Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis

Yu-Chen Huang, MD,[a,b] and Ying-Chih Cheng, MD[c,d]
Taipei and New Taipei City, Taiwan

Background: The relationship between isotretinoin treatment for acne and depression is controversial. Quantitative analysis has not yet been conducted.

Objective: To conduct a meta-analysis, evidence-based examination of the relationship between isotretinoin and depression.

Method: A systematic review and meta-analysis of the literature published from inception to September 30, 2016, was conducted. Controlled or prospective non-controlled trials on ≥15 acne patients receiving isotretinoin treatment were included. The prevalence of depression and change in depression scores were calculated.

Result: Thirty-one studies met the inclusion criteria. In the controlled studies, the change in depression scores from baseline was not significantly different between patients receiving isotretinoin treatment and those receiving an alternative treatment (standardized mean difference [SMD] −0.334, 95% confidence interval [CI] −0.680 to 0.011). The prevalence of depression after isotretinoin treatment significantly declined (relative risk [RR] 0.588, 95% CI 0.382−0.904). The mean depression scores significantly decreased from baseline (SMD −0.335, 95% CI −0.498 to −0.172).

Limitations: No randomized controlled trials were reviewed; a large inter-study variation was observed.

Conclusions: Isotretinoin treatment for acne does not appear to be associated with an increased risk for depression. Moreover, the treatment of acne appears to ameliorate depressive symptoms. (J Am Acad Dermatol 2017;76:1068-76.)

Key words: acne; depression; isotretinoin; meta-analysis; psychological impact; systemic review.

Acne is a common, chronic skin condition that affects nearly all adolescents. Isotretinoin is the most effective treatment available for recalcitrant nodulocystic acne.[1] The possible induction of depressive symptoms by isotretinoin treatment for acne was first reported in 1983.[2] In 1998, the US Food and Drug Administration issued a warning regarding the possible associations of isotretinoin with depression, psychosis, suicidal ideation, and suicide. However, 2 large population-based studies in 2000[3] and 2003,[4] as well as several controlled[5-8] and noncontrolled studies,[9-14] failed to

Abbreviations used:

CI:	confidence interval
RCT:	randomized controlled trial
RR:	risk ratio
SD:	standard deviation
SMD:	standardized mean difference

From the Department of Dermatology, Wan Fang Hospital, Taipei Medical University[a]; Department of Dermatology, School of Medicine and College of Medicine, Taipei Medical University[b]; Department of Psychiatry, Cardinal Tien Hospital, New Taipei City[c]; and Department of Public Health and Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei.[d]

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Correspondence to: Yu-Chen Huang, MD, Department of Dermatology, Wan Fang Hospital, Taipei Medical University, 111, Hsing-Long Road Sec 3, Wenshan District, Taipei City 116, Taiwan. E-mail: dhist2002@yahoo.com.tw.

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demonstrate an increased risk for depression or suicide associated with isotretinoin. In 2008, a case cross-over study by Azoulay et al[15] revealed a statistically significant association between isotretinoin and depression. However, a large population-based study[16] found acne alone to be significantly associated with depression and suicidal ideation. Despite the controversy surrounding isotretinoin, the potential increase in the risk for psychological problems associated with severe acne should also be considered. Multiple studies on the relationship between isotretinoin and depression have been conducted, some of which demonstrated that treating acne with isotretinoin improved depressive symptoms.[17-23] Considering whether sex, isotretinoin dose, treatment time, and the patient baseline psychologic condition affected the results of these studies is crucial. However, with only limited data and small sample sizes, assessing these confounding factors is difficult. Further, 3 systematic reviews by Strahan et al in 2006,[24] Marqueling et al in 2007,[25] and Bremner et al in 2012[26] did not achieve consistent results. Strahan et al[24] and Marqueling et al[25] concluded that the current literature does not support a causative association between isotretinoin and depression. However, Bremner et al[26] concluded that isotretinoin has a causal link with depression. Here we sought to determine the relationship between isotretinoin and depression by providing a thorough, evidence-based meta-analysis of this controversy.

CAPSULE SUMMARY

- The relationship between isotretinoin treatment for acne and depression is controversial.
- Meta-analysis did not show a positive association between isotretinoin use and depression. In fact, incidence of depression declined after isotretinoin use.
- Although individual susceptibility to depression during isotretinoin use cannot be ruled out, the available evidence suggests that patients with nodulocystic acne can safely be treated with isotretinoin without increasing their risk for depression.

METHODS

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org/).

Data source and search strategy

We identified studies indexed in PubMed, MEDLINE, EmBase, and the Cochrane Library databases from inception of isotretinoin treatment to September 30, 2016, (last literature search day October 4, 2016). All articles included in the present study involved human clinical studies written in English. The search parameters included the terms "depression" combined with "isotretinoin," "accutane," or "13-cis-retinoic acid."

Study selection

We primarily focused our literature search on randomized controlled trials (RCTs). However, in the absence of an RCT, we included large-scale population-based studies, non-RCT, and prospective open-label studies with ≥15 patients with acne who had received isotretinoin therapy. Only studies that provided the prevalence of depression or depression scores were included. Articles from adverse event reporting systems, review articles, case reports, correspondence, and conference report were excluded. Quality assessment was performed using methodological index for nonrandomized studies.[27] The studies with quality scores <12 were also excluded.

Outcomes

The primary outcomes of the present study were the prevalence of depression and change in the depression score following isotretinoin therapy.

Data extraction

Data were independently extracted by 2 authors (Dr Huang and Dr Cheng). Any disagreement was resolved by consensus. Data on the following measures were extracted: study design, inclusion criteria, sample size, treatment regimen, study results, and quality scores (Supplemental Table I; available at http://www.jaad.org). For population-based studies, we extracted the outcome (relative risk [RR]) (Supplemental Table II; available at http://www.jaad.org). Age, the proportion of male patients, follow-up time, cumulative isotretinoin dose, depression scale, and depression score with standard deviation (SD) before, during, and after treatment were also extracted (Supplemental Tables III and IV; available at http://www.jaad.org). We extracted the number of depression cases (Table I), if provided by the study. The non-RCTs consisted of 2 groups of patients with acne who received isotretinoin or alternative therapy within the same study. Depression was defined by the original study. The cumulative isotretinoin dose was calculated

