.8)	13 (54.2)
Age (mean ± SD)[2]			
23.0 ± 3.2	20.3 ± 2.9	22.9 ± 3.8	23.4 ± 4.4
Marital status [n (%)][3]			
Single	Others	Single	Others
34 (94.4)	2 (5.6)	15 (62.5)	9 (37.5)
Education [n (%)][4]			
College	Others	College	Others
6 (16.6)	35 (83.4)	4 (16.7)	(83.3)

[1]χ^2 (1) = 0.01, P = 0.9; [2]F (3) = 2.9, P = 0.04; post-hoc Tukey HSD test = 0.07; [3]χ^2 (1) = 7.8, P = 0.005; [4]χ^2 (1) = 0.00, P = 1.

baseline only by using a 5-point, likert-type, clinical global impression scale, from 0 as "minimally severe" to 5 as "very severe". At weeks 6 and 12, the patients and the treating physician assessed the changes in acne severity compared to baseline by using a 7-point, likert-type scale, from 0 as "markedly worst" to 7 as "very much improved".

Depression and anxiety were evaluated at baseline and at weeks 6 and 12 with categorical and continuous self-administered scales. The former consisted in the validated Spanish versions of the Zung depression and anxiety scales that provided a categorical classification[9-11]. Every scale consisted of 20 items with positive or negative valence that explored the frequency of depression or anxiety signs and symptoms, as follows: From 1 = rarely to 4 = always. Each subject was then classified as non-depressed or non-anxious when scoring < 50 points, or slightly, moderately or severely depressed and/or anxious when scoring 50-59, 60-69 and ⩾ 70 points, respectively.

The continuous scales corresponded to the previously mentioned Zung scales plus the following two scales for continuous quantification of depression or anxiety levels. The "Ge-Depr" is a two-factor scale consisting of 16 depression-related items. It was validated in 249 Venezuelan subjects and reported a Cronbach alpha coefficient of 0.88 and Pearson correlation coefficients of 0.65 *vs* an aggression scale, of 0.68 *vs* an anxiety scale, and of 0.65 *vs* a general scale of psychological maladjustment[12].

The "Ansilet" is a one-factor scale consisting of 15 anxiety-related items. It was validated in 264 Venezuelan university students and reported a Cronbach alpha coefficient of 0.82 and a Pearson correlation coefficient of 0.59 *vs* the self-esteem Rosemberg scale[13].

Both local scales were scored with a 6-point likert-type scale from 0 = complete disagreement to 6 = complete agreement and no neutral score. These scales did not include a cut-off point but are aimed to assess changes over time in a continuous scale.

A separate analysis was conducted with the Zung depression scale items that explore suicide-related ideation (items 17 and 19).

Statistical analysis

Categorical data (frequency of depression or anxiety according to the Zung scales from baseline to week 12 with intra-group and inter-group comparisons) were analyzed with the χ^2 test.

Continuous data (depression and anxiety scores) were analyzed with the univariate general linear model with treatment and time as between- and within-group variables, respectively, and age as covariate.

Bivariate correlation analysis was conducted with the Pearson correlation coefficient. Results were considered significant when $P < 0.05$.

RESULTS

Sixty consecutively admitted patients were assigned either to the ITT-group (n = 36) or to the OT-group (n = 24). No subject was excluded in any group. Gender distribution and education level were similar in both groups, but the ITT-treated males tended to be younger, and the proportion of single (unmarried) subjects was significantly higher in the ITT group (Table 1). Most patients (35 out of 36) received 30 mg/d of ITT; hence, the treatment protocol consisted of a fixed-dose schedule.

Acne severity was higher in the ITT - than in the control group. Severe and very severe acne was only observed in the ITT group: 9 subjects (25%) *vs* 0 subjects (0%): Mann Whitney test: Z = 2.6, P = 0.008.

Depression and anxiety frequency and scores

The frequency of depression or anxiety categorically defined according to the Zung scales and the scores obtained in the continuous scale analysis were similar in both treatment groups at baseline and did not display significant changes over time (Tables 2 and 3). The scores in the depression Zung scale suicide related items were similar in both treatment groups at baseline and at weeks 6 and 12: Item 17: F (1) = 0.001, P = 0.9; item 19: F (1) = 0.5, P = 0.5 (data not shown).

The Zung depression and anxiety scale scores showed a highly significant positive correlation with the GeDepr and Ansilet scale scores, respectively: The r coefficient value was over 0.60, P = 0.000 in all the analyses (data not shown).

Correlation analysis

Clinical assessment of acne severity and depression/anxiety scores: For the sake of concision, we only present the data related to the GeDepr and Ansilet scale scores.

No significant correlations were observed between the clinical severity assessment of acne at baseline and the depression and anxiety scores at any time-point in the ITT group. However, in the OT group, significant correlations were observed in the depression scores,

Table 2 Frequency of depression and anxiety according to the Zung scales at baseline and during treatment

	ITT			OT		
	Categorical level of depression [*n* (%)][1]					
	Basal	Week 6	Week 12	Basal	Week 6	Week 12
Mild	1 (2.8)	3 (8.3)	3 (8.3)	2 (8.3)	2 (8.3)	2 (8.3)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (2.8)	3 (8.3)	3 (8.3)	2 (8.3)	2 (8.3)	2 (8.3)
	Categorical level of anxiety [*n* (%)][2]					
	Basal	Week 6	Week 12	Basal	Week 6	Week 12
Mild	1 (2.8)	2 (5.5)	1 (2.8)	1 (4.2)	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	1 (2.8)	2 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	1 (4.2)
Total	1 (2.8)	3 (8.3)	4 (11.1)	1 (4.2)	0 (0.0)	1 (4.2)

Values represent number and percentage in parentheses of subjects with depression or anxiety. [1]Within-group comparisons: ITT group: χ^2 (2) = 1.2, P = 0.5; OT group: χ^2 (2) = 0.0, P = 1; between-group comparison: χ^2 (5) = 1.3, P = 0.9; [2]Within-group comparisons: ITT group: χ^2 (2) = 4.6, P = 0.6; OT group: χ^2 (2) = 4.0, P = 0.4; between-group comparison: χ^2 (5) = 4.8, P = 0.4. OT: Other treatments; ITT: Isotretinoine.

and marginally significant correlations were detected in the anxiety value sets (Table 4).

Patient and physician perceived changes in acne severity *vs* depression/anxiety scores: Several negative correlations reached statistical significance in the ITT group but not in the OT group (Table 5). The negative correlations reveal the improvement in psychological symptoms (decreased depression or anxiety scores) along with the decrease in acne severity (magnitude of the improvement perceived by the patient and the physician at a given time point).

Narrative description of the subjects who developed anxiety and/or depression during treatment

Five ITT-treated subjects (13.8% of the ITT group) and two receiving other treatments (8.3% of the OT group patients) developed clinically significant anxiety and/or depression during treatment [χ^2 (1) = 0.06, P = 0.8] (Table 6). In the five subjects of the ITT group, three were females (60%) and two (40%) reported previous symptoms of depression and/or anxiety.

One subject in each group increased their scores in the suicide-related items in the Zung depression scale (items 17 and 19, data not shown). However, because of the very small number of subjects (5 only), an association between gender and previous psychiatric disorders with ITT-induced psychopathology cannot be inferred.

DISCUSSION

This study showed that oral ITT in a fixed-dose schedule of 30 mg/d, compared to a control group of subjects treated with antibiotics or antibacterial agents, was not associated with a significant increase in the frequency of depression or anxiety or in the scores of the corresponding scales up to 12 wk of treatment. This result points to a safe profile of short-term ITT administration in a typical group of non-psychiatric outpatients with acne.