Table I. The prevalence of depression before, during, and after treatment

Study	Cases of depression at baseline, n (%)	Cases of depression during treatment, n (%)	Cases of depression at final follow-up, n (%)	Definition of depression
Bruno et al, 1984[28]	1 (1.1) major depression	10 (11) minor depression	N/A	No definition
Kellett et al, 1999[10]	6 (18)	N/A	0 (0)	HADS-D > 10
Hull et al, 2000[29]	1 (0.5) had history of depression	4 (4.4)	2 (4)	Self-reported
Strauss et al, 2001[14]	N/A, 15 (5) had history of psychiatric medication	10 (3.3)	N/A	BDI > 13
Kellett et al, 2005[11]	8 (25.81)	4 (19.05)	4 (18.19)	BDI > 13
Chia et al, 2005[5]	9 (15.3)	N/A	5 (8.2)	CES-D > 16
Kaymak et al, 2006[9]	0 (0)	1 (1)	0 (0)	HSRD > 13
Cohen et al, 2007[6]	1 (1)	N/A	2 (2)	CES-D > 15
Kaymark et al, 2009[30]	12 (33.3)	7 (19.4)	4 (11.1)	BDI > 13
Rehn et al, 2009[22]	9 (7.1)	7 (5.6)	4 (3.2)	BDI ≥ 10
Ergun et al, 2011[17]	5 (7.9) had depression history, 4 of them taking antidepressants	5 (7.9)	2 (40) no follow-up, 3 (60) improved	Self -reported
Marron et al, 2013[20]	12 (3.5)	N/A	6 (1.7)	HADS-D > 10
Webster et al, 2014[31]	N/A	4 (0.9)	0 (0)	Self-reported
Suarez et al, 2016[32]	1 (2.8)	3 (8.3)	3 (8.3)	Zung scale > 50

BDI, Beck Depression Inventory; *CES-D*, Center for Epidemiological Studies Depression; *HADS-D*, Hospital Anxiety Depression Scale-Depression; *HRSD*, Hamilton Rating Scale for Depression; *N/A*, not available.

according to the dose provided in the original study. If the follow-up time was provided in weeks, we calculated a week to be 7 days; if given in months, we calculated a month to be 30 days. The details of the depression scales are shown in Supplemental Table V (available at http://www.jaad.org).

Data analysis

For the controlled trials, we produced a pooled estimate of the mean difference in the depression score change for patients treated with isotretinoin compared with patients who received alternative therapy. For all studies that provided depression scores, we performed a pooled estimate for the change in depression score. If there were ≥3 studies using the same depression scales, a pooled estimate was also performed. Data were then stratified by follow-up time into 3 groups: 1) 1-2 months; 2) 3-4 months; and 3) past 4 months. Separate meta-analyses were then conducted for each subgroup, as well as a pooled analysis of the prevalence of depression before and after treatment for studies with a clear definition of depression and a depression case number. Continuous data were analyzed using the weighted mean difference when comparing grouped studies using the same scale or standardized mean difference (SMD) when comparing variable and non-standardized outcome scales reported across studies. Dichotomous analyses were conducted using RR.

For meta-analyses of controlled trials, some studies reported the baseline and final scores for 2 groups. We computed the mean change in the scores from baseline and SD for both the isotretinoin and controlled groups. The data were combined in the same analysis as the studies that reported only the final scores of the 2 groups. This computation requires the pre−post correlation value to be input. However, no studies reported the pre−post correlation values necessary to conduct an appropriately paired analysis. We used a pre−post correlation of 0.5.[33] The same computations were conducted for all meta-analyses in prospective open-label studies with before and after data. Sensitivity analyses were conducted for each case by using pre−post correlations of 0.2 and 0.8. If studies lacked necessary data, they were not pooled in the meta-analysis. Similarly, none of the uncontrolled studies that measured dichotomous outcomes before and after treatment reported data in a matched format; therefore, these outcomes were analyzed as unmatched data, shown to be similar and easier to interpret than matched analyses.[34] Homogeneity testing was performed using the I^2 test. A fixed-effects model was used if there was a lack in heterogeneity. When I^2 was >60%, a random-effect model was used.

A meta-regression was performed to determine the effect of the cumulative isotretinoin dose, proportion of male patients, high baseline depression scores (studies with baseline scores exceeding the definition of depression, categorical variable), and quality scores on the change of depression