The correlation analysis showed complex results in both treatment groups: On the one hand, only the OT group showed significant correlations (positive ones, mainly in the depression scores) between the physician basal evaluation of acne severity and the psychopathological scales over time (Table 4). This may reveal a poor response to OT because one might have expected a trend toward negative correlations, that is the greater the physician appreciation of the acne severity at baseline, the lower the depression or anxiety scores after successful treatment.

On the other hand, only the ITT-treated patients showed the expected negative correlations between the changes in acne severity observed by the physician and those perceived by the patients (higher scores over time) and the scores in depression and anxiety at each evaluation time point (lower punctuations along time (Table 5). As the correlation data in Table 4 show, this result may imply a better response of the ITT-treated group. However, this is only speculative, because the present investigation was not designed to properly assess the comparative treatment response.

Five ITT-treated subjects developed clinically significant psychopathology: Two patients with pure anxiety, one with pure depression and two with both diagnoses. Personal antecedents of depression or anxiety or significant symptoms at baseline were observed only in two of these five ITT-treated patients. Hence, this small sub-sample of patients does not allow us to explore the predisposing features that favored the development of psychopathology during ITT administration.

The frequency of depression in the ITT group, alone or in combination with anxiety, was 8.3% (3 out of 36 subjects). This value is within the range reported in the literature which is between 1% and 11%[14].

Most research on the psychological deleterious effects of ITT has focused on depression development or aggravation and suicide ideation and/or suicide attempts during treatment[4,5,15-27]. Most recent reviews point to a safe profile of ITT regarding depression and/or suicide[28-31] with the exception of a study conducted by an Australian research group[32]. According to a comprehensive review[4], important methodological differences among the studies would explain the divergent results.

The present research agrees with the conclusion that depression occurs in a minority of ITT-treated patients[4]. Recent studies suggest that these depression-prone patients may be susceptible to other neural side effects of ITT, such as headache[6]. Interestingly, preliminary data suggest that subjects with bipolar disorders may be particularly susceptible of symptom worsening during ITT treatment[33,34]. Since migraine is common in bipolar disorder, particularly in the predominantly depressive type[35], and since psychoses, panic attacks

Table 3 Depression and anxiety levels at baseline and during treatment

	ITT			OT		
			Depression scores			
	Basal	Week 6	Week 12	Basal	Week 6	Week 12
GeDep scale[1]	38.3 ± 2.5	38.1 ± 2.3	36.8 ± 2.3	36.9 ± 3.1	34.9 ± 2.9	34.9 ± 2.9
Zung scale[2]	35.2 ± 1.3	33.8 ± 1.4	34.2 ± 1.4	34.9 ± 1.6	34.6 ± 1.7	35.0 ± 1.7
			Anxiety scores			
	Basal	Week 6	Week 12	Basal	Week 6	Week 12
GegDep scale[3]	43.3 ± 2.4	41.9 ± 2.3	40.8 ± 2.3	40.9 ± 2.9	38.1 ± 2.9	36.8 ± 2.9
Zung scale[4]	37.2 ± 1.1	36.7 ± 1.4	36.6 ± 1.6	34.5 ± 1.4	32.4 ± 1.7	32.8 ± 1.9

Values represent mean ± SD scores in the depression and anxiety scales. [1]Within-subject effect: F (2) = 0.5, P = 0.6; between-subject effect: F (1) = 0.3, P = 0.6; [2]Within-subject effect: F (2) = 0.6, P = 0.6; between-subject effect: F (1) = 0.6, P = 0.5; [3]Within-subject effect: F (2) = 0.5, P = 0.6; between-subject effect: F (1) = 0.9, P = 0.4; [4]Within-subject effect: F (2) = 0.8, P = 0.5; between-subject effect: F (1) = 3.1, P = 0.09. OT: Other treatments; ITT: Isotretinoine.

Table 4 Correlation matrix between the physician assessment of the acne severity at baseline and the depression and anxiety scores before and during treatment

Treatment group		Depression score (baseline)	Depression score (week 6)	Depression score (week 12)	Anxiety score (baseline)	Anxiety score (week 6)	Anxiety score (week 12)
ITT	PAB *vs*	0.1 (0.4)	0.08 (0.6)	0.02 (0.9)	0.1 (0.5)	0.1 (0.4)	0.05 (0.8)
OT	PAB *vs*	0.48 (0.01)[1]	0.5 (0.01)[1]	0.5 (0.01)[1]	0.25 (0.2)	0.39 (0.054)	0.37 (0.07)

PAB: Physician assessment of acne severity at baseline with a scale ranging from minimal = 0 to very severe = 5. Values are the Pearson correlation coefficient and its associated probability in parentheses. [1]Significant association. OT: Other treatments; ITT: Isotretinoine.

Table 5 Correlation matrix of the patient and physician assessments of the acne severity change and the depression and anxiety scores during treatment

Treatment group		Depression score (week 6)	Depression score (week 12)	Anxiety score (week 6)	Anxiety score (week 12)
ITT	Patient evaluation *vs*	-0.31 (0.067)	-0.43 (0.009)[1]	-0.43 (0.01)[1]	-0.38 (0.02)[1]
	Physician evaluation *vs*	-0.28 (0.1)	-0.33 (0.049)[1]	-0.35 (0.03)[1]	-0.32 (0.057)
OT	Patient evaluation *vs*	-0.1 (0.6)	-0.-08 (0.7)	-0.3 (0.9)	0.25 (0.2)
	Physician evaluation *vs*	-0.15 (0.5)	-0.18 (0.4)	-0.03 (0.9)	-0.08 (0.7)

The assessment in acne severity change was conducted with a Likert-type scale ranging from severely worst = 1 to very much improved = 7. Values are the Pearson correlation coefficient and its associated probability in parentheses. [1]Significant association. OT: Other treatments; ITT: Isotretinoine.

Table 6 Demographic and clinical features of the subjects who developed clinically significant depression or anxiety

Treatment	Age (yr)	Gender	Personal history of depression	Personal history of anxiety	Diagnosis before treatment (categorical Zung scales)	Diagnosis during treatment (categorical Zung scales)
ITT	18	M	Yes	Yes	-	Anxiety
ITT	28	M	No	Yes	Anxiety and depression	Anxiety and depression
ITT	25	F	No	No	-	Anxiety and depression
ITT	23	F	Yes	No	-	Anxiety
ITT	23	F	No	No	Depression	Depression
OT	18	M	Yes	Yes	Anxiety and depression	Anxiety and depression
OT	24	M	Yes	No	Depression	Depression

ITT: Isotretinoin; OT: Other treatments; F: Female; M: Male.

and obsessive doubting worsening have also being reported during ITT treatment[8,36-38], the predictive value of headache as a relatively specific marker for ITT-induced depression should be assessed in future studies.

This research field would also benefit from animal studies that would explore the pathways involved in the induction of depression-related behaviors in rodents, such as changes in brain monoamine transmission and corticotrophin-releasing hormone[39,40]. Finally, it is worthwhile mentioning that genetic studies are currently under way to identify genetic polymorphisms in the retinoic receptors that may predispose to or protect from ITT-unintended effects[41].

The present study has the following strengths: A longitudinal evaluation, a control group, the administration of scales for psychopathological assessment that provided categorical and continuous evaluation and the use of locally-developed scales that provided an adequate wording for this specific clinical population. However, it has several limitations: A relatively small sample size and a relatively short period of psychological assessment; the patients were older than those who typically request acne therapy (*i.e.*, adolescents); evaluations were not blind; treatment assignment was not random, and hence, the acne severity was higher in the ITT group than in the control group, and there was no formal scale to assess such a severity.