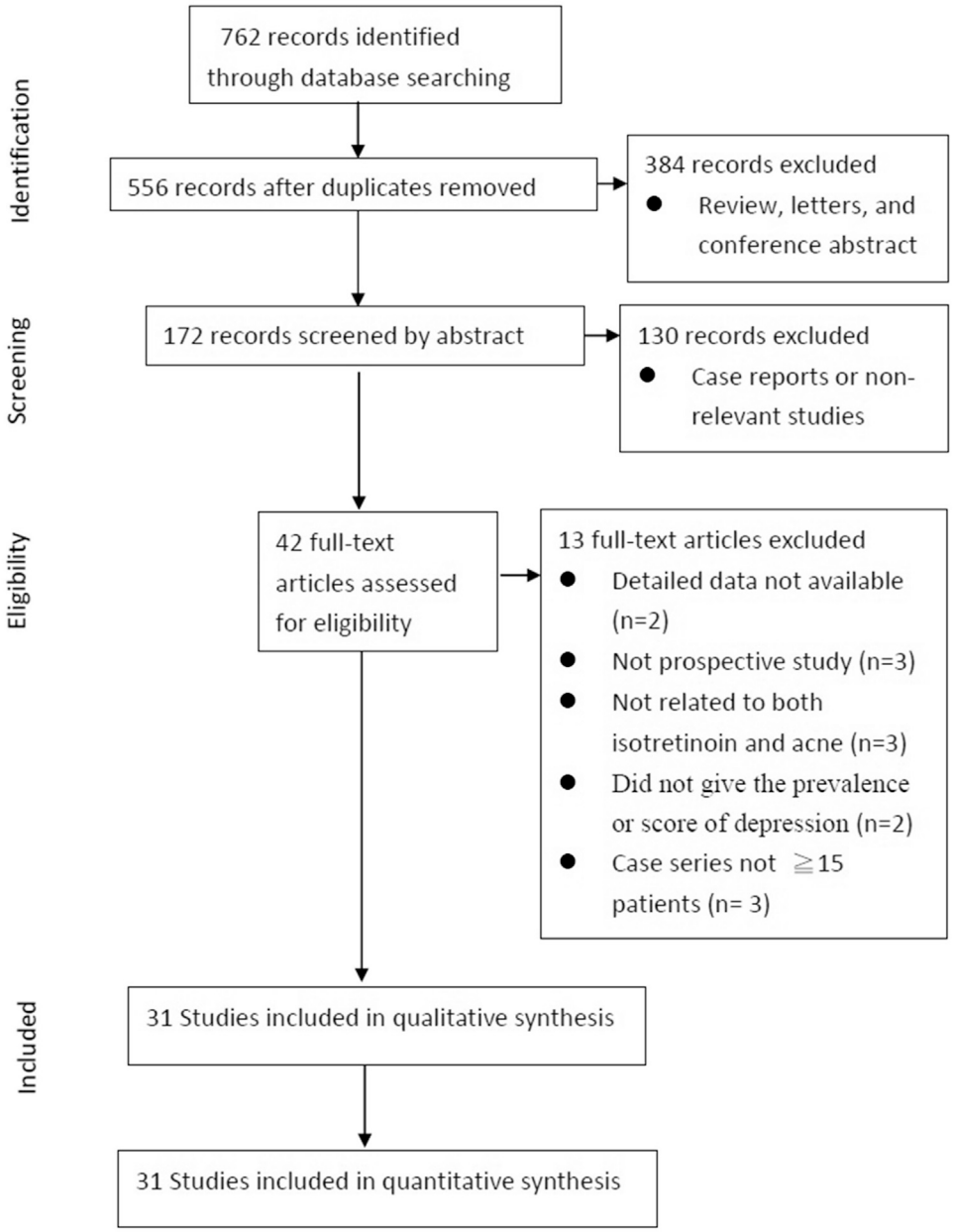

Fig 1. Selection of studies included in the present systematic review and meta-analysis.

scores for patients who received isotretinoin. Publication bias was tested by the Egger test. All of the above analyses were performed using the Comprehensive Meta-Analysis software version 3 (Biostat, Inc, Englewood, NJ).

RESULTS

Search results and trial characteristics

Of the 172 studies screened, the inclusion criteria were met in 31 studies (Fig 1): 3 population-based studies, 8 controlled studies, and 20 prospective open-label studies, of which 4 provided only the prevalence of depression without before and after depression scores. A summary of the trial characteristics is presented in Table I.

Of the 31 studies, 1 population-based study found that isotretinoin significantly increased the risk of depression, while 2 open-label studies found increased depression scores following isotretinoin therapy (1 significantly and the other nonsignificantly increased). The other 10 controlled studies and 15 open-label studies found no association between isotretinoin use and the risk for depression. Eleven out of 25 studies (2 controlled[5,30] and 9 open-label studies[10,11,17,19-23,35]) found a significant improvement in the depression scores or a

Table II. The results of meta-analysis of controlled studies and non-controlled studies about depression scores

	No of study/ patient	Effect measure	Correlation 0.5			Correlation 0.2			Correlation 0.8				
			Effect estimate mean (95% CI)	I^2	*P*	Effect estimate mean (95% CI)	I^2	*P*	Effect estimate mean (95% CI)	I^2	*P*
Controlled study	6/210 vs 158	SMD	−0.334 (−0.680 −0.011)	62.4	.058	−0.257 (−0.465 to −0.049)	40.9	.015	−0.500 (−0.103 to 0.029)	83.6	.064
Depression scores before and after isotretinoin treatment (include controlled and open-label studies)											
Total	19/1411	SMD	−0.335 (−0.498 to −0.172)	87.2	<.001	−0.342 (−0.512 to −0.169)	81.3	<.001	−0.316 (−0.461 to −0.170)	93.9	<.001
BDI	8/812	WMD	−1.068 (−2.120 to −0.017)	85.6	.046	−1.087 (−2.169 to −0.006)	77.5	.049	−1.058 (−2.041 to −0.074)	93.7	.035
HADS-D	4/132	WMD	−2.422 (−3.897 to −0.948)	80.4	.001	−2.337 (−3.809 to −0.864)	68.8	.002	−2.516 (−4.005 to −1.028)	92.1	.001
1-2 months	8/544	SMD	−0.399 (−0.647 to −0.152)	85.4	.002	−0.386 (−0.639 to −0.134)	76.9	.003	−0.405 (−0.643 to −0.167)	93.9	.001
3-4 months	15/1002	SMD	−0.199 (−0.420 to 0.022)	90.6	.078	−0.210 (−0.446 to −0.026)	86.4	.081	−0.174 (−0.369 to − 0.021)	95.4	.081
>4 months*	5/645	SMD	−0.347 (−0.571 to −0.123)	84.2	.002	−0.328 (−0.555 to −0.101)	77.8	.005	−0.370 (−0.589 to −0.152)	93.6	.001

BDI, Beck Depression Inventory; *CI*, confidence interval; *HADS-D*, Hospital Anxiety Depression Scale-Depression; *SMD*, standardized mean difference; *WMD*, weighted mean difference.
*This group contained 2 studies (Simic et al[36] and Gnanarai et al[18]) without follow-up after completion of isotretinoin treatment.

reduced frequency of depression following isotretinoin therapy. The improved depression score was significantly greater than the control group in 1 controlled study and nonsignificant in the other controlled study. The remaining 3 studies only provided the prevalence of depression: 1) 11% mild depression after 1 month of therapy; 2) 4% prevalence of depression from the start to therapy completion; and 3) 0.9% during therapy which resolved with continued treatment (Supplemental Table I; available at http://www.jaad.org).

Characterization of patients with acne and isotretinoin use

Clinical and outcome data for patients with acne are summarized (Table I, Supplemental Tables II-IV; available at http://www.jaad.org). Excluding the 3 population-based studies, 2932 acne patients were treated with isotretinoin, of which 2611 completed the studies. The isotretinoin regimen was 0.5-1 mg/kg/day in all studies except for 2 with doses of 0.1-0.22 mg/kg/day and 2 mg/kg/day. The cumulative isotretinoin dose ranged from 15-150 mg/kg. In 4 studies, the mean scores before treatment exceeded the definition of depression using their own scale. The after score increased in 1 study and decreased below the definition point in the 3 others.

Statistical analysis results

The results of the meta-analysis are presented in Table II. For the 6 controlled studies, the depression score changes from baseline were not significantly different (both improved) among the patients treated with isotretinoin or an alternative therapy (SMD −0.334, 95% confidence interval [CI] −0.680 to 0.011) when imputing a 0.5 correlation (Fig 2).

The prevalence of depression following isotretinoin treatment significantly declined (RR 0.588, 95% CI 0.382-0.904). For the pre- and post-test scores for isotretinoin treatment, the mean depression scores significantly decreased from baseline regardless of the correlation value (SMD −0.335, 95% CI −0.498 to −0.172). The mean depression scores also significantly decreased when assessed by Beck Depression Inventory, Hospital Anxiety Depression Scale—Depression (HADS-D), follow-up at 1-2 months, and follow-up past 4 months. The meta-regression revealed that a high proportion of male patients (coefficient 0.0107, 95% CI 0.0015-0.0199; $P = .022$) and a high quality score (coefficient 0.2403, 95% CI 0.0638-0.4108; $P = .0076$) were significantly related to less decrement in depression scores. The funnel plot (Fig 3) for change in depression scores in 19 studies showed no publication bias (Egger test, $P = .5158$).

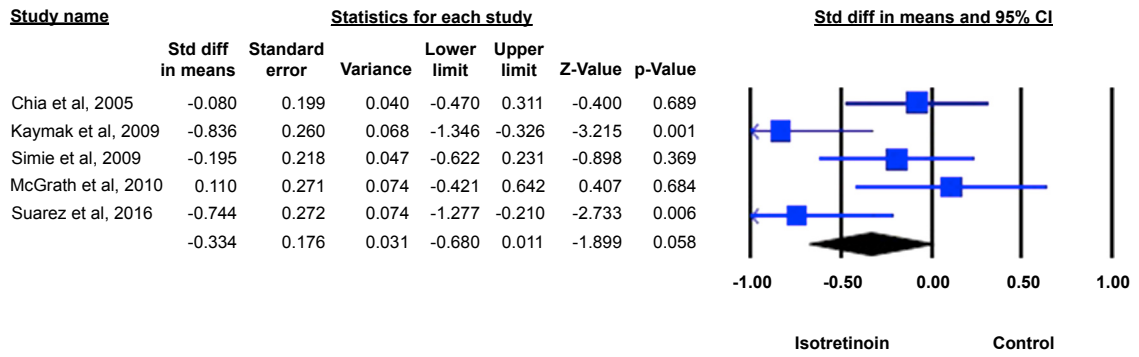

Fig 2. Forest plot. Standardized mean difference in depression score change from baseline (post-score minus pre-score) between the isotretinoin group and the control group (isotretinoin group minus control group). The more negative a standardized mean difference is the greater the improvement in depression scores in the isotretinoin group in comparison with the control group.

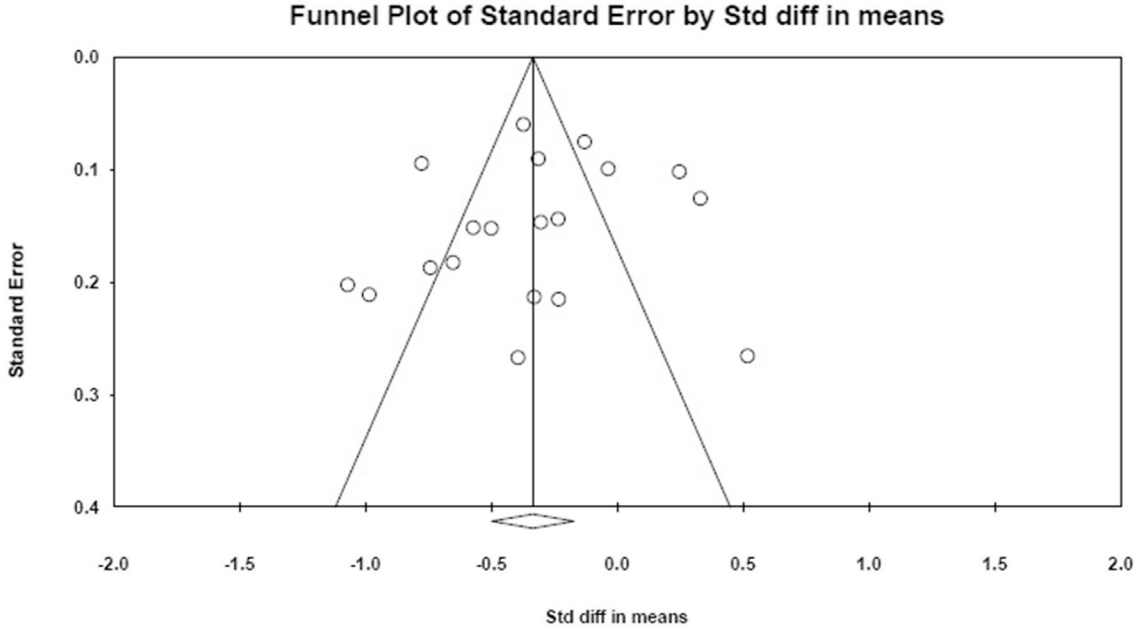

Fig 3. Funnel plot analysis for potential publication bias. The funnel plot for change in depression scores in 19 studies showed no asymmetry, which means no publication bias. Each dot represents a study; the y-axis represents the standard error of the study and the x-axis shows the study result (standardized mean difference of pre- and post-treatment depression scores in each study).

DISCUSSION

The relationship between isotretinoin treatment for acne and depression remains controversial both clinically and scientifically. Because isotretinoin is a fat-soluble compound, it can easily cross the blood–brain barrier and interact with brain tissue wherever intracellular retinoid receptors are present. It can affect the dopaminergic[36] and serotonergic systems,[37] hippocampal neurogenesis,[38] and frontal orbital activity.[8] The chronic administration of 1-mg/kg dose of isotretinoin has been shown to increase depression-related behavior in mice and rats in some studies[39,40] but not in others.[41,42]

This meta-analysis found no association between isotretinoin and depression. Moreover, symptoms of depression improved following isotretinoin treatment, but this effect was not significantly different from alternative therapy. Among studies that could not be used in this meta-analysis, only the population-based study by Azoulay et al[15] concluded that isotretinoin significantly increased the risk for depression in acne patients. All 3 population-based studies

underestimated the incidence of depression because diagnostic codes and antidepressant prescriptions were used as inclusion criteria and patients with inadequate data were excluded. Moreover, this underestimation might be particularly problematic for the study by Azoulay et al[15] because the RR estimate was based on a small subset of patients who met strict depression and data availability criteria; therefore, the results might not be applicable to a general population of patients treated with isotretinoin.[43]