Further research should take into account that, while random treatment assignment appears problematic from an ethical point of view, semi-quantitative scales for acne severity have been developed[42]. Since severe acne is in many cases a chronic and severe condition and since ITT is often prescribed in doses higher than 30 mg/d and for prolonged periods, long-term studies with high ITT doses are also needed. In those studies, other physical ITT side effects must be assessed. The influence of ethnicity and previous psychiatric disorders on ITT safety should also be examined in further research.

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COMMENTS

Background

Concerns exist about the risk of depression, suicide risk and/or anxiety during isotretinoin (ITT) administration in acne-treated patients.

Research frontiers

Limited information exists about the psychopathology background and the pretreatment mental status of subjects who developed clinically significant depression/anxiety during ITT administration.

Innovations and breakthroughs

Few studies in ITT-treated subjects include an adequate control group, locally-developed psychopathological scales and a pretreatment evaluation. The authors aimed to overcome these limitations in the present study.

Applications

Approximately one out of ten subjects treated for acne either with ITT or antibiotics in the short term may develop clinically-significant depression or anxiety. Subjects at risk for psychopathology must be identified before starting ITT administration.

Terminology

ITT is a vitamin. A-related compound widely used in the treatment of severe cystic acne vulgaris.

Peer-review

Well written manuscript.

REFERENCES

1 **On SC**, Zeichner J. Isotretinoin updates. *Dermatol Ther* 2013; **26**: 377-389 [PMID: 24099068 DOI: 10.1111/dth.12084]
2 **Nickle SB**, Peterson N, Peterson M. Updated Physician's Guide to the Off-label Uses of Oral Isotretinoin. *J Clin Aesthet Dermatol* 2014; **7**: 22-34 [PMID: 24765227]
3 **Hazen PG**, Carney JF, Walker AE, Stewart JJ. Depression--a side effect of 13-cis-retinoic acid therapy. *J Am Acad Dermatol* 1983; **9**: 278-279 [PMID: 6577039]
4 **Bremner JD**, Shearer KD, McCaffery PJ. Retinoic acid and affective disorders: the evidence for an association. *J Clin Psychiatry* 2012; **73**: 37-50 [PMID: 21903028 DOI: 10.4088/JCP.10r05993]
5 **Thomas KH**, Martin RM, Potokar J, Pirmohamed M, Gunnell D. Reporting of drug induced depression and fatal and non-fatal suicidal behaviour in the UK from 1998 to 2011. *BMC Pharmacol Toxicol* 2014; **15**: 54 [PMID: 25266008 DOI: 10.1186/2050-6511-15-54]
6 **Schulpis KH**, Georgala S, Papakonstantinou ED, Michas T. Psychological and sympatho-adrenal status in patients with cystic acne. *J Eur Acad Dermatol Venereol* 1999; **13**: 24-27 [DOI: 10.1111/j.1468-3083.1999.tb00839.x]