The systematic review by Bremner et al[26] concluded that isotretinoin had a causal link with depression. Despite their finding that multiple studies demonstrated no association between isotretinoin and depression or an improvement in depressive symptoms following isotretinoin treatment, they concluded that the sample sizes were too small to confirm that most patients receiving isotretinoin did not develop depression. The systematic reviews by Strahan et al,[24] Marqueling et al,[25] and Bremner et al[26] did not include a pooling analysis to derive their conclusion. In our meta-analysis, we pooled the results of 1411 patients who received depression evaluations at baseline and after treatment, which revealed a significant improvement in the depression scores. Bremner et al[26] used the study by Meysken et al[44] to support a dose-response relationship of up to 3 mg/kg/day isotretinoin for advanced cancer patients, 25% of whom exhibited depression. However, high doses that might cause symptoms of depression are not usually prescribed for acne. In our study, the typical dose prescribed for acne (0.5-1 mg/kg) was not found to have a dose-related risk for depression, consistent with the results of the study by Azoulay et al.[15]

Bremner et al[26] stated that depression usually develops 1-2 months or sometimes around 2-4 months after treatment and further emphasized that challenge—rechallenge cases support a causal link. In our study, the depression scores significantly decreased within the first 1-2 months and after 4 months and tended to decrease (but not significantly) within 3-4 months. Although 4 studies found increased scores at 3-4 months, 2 of them found that scores at 6 months had decreased below baseline despite continued treatment. The other 2 studies involved follow-up for only 3-4 months. Webster et al[31] found that in all patients who reported depression, the condition resolved without discontinuing isotretinoin. Increased depression scores or newly reported depression cases might be explained by the persistence of acne or other side effects of isotretinoin, which might resolve over the course of treatment.

In our study, similar to that in the study by Halvorsen et al,[16] the patients with acne had high baseline depression scores, which exceeded the depression cut-off points of 4 studies. However, meta-regression results revealed that high baseline scores did not affect depression score changes and male patients were as capable of improving depression scores as female patients.

From the view of prevalence of depression, the risk was significantly decreased after treatment. However, some studies described newly developed depression during treatment. In the controlled trial conducted by Suarez et al,[32] new onset of depression was noted in both the isotretinoin and antibiotic groups, implying that depression is associated with acne, independently of isotretinoin. Thus, physicians should consider the possibility of depression among all acne patients regardless of the treatment method. We also agree with Bremner et al[26] that some patients are more susceptible to depression. However, if there is a link between isotretinoin and depression, no predictive tests exist for quantifying the level of risk to patients; perhaps it is an idiosyncratic reaction.[45]

Our study has some limitations. The first limitation was that no RCTs were included; however, we included recent studies with the highest level of evidence, all of which demonstrated a weak relationship between isotretinoin and depression. The second limitation was high inter-study variability (eg, different evaluation tools). Therefore, we used the standardized mean difference outcome measure for the meta-analyses of continuous data and performed meta-regression for sensitivity analysis. The quality score affected the change in depression scores: when omitting the studies with the lowest scores, the improvement in depression score remained significant.

In conclusion, this meta-analysis demonstrated that isotretinoin treatment for acne at the typical therapeutic dose is not associated with an increased risk for depression. Moreover, the treatment of acne improved symptoms of depression for most patients. Some patients might be more prone to depression regardless of acne or other conditions. Thus, closely monitoring acne patients for depression is essential to identify patients at a high risk.

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Supplemental Table I. Summary of included studies

Study	Study design	Patient inclusion criteria	Sample size	Isotretinoin dose	Study result	Score
Population-based studies						
Jick et al, 2000[3]	Case control study	Between 6 months and 5 years before, and at least 12 months after, their first isotretinoin or antibiotic prescription.	7195 isotretinoin vs 13,700 antibiotic 340 isotretinoin vs 676 antibiotic	N/A	No association	
Hersom et al, 2003[4]	Sequence symmetry analysis	12-49 years Isotretinoin prescriptions between June 1, 1999, and March 31, 2000	2821 isotretinoin vs 7360 antibiotic	N/A	No association	
Azoulay et al, 2008[15]	Case crossover study	Received ≥1 isotretinoin prescription during 1984-2003	30,496 (126 depression patients)	N/A	Statistically significant association between isotretinoin and depression	
Nonrandomized controlled trials						
Ng et al, 2002[7]	Prospective controlled study	Severe cystic acne No current diagnosis of depression, concomitant antidepressants, corticosteroids, anabolic steroids, or other depression-inducing medications	174 (171) vs 41 antibiotic/topical	Started at 40 mg/day, increased to a dosage of 1.0 mg/kg/day over 1 month and continued to total cumulative dose of 120 mg/kg (over 5-6 months)	No association	14 + 7
Chia et al, 2005[5]	Prospective controlled study, intent-to-treat analysis	12-19 years Moderate-to-severe inflammatory and cystic acne, no history of or current DSM-IV Axis I diagnosis	59 isotretinoin vs 73 conservative therapy (49 vs 52)	1 mg/kg/day	Both treatments associated with a decreased depression symptoms but no significant difference	14 + 7

Continued

Supplemental Table I. Cont'd

Study	Study design	Patient inclusion criteria	Sample size	Isotretinoin dose	Study result	Score
Bremner et al, 2005[8]	Prospective, controlled study	18 and 50 years Treatment-resistant acne, defined as a failed 3-month antibiotic trial, no current psychiatric illness according to the Structured Clinical Interview for DSM-IV	14 isotretinoin vs 16 oral antibiotics (13 vs 15)	1 mg/kg/day for 4 months	No association	13 + 7
Cohen et al, 2007[6]	Prospective, controlled study	≥14 years, not under treatment with antidepressants	100 isotretinoin vs 100 oral antibiotics or topical cream	N/A	No association	12 + 8
Kaymak et al, 2009[30]	Prospective, controlled study	No	37 isotretinoin vs 41 topical treatment (36 vs 29)	0.5-0.8 mg/kg/d of isotretinoin for at least 20 weeks, ensuring that the cumulative dose was 100 mg/kg	Isotretinoin treatment of acne improved depression symptoms more than control group.	13 + 7
Simic et al, 2009[46]	Prospective, controlled study	No	41 isotretinoin vs 44 vitamin C (40 vs 44)	1 mg/kg/day	No association	14 + 5
McGrath et al, 2010[47]	Prospective, controlled study	12-50 years	65 isotretinoin vs 31 antibiotic (48 vs 23)	0.5 mg/kg/day for the first 2 weeks, then 1 mg/kg/day until cumulative dose of 120 mg/kg	No association	13 + 8
Suarez et al, 2016[32]	Prospective, controlled study	≥18 years	36 vs 24 oral or topical antibiotic with benzoyl peroxide	30mg/day	No association	12 + 7
Noncontrolled trials						
Bruno et al, 1984[28]	Prospective, open-label study	No	94 (92)	(1) 0.75-1.21 mg/kg/day for 16 weeks (2) 0.1-0.22 mg/kg/day for 16 weeks	Minor depression reported in 11% of patients in both groups	13

Continued

Supplemental Table I. Cont'd

Study	Study design	Patient inclusion criteria	Sample size	Isotretinoin dose	Study result	Score
Rubinow et al, 1987[12]	Prospective, open-label study	Treatment-resistant cystic acne and >10 active cysts	72 (66)	High dose (2 mg/kg/day) and low dose (0.5 mg/kg/day): (1) high doses for 2 weeks and low doses for 14 weeks (n = 24) (2) high doses for 2 weeks and placebo for 14 weeks (n = 24) (3) low doses for 16 weeks (n = 24)	No association	13
Kellett et al, 1999[10]	Prospective, open-label study	Unresponsiveness to standard acne treatment regimens	34 (15)	1 mg/kg/day for 16 weeks	Significant improvement of depression scores	13
Schulpis et al, 1999[13]	Prospective, open-label study	No	38	0.5 mg/kg/day for 30 days	No association	12
Hull et al, 2000[29]	Prospective, open-label study	Severe acne	189 (82)	1 mg/kg/day for 4 months	Around 4% depression before and after treatment	12
Strauss et al, 2001[14]	Prospective, open-label study*	Severe recalcitrant nodular acne BDI-II $\geq$ 31 were excluded	300 (290)	1 mg/kg/day for a mean of 129.2 days	No association	13†
Kellett et al, 2005[11]	Prospective, open-label study	Nonresponsiveness to standard acne treatment	33 (21)	1 mg/kg/day for 16 weeks	Significant improvement of cognitive-affective features of depression within first 8 weeks	13
Kaymak et al, 2006[9]	Prospective, open-label study	No	100	0.75-1.00 mg/kg/day of isotretinoin for 20-28 weeks, ensuring that the cumulative dose was 100 mg/kg	Depression scores increased at month 3 but decreased below baseline at the end of month 6	15
Hahm et al, 2009[19]	Prospective, open-label study	Grades 1-7 by the Leeds RAGS	38	0.5—1 mg/kg per day for 8 weeks	Significant improvement of depression scores	14

Continued

Supplemental Table I. Cont'd

Study	Study design	Patient inclusion criteria	Sample size	Isotretinoin dose	Study result	Score
Ferahbas et al, 2009[48]	Prospective, open-label study	Severe recalcitrant acne, no one with any major psychiatric illnesses	45 (23)	0.5-1 mg/kg/day for 16 weeks.	No association	13
Bozdag et al, 2009[35]	Prospective, open-label study	Moderate-to-severe recalcitrant acne, no prior diagnosis of depression	50	1 mg/kg/day for 16 weeks	Significant improvement of depression scores	12
Rehn et al, 2009[22]	Prospective, open-label study	No	135 (126)	0.5 mg/kg/day	Significant improvement of depression scores	13
Ergun et al, 2011[17]	Prospective, open-label study	No	63 (48)	0.5 mg/kg/day for the first month, then 1 mg/kg/day until a cumulative dose of 130-150 mg/kg	Significant improvement of depression scores	13
Yesilova et al, 2012[23]	Prospective, open-label study	≥15 years	43 (33)	0.5−1.0 mg/kg/day for 6 months, cumulative dose of 120 mg/kg	Significant improvement of depression scores	13
Ormerod et al, 2012[49]	Prospective, open-label study	≥16 years Severe acne, no pre-existing mental health problems	17 (16)	0.5−1 mg/kg/day for 3-6 months until satisfactory clearance of acne lesions was achieved, (initial dosage 0.48 mg/kg/day, mid-treatment dosage 0.62 mg/kg/day)	Nonsignificant trends toward an increased BDI score with treatment	13
Nevoralova et al, 2013[21]	Prospective, open-label study	≥12 years Moderate-to-severe acne	100	Total cumulative dose of isotretinoin was 110-150 mg/kg, mean length 9 months	Significant improvement of depression scores	14
Marron et al, 2013[20]	Prospective, open-label study, intention-to-treat analysis	≥16 years Moderate acne, no antecedents of mental illness (personal or family members)	346 (334)	Total cumulative dose of 120 mg/kg for 30 weeks	Significant improvement of depression scores	15

Continued

Supplemental Table I. Cont'd

Study	Study design	Patient inclusion criteria	Sample size	Isotretinoin dose	Study result	Score
Fakour et al, 2014[50]	Prospective, open-label study	12-50 years No documented history of mood disorders, not under treatment with psychologic drugs	98	0.5 mg/kg/day for 16 weeks	Depression symptoms increased in patients to some extent.	15
Webster et al, 2014[31]	Prospective, open-label study*	12-54 years Severe recalcitrant nodular acne; no psychosis, psychotic symptoms, or suicidal behavior	461 (401)	0.5 mg/kg/day for 4 weeks and then 1 mg/kg/day for 12 weeks	0.9% depression, all cases resolved	12†
Gnanarai et al, 2015[18]	Prospective, open-label study	Grade 2 to grade 4 acne by the classification by Tutakne et al, no treatment history or family history of psychiatric illnesses	150 (143)	0.5 mg/kg/day for 3 months	Significant improvement of depression scores	14

Only patient inclusion criteria extracted were age, severity of acne, and psychiatric illness.
Sample size presented as before treatment patient number (end treatment patient number).
Score in controlled studies presented as uncontrolled part (highest 16) + controlled part (highest 8).
BDI, Beck Depression Inventory; *DSM-IV*, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; *Leeds RAGS*, Leeds Revised Acne Grading System; *N/A*, not available.
*These studies are randomized controlled studies (regular isotretinoin vs other isotretinoin), but we only extracted the data on the regular isotretinoin group.
†Score only refers to the isotretinoin group and depression score results.