7 **Wysowski DK**, Swartz L. Relationship between headache and depression in users of isotretinoin. *Arch Dermatol* 2005; **141**: 640-641 [PMID: 15897395]
8 **Yesilova Y**, Bez Y, Ari M, Kaya MC, Alpak G. Effects of isotretinoin on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris. *J Dermatolog Treat* 2012; **23**: 268-271 [PMID: 21815780 DOI: 10.3109/09546634.2011.608782]
9 **Lusilla MP**, Sánchez A, Sanz C, López J. Validación estructural de la escala heteroevaluada de ansiedad de Zung (XXVIII Congreso de la Sociedad Española de Psiquiatría). *Anal Psiquiatr* 1990; **6** Supp 1: 39
10 **Peña-Casanova J**, Aguilar M, Bertran-Serra I, Santacruz P, Hernández G, Insa R, Pujol A, Sol JM, Blesa R. [Normalization of cognitive and functional assessment instruments for dementia (NORMACODEM) (I): objectives, content and population]. *Neurologia* 1997; **12**: 61-68 [PMID: 9147453]
11 **Ruiz-Grosso P**, Loret de Mola C, Vega-Dienstmaier JM, Arevalo JM, Chavez K, Vilela A, Lazo M, Huapaya J. Validation of the Spanish Center for Epidemiological Studies Depression and Zung Self-Rating Depression Scales: a comparative validation study. *PLoS One* 2012; **7**: e45413 [PMID: 23056202 DOI: 10.1371/journal.pone.0045413]
12 **Escalante G.** Escala para medir Depresión. Estudio Técnico. Centro de Investigaciones Psicológicas, Universidad de los Andes (ULA); Mérida-Venezuela, 2005
13 **Esqueda L.** Escala para medir Ansiedad. Estudio Técnico. Centro de Investigaciones Psicológicas, Universidad de los Andes (ULA); Mérida-Venezuela, 1990
14 **Borovaya A**, Olisova O, Ruzicka T, Sárdy M. Does isotretinoin therapy of acne cure or cause depression? *Int J Dermatol* 2013; **52**: 1040-1052 [PMID: 23962262 DOI: 10.1111/ijd.12169]
15 **Marron SE**, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol* 2013; **93**: 701-706 [PMID: 23727704 DOI: 10.2340/00015555-1638]
16 **Nevoralová Z**, Dvořáková D. Mood changes, depression and suicide risk during isotretinoin treatment: a prospective study. *Int J Dermatol* 2013; **52**: 163-168 [PMID: 23347302 DOI: 10.1111/j.1365-4632.2011.05334.x]
17 **McGrath EJ**, Lovell CR, Gillison F, Darvay A, Hickey JR, Skevington SM. A prospective trial of the effects of isotretinoin on quality of life and depressive symptoms. *Br J Dermatol* 2010; **163**: 1323-1329 [PMID: 21137117]
18 **Bozdağ KE**, Gülseren S, Güven F, Cam B. Evaluation of depressive symptoms in acne patients treated with isotretinoin. *J Dermatolog Treat* 2009; **20**: 293-296 [PMID: 19701845 DOI: 10.1080/09546630903164909]
19 **Rehn LM**, Meririnne E, Höök-Nikanne J, Isometsä E, Henriksson M. Depressive symptoms, suicidal ideation and acne: a study of male Finnish conscripts. *J Eur Acad Dermatol Venereol* 2008; **22**:

561-567 [PMID: 18221339 DOI: 10.1111/j.1468-3083.2007.02514.x]
20 **Azoulay L**, Blais L, Koren G, LeLorier J, Bérard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008; **69**: 526-532 [PMID: 18363422]
21 **Kaymak Y**, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. *Int J Dermatol* 2009; **48**: 41-46 [PMID: 19126049 DOI: 10.1111/j.1365-4632.2009.03806.x]
22 **Hahm BJ**, Min SU, Yoon MY, Shin YW, Kim JS, Jung JY, Suh DH. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. *J Dermatol* 2009; **36**: 255-261 [PMID: 19382995 DOI: 10.1111/j.1346-8138.2009.00635.x]
23 **Cohen J**, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. *Can J Clin Pharmacol* 2007; **14**: e227-e233 [PMID: 17556790]
24 **Chia CY**, Lane W, Chibnall J, Allen A, Siegfried E. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol* 2005; **141**: 557-560 [PMID: 15897376]
25 **Ferahbas A**, Turan MT, Esel E, Utas S, Kutlugun C, Kilic CG. A pilot study evaluating anxiety and depressive scores in acne patients treated with isotretinoin. *J Dermatolog Treat* 2004; **15**: 153-157 [PMID: 15204147]
26 **Kellett SC**, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273-282 [PMID: 10233222]
27 **Sundström A**, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. *BMJ* 2010; **341**: c5812 [PMID: 21071484 DOI: 10.1136/bmj.c5812]
28 **Marqueling AL**, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2007; **26**: 210-220 [PMID: 18395669 DOI: 10.1016/j.sder.2008.03.005]
29 **Misery L**, Feton-Danou N, Consoli A, Chastaing M, Consoli S, Schollhammer M. [Isotretinoin and adolescent depression]. *Ann Dermatol Venereol* 2012; **139**: 118-123 [PMID: 22325750 DOI: 10.1016/j.annder.2011.11.012]
30 **D'Erme AM**, Pinelli S, Cossidente A, Campolmi E, Lotti T, Gola M. Association between isotretinoin and mood changes: myth or reality? An updated overview. *Int J Dermatol* 2013; **52**: 499-500 [PMID: 21913911 DOI: 10.1111/j.1365-4632.2011.05182.x]
31 **Wolverton SE**, Harper JC. Important controversies associated with isotretinoin therapy for acne. *Am J Clin Dermatol* 2013; **14**: 71-76 [PMID: 23559397 DOI: 10.1007/s40257-013-0014-z]
32 **Rowe C**, Spelman L, Oziemski M, Ryan A, Manoharan S, Wilson P, Daubney M, Scott J. Isotretinoin and mental health in adolescents: Australian consensus. *Australas J Dermatol* 2014; **55**: 162-167 [PMID: 24283385 DOI: 10.1111/ajd.12117]
33 **Schaffer LC**, Schaffer CB, Hunter S, Miller A. Psychiatric reactions to isotretinoin in patients with bipolar disorder. *J Affect Disord* 2010; **122**: 306-308 [PMID: 19783054 DOI: 10.1016/j.jad.2009.09.005]
34 **Barak Y**, Wohl Y, Greenberg Y, Bar Dayan Y, Friedman T, Shoval G, Knobler HY. Affective psychosis following Accutane (isotretinoin) treatment. *Int Clin Psychopharmacol* 2005; **20**: 39-41 [PMID: 15602115]
35 **Baptista T**, Uzcátegui E, Arapé Y, Serrano A, Mazzarella X, Quiroz S, Ramirez CI, Padrón de Freytez A. Migraine life-time prevalence in mental disorders: concurrent comparisons with first-degree relatives and the general population. *Invest Clin* 2012; **53**: 38-51 [PMID: 22524107]
36 **Segmiller FM**, Rüther T, Linhardt A, Dehning S, Möller HJ, Zetzsche T. Psychosis during treatment with isotretinoin. *Ther Adv Psychopharmacol* 2013; **3**: 244-245 [PMID: 24167696 DOI: 10.1177/2045125312470129]
37 **Rajagopal S**. Acute psychosis induced by isotretinoin. *Indian J Psychiatry* 2014; **56**: 295-297 [PMID: 25316943 DOI: 10.4103/0019-5545.140652]
38 **Poblete A C**, Herskovic M V, Eva C P. [Panic attacks in a patient treated with isotretinoin for acne. Report of one case]. *Rev Med Chil* 2006; **134**: 1565-1567 [PMID: 17277875]
39 **O'Reilly KC**, Shumake J, Gonzalez-Lima F, Lane MA, Bailey SJ. Chronic administration of 13-cis-retinoic acid increases depression-related behavior in mice. *Neuropsychopharmacology* 2006; **31**: 1919-1927 [PMID: 16395305]
40 **O'Reilly K**, Bailey SJ, Lane MA. Retinoid-mediated regulation of mood: possible cellular mechanisms. *Exp Biol Med* (Maywood) 2008; **233**: 251-258 [PMID: 18296731 DOI: 10.3181/0706-MR-158]
41 **Alzoubi KH**, Khabour OF, Hassan RE, Qarqaz F, Al-Azzam S, Mhaidat N. The effect of genetic polymorphisms of RARA gene on the adverse effects profile of isotretinoin-treated acne patients. *Int J Clin Pharmacol Ther* 2013; **51**: 631-640 [PMID: 23782583 DOI: 10.5414/CP201874]
42 **O'Brien SC**, Lewis JB, Cunliffe WJ. The Leeds revised acne grading system. *J Dermatol Treat* 1998; **9**: 215-220 [DOI: 10.3109/09546639809160698]

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