Supplemental Table II. Detailed data and results of three large population-based studies

Study	Database	Depression definition	Result (risk for depression) adjusted RR (95% CI)	Adjusted covariate
Jick et al, 2000[3]	Canadian Saskatchewan Health database	ICD-9 codes 296-301	Isotretinoin vs nonexposed Current isotretinoin use: 1 (0.7-1.3) Recent isotretinoin use: 0.9 (0.6-1.4) Antibiotics vs nonexposed Current antibiotics use: 1.3 (1.0-1.5) Recent antibiotics use: 0.9 (0.7-1.1)	Age and sex
	United Kingdom General Practice Research database	ICD-9 codes 306-311	Isotretinoin vs nonexposed Current isotretinoin use: 1.8 (0.4-5.2) Recent isotretinoin use: 1.8 (0.3-6.1) Antibiotics vs nonexposed Current antibiotics use: 1.5 (0.9-2.5) Recent antibiotics use: 1.7 (0.8-3.4)	
Hersom et al, 2003[4]	Quintiles Informatics database	Patients who received antidepressants: selective serotonin reuptake inhibitors, secondary and tertiary amine tricyclics, and other antidepressants	Isotretinoin cohort: 0.97 (0.92-1.02) Minocycline cohort: 0.98 (0.95-1.02)	Changes in prescribing patterns
Azoulay et al, 2008[15]	Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Echo) administrative databases	Patients first diagnosed with depression or hospitalized for depression (ICD-9 codes 296.2, 298.0, 300.4, 309.0, 308.1, and 311); patients needed to receive antidepressants in the 30 days following their diagnosis or hospitalization.	Exposure to Isotretinoin (5-month risk vs control period) 2.68 (1.10-6.48)	Nondermatology visit, dermatology visit, at least 1 hospitalization, at least 1 emergency department visit, number of medication other than isotretinoin

CI, Confidence interval; *ICD-9*, International Classification of Diseases-Ninth Revision; *RR*, relative risk.

Supplemental Table III. Detailed data of controlled studies included in the meta-analysis

			Isotretinoin					Controlled			
Study	**Depression scale**	**Follow-up time**	**Isotretinoin cumulative does**	**Age**	**Sex**	**Score**	**SD**	**Age**	**Sex**	**Score**	**SD**
Ng et al, 2002[7]*	BDI	Baseline	0	20.2 (5.8)	102 (58.6)	3.5	4	N/A	17 (41.5)	N/A	N/A
		1 month	N/A			3.4	3.7			N/A	N/A
		3 months	N/A			3.1	3.7			N/A	N/A
		6 months	120 mg/kg			3	3.9			N/A	N/A
Chia et al, 2005[5]	CES-D	Baseline	0	N/A	36 (73.5)	8.1	6.8	N/A	19 (36.5)	9.3	8.7
		3-4 months	90-120 mg/kg			6.6	6.1			8.4	8.1
Bremner et al, 2005[8]†	HRSD	Baseline	0	26 (6)	4 (31)	0.8	1.2	31 (7)	3 (20)	0.5	1.1
		4 months	120 mg/kg			N/A	N/A			N/A	N/A
Cohen et al, 2007[6]†	CES-D	Baseline	N/A	21.5	41 (41)	3	N/A	N/A	25 (25)	3	N/A
		2 months	N/A			N/A	N/A			N/A	N/A
	Zung scale	Baseline	N/A			30	N/A			31.25	N/A
		2 months	N/A			N/A	N/A			N/A	N/A
Kaymak et al, 2009[30]	BDI	Baseline	0	20.61 (1.87)	11 (30.6)	9.77	6.62	20.51 (2.01)	9 (31.0)	9.2	7.52
		2 months	30-48 mg/kg			7.55	6.27			10.6	6.07
		4 months	60-96 mg/kg			5.86	5.16			10.6	5.49
	HADS-D	Baseline	0			5.33	3.51			5.27	3.3
		2 months	30-48 mg/kg			4.44	3			6.27	3.48
		4 months	60-96 mg/kg			3.41	3.08			6.31	3.23
Simic et al, 2009[46]‡	BDI	Baseline	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		8 weeks	56 mg/kg			4.75	5.21			5.79	5.83
		After 4 weeks	N/A			4.78	5.65			5.83	5.1
McGrath et al, 2010[47]	CES-D	Baseline	0	19.8 (3.8)§	45 (69.2)§	10.46	8.56	19.3 (3.9)§	16 (51.6)§	11.16	9.15
		3 months	84 mg/kg			8.08	7.06			7.89	7.42
Suarez et al, 2016[32]	Zung scale	Baseline	0	21.5	20 (55.6)	35.2	1.3	23.17	13 (54.2)	34.9	1.6
		6 weeks	1260 mg			33.8	1.4			34.6	1.7
		12 weeks	2520 mg			34.2	1.4			35	1.7
	GeDepr scale	Baseline	0			38.3	2.5			36.9	3.1
		6 weeks	1260 mg			38.1	2.3			34.9	2.9
		12 weeks	2520 mg			36.8	2.3			34.9	2.9

Age presented as mean (SD) and sex presented as male patients (%) except in the study of Cohen et al, in which the age and scores presented as median.
BDI, Beck Depression Inventory; *CES-D*, Center for Epidemiological Studies Depression; *HADS-D*, Hospital Anxiety Depression Scale-Depression; *HRSD*, Hamilton Rating Scale for Depression; *N/A*, not available; *SD*, standard deviation.
*Study did not provide enough controlled group data, so pooled analysis was performed with other open-label studies.
†Study did not provide enough data, so it was not included in the pooled analysis.
‡Study lacked the baseline depression score, so it could only be included in pooled meta-analysis of controlled studies.
§In this study, the age and proportion of male patients were collected before treatment but not after treatment.

Supplemental Table IV. Detailed data of noncontrolled studies included in the meta-analysis

Study	Age	Sex	Follow-up time	Isotretinoin cumulative does	Depression scale	Score	SD
Rubinow et al, 1987[12]	21.1 (4.7)*	64 (88.9)*	Baseline	0	HSCL	1.48	0.06
			4 months	28/56/77 mg/kg		1.5	0.06
			Baseline	0	POMS	8.71	1.11
			4 months	28/56/77 mg/kg		8.21	1.33
			Baseline	0	MS	12.82	0.56
			4 months	28/56/77 mg/kg		12.61	0.6
Kellett et al, 1999[10]	24.0 (5.0)*	19 (55.9)*	Baseline	0	HADS-D	6.06	4.16
			16 weeks	112 mg/kg		4.6	3.06
Schulpis et al, 1999[13]	17.5 (1.9)	20 (52.6)	Baseline	0	HSCL	1.52	0.07
			1 month	15 mg/kg		1.45	0.06
			Baseline	0	POMS	9.8	1.3
			1 month	15 mg/kg		9.2	1.6
			Baseline	0	MS	13.0	0.6
			1 month	15 mg/kg		13.0	0.7
Strauss et al, 2001[14]	N/A	N/A	Baseline	0	BDI-II	3.6	4.5
			20 weeks	129.2 mg/kg		1.9	4.7
Kellett et al, 2005[11]	24.91 (6.05)*	21 (63.6)*	Baseline	0	BDI	13.29	14.82
			8 weeks	56 mg/kg		10.35	12.64
			16 weeks	112 mg/kg		10.11	12.64
Kaymak et al, 2006[9]	24.2	42 (42.0)	Baseline	0	HRSD	4.1	3.4
			3 months	67.5-90 mg/kg		5.8	3.2
			6 months	100 mg/kg		4	2.5
Hahm et al, 2009[19†]	23	11 (28.9)	Baseline	0	BDI	7.3	N/A
			2 weeks	7-14 mg/kg		N/A	N/A
			8 weeks	28-56 mg/kg		N/A	N/A
Ferahbas et al, 2009[48]	20.26 (2.09)	13 (56.5)	Baseline	0	MADRS	4.6	3.08
			16 weeks	56-112 mg/kg		3.65	2.7
Bozdag et al, 2009[35]	20.4 (3.7)	24 (48.0)	Baseline	0	BDI	10.94	8.4
			4 weeks	28 mg/kg		7.14	5.1
			16 weeks	112 mg/kg		6.8	4.5
Rehn et al, 2009[22]	20 (0.884)*	135 (100)	Baseline	0	BDI	3	3.948
			4-6 weeks	14-21 mg/kg		2	3.589
			10-12 weeks	35-42 mg/kg		1.8	3.783
Ergun et al, 2011[17]	21.71 (4.2)*	17 (27.0)*	Baseline	0	HADS-D	4.1	3.1
			1 month	15 mg/kg		4.2	2.9
			4-5 months	130-150 mg/kg		2.7	2.4
Yesilova et al, 2012[23]	22.5 (4.2)	12 (36.4)	Baseline	0	HADS-D	14.9	5.7
			6 months	120 mg/kg		9.4	5.5
Ormerod et al, 2012[49]	22.29 (5.15)*	13 (76.5)*	Baseline	0	BDI	3.76	3.36
			3 months	45-90 mg/kg		5.76	4.19
Nevoralova et al, 2013[21†]	18.1	71 (71.0)	Baseline	0	BDI-II	4.53	N/A
			1 month			3.12	N/A
			4 months			3.31	N/A
			7 months			2.57	N/A
			9 months	110-150 mg/kg		2.35	N/A
Fakour et al, 2014[50]	22 (4.4)	38 (38.8)	Baseline	0	BDI	15.53	10.65
			16 weeks	56 mg/kg		18.23	10.98
Gnanarai et al, 2015[18]	20.71 (3.2)	94 (65.7)	Baseline	0	HRSD	3.89	4.9
			3 months	45 mg/kg		0.45	1.12
			6 months[‡]	45 mg/kg		0.18	0.51

Age presented as mean (SD) and sex presented as male patients (%).

BDI, Beck Depression Inventory; *BDI-II*, Beck Depression Inventory-Version II; *HADS-D*, Hospital Anxiety Depression Scale-Depression; *HRSD*, Hamilton Rating Scale for Depression; *HSCL*, Hopkins Symptoms Checklist; *MADRS*, Montgomery–Åsberg Depression Rating Scale; *MS*, National Institute of Mental Health Mood Scale; *N/A*, not available; *POMS*, Profile of Mood States Scale; *SD*, standard deviation.

*In this study, the age and proportion of male patients were collected before treatment but not at the end of the study.

†Study did not provide enough data, so it was not include in pooled analysis.

‡This follow-up time is after treatment for 3 months.

Supplemental Table V. The scales for depression evaluation used in the included studies

Scale	Scale description	Cut-off points
BDI[S1,S2]	A patient reporting instrument including 21 groups of 4 statements, in which patients are asked to select the statement that most clearly describes the way they felt in the previous week. The scores are used for measuring symptoms of depression.	1. Scores ≥10 indicate mild depression. 2. Scores 0-13 indicate minimal, 14-19 mild, 20-28 moderate, and 29-63 severe depression.
CESD[S3]	It consists of 20 items, addressing depression symptoms across 4 dimensions of depressed affect. It is a self-reported scale, and participants indicate how often they experienced each symptom in the preceding week.	Scores range from 0 to 60, where scores >16 indicate depression.
HADS[S4]	A self-administrated screening scale for symptoms of anxiety and depression. There are 14 questions: 7 refer to symptoms of anxiety and 7 refer to depression. The intensity and frequency of symptoms is evaluated on a 4-point Likert scale (range 0-3), with differing response formulations.	The range of scores is 0-21 for each subscale and 0-42 for the global result. The cut-off point of ≥11 was used to identify a clinical case and 8-10 to identify a probable case.
HRSD[S5]	This scale gives a rating of depression and changes in violent behavior of the patient. There are 17 questions, which are rated from 0 to 4.	0-13 points: no depression, 14-27 points: mild depression, 28-41 points: moderate depression, 42-53 points: severe depression
HSCL[S6]	A 58-item questionnaire scored on 5 symptom dimensions. Eleven items contribute to the depression subscale. The intensity and frequency of symptoms is evaluated on a 4-point scale (1-4).	
GeDepr scale[S7]	A continuous scale corresponding to the previously mentioned Zung scale plus the following 2 scales for continuous quantification of depression and anxiety levels. The Ge-Depr scale has 2 factors consisting of 16 depression-related items. Scored with a 6-point Likert type scale from 0 (complete disagreement) to 6 (complete agreement) and no neutral score.	No cut-off points
MADRS[S8]	A widely used scale that was designed specifically to measure some of the most important symptoms of a depressive disorder. It includes 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimism, and suicidal thoughts), each of which is scored from 0 to 6.	Ratings can be added to form an overall score (range 0-60); no weights are used. Cut-off points include: 0-6 (symptoms absent), 7-19 (mild depression), 30-34 (moderate depression), and 35-60 (severe depression).
MS[S9]	A 53-item questionnaire producing an 8-factor score.	
POMS[S10]	A 65-item questionnaire generating a 6-factor score. Fifteen items contributed to the depression subscale. The intensity and frequency of symptoms is evaluated on a 5-point scale (0-4) with score range 0-60.	
Zung scale[S11]	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 nondepressed or nonanxious when scoring <50 points or slightly, moderately, or severely depressed or anxious when scoring 50-59, 60-69, and ≥70 points, respectively.

Scales are enumerated S1-S11.

BDI, Beck Depression Inventory; *CES-D*, Center for Epidemiological Studies Depression; *HADS-D*, Hospital Anxiety Depression Scale-Depression; *HRSD*, Hamilton Rating Scale for Depression; *HSCL*, Hopkins Symptoms Checklist; *MADRS*, Montgomery–Åsberg Depression Rating Scale; *MS*, National Institute of Mental Health Mood Scale; *POMS*, Profile of Mood States Scale.