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Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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ABSTRACT

Objectives: Oral isotretinoin is the first-line treatment of severe acne vulgaris, while isotretinoin may associate with depressive disorders risk. The purpose of this study was to investigate the association between the use of isotretinoin and risk of depression in patients with acne vulgaris.

Design: meta-analysis**.** The standardized mean difference (SMD) and the relative risk (RR) were used employed for data synthesis by using random-effects model.**Setting:** Studies were identified by electronic searches of PubMed, Embase, and the Cochrane Library up to December 2017.

Participants: acne patients.

Interventions: Studies comparing isotretinoin with other interventions in acne patients were included.

Results: Twenty studies were selected. The analysis of 17 studies showed that the use of isotretinoin was significantly associated with improved symptoms measured on the depression scales compared with the baseline before treatment [SMD = −0.33, 95% confidence interval(CI) −0.51 to −0.15, $P< 0.05$; $I^2 = 76.6\%$, $P< 0.05$)]. Four studies were related to the analysis of the risk of depression, and the pooled data indicated the use of isotretinoin was not associated with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, $P = 0.14$). Further, the risk of depressive disorders was increased when pooled retrospective studies (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$), but the use of isotretinoin

has no significant effect on the risk of depressive disorders when pooled prospective studies (RR = 0.85, 95% CI 0.60–2.21, *P* = 0.86).

Conclusions: The findings of this study suggested acne patients received isotretinoin was associated with significantly improved depression symptoms. However, it may play an important role on the progression of depression. Future randomized controlled trials are needed to verify the present findings.

Strengths and limitations of this study

1. Most included studies were prospectively designed, and the quality of included studies was largely moderate to high.
2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
3. The small sample sizes of some included studies might have limited the statistical power and increased the chance of missing small effects.
4. No RCT was available so far, which was a major drawback for studies on this topic.
5. The treatment duration, drug dose, and depression scale varied between different studies.

Keywords: acne; depression; isotretinoin; meta-analysis

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back [1]. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules) [2]. It is the most common skin disease around the world, with an estimated prevalence of 70%–87% [3]. The economic burden of acne was substantial. The cost is estimated to exceed $1 billion per year in the United States for direct acne therapy, with $100 million spent on various acne products [4]. Acne vulgaris may cause cosmetic defects and significantly impact on the quality of life [5]. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social-phobia, and even suicide attempts [6].

The optimal treatment approach is dependent on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice [1, 2, 4, 7]. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects [2, 7, 8]. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months [9].

Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of major depressive disordersin the United States and Western Europe is around 13%–16% [10]. The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11% [11]. Theoretically, effective treatment may lead to an improvement in depressive symptoms of acne patients. However, the use of systemic isotretinoin itself may potentially increase the risk of depression [12]. Experimental studies showed that isotretinoin could affect the central nervous system and was involved in the pathogenesis of depression [13]. However, some researchers disputed that the risk was extremely small and might be influenced by the background risk or nondrug confounding factors [12]. The evidence for this controversy remained incomplete and unclear. Therefore, this systematic review and meta-analysis was performed to explore the association between the use of isotretinoin and risk of depression among acne patients. Further, whether this relationship is differing in patients with specific characteristics were also performed.

METHODS

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was followed to conduct this meta-analysis [14]. A literature searches up to December 2017 was performed, using PubMed, Embase, and the Cochrane Library. The following groups of keywords were used in our search: (“depression” OR “depressive”) AND “acne” AND “isotretinoin.” Also, the manual search of references listed in included studies and published

reviews were also performed to search for potentially eligible studies. The language was restricted to English.

Selection criteria

Studies were included if they fulfilled the following criteria: (1) being randomized controlled trial (RCT), prospective or retrospective study, nested case–control study, or population-based case–control study; (2) comparing the outcomes before and after the use of isotretinoin in acne patients; or comparing isotretinoin with other treatment regimens in patients with acne; (3) presenting the change in depressive symptoms measured by a continuous depression scale [15]; or reporting the number of depressive patients before and after the use of isotretinoin; or directly presenting the relative risk (RR), odds ratio (OR), or hazard ratio (HR) between the use of isotretinoin and risk of depression.

Data extraction and quality assessment

Two authors independently assessed the titles and abstracts for eligibility and extracted data in standardized electronic tables. The following data were extracted from included studies: publication year, author, study design, sample size, participant sex and age, severity of acne, compared groups, dose and duration of isotretinoin, and depression assessment tool. The quality of included studies was assessed by the 9-star Newcastle–Ottawa Scale. This scale evaluated the study quality based on three parameters: selection, comparability, and exposure (case–control study) or outcome (cohort study). A maximum of 4 points was assigned for the item of selection, 2 points for comparability, and 3 points for

exposure/outcome [16]. Studies were deemed as high quality for a score of 8–9, moderate quality for a score of 6–7, and low quality for a score ≤5.

Statistical analysis

The continuous outcome of interest was the alteration in depressive symptoms assessed by a continuous depression scale after the use of isotretinoin. For the continuous parameter of depression score, the mean and standard difference (SD) of the score was extracted. The standard mean difference (SMD) was used as the outcome measure. The SMD was a unitless effect size estimate, which was the mean difference in the depression score between the compared groups divided by the pooled SD of the distribution of the score used in the study. The conversion of median (range/ interquartile range) to mean ± SD was done by a previously proposed method [17]. The binary outcome of interest was the number of participants whose conditions were regarded as depression. RR and its corresponding 95% confidential interval (CI) were used as the outcome measure. HR was regarded as equivalent to RR in cohort studies. Given the overall low incidence of depression among the general population, OR was assumed to be an accurate estimate of RR. It was preferred to use the effect measures that reflected the greatest degree control for confounding factors. Both adjusted and crude data were analyzed. When data on different subgroups were reported by the same cohort, they were first pooled by the fixed-effects model. As the random-effects model was more robust than the fixed-effects model, the DerSimonian–Laird random-effects model was used to calculate the overall effect estimates for the association between the use of isotretinoin and risk of depression [18]. The heterogeneity was

evaluated by the Cochrane Q test and the I^2 statistic. Heterogeneity was considered low, moderate, or high for I^2<25%, 25%–50%, and >50%, respectively [19, 20]. Subgroup analyses were conducted based on the following confounders: region, study design, sample size, female percentage, and depression scale. Furthermore, meta-regression analyses were performed for the continuous confounders of sample size and female percentage. A sensitivity analysis was conducted by excluding a single study at a time. Also, a sensitivity analysis was conducted using the weighted mean difference (WMD) as the effect estimate for studies employing the same depression symptom scale. The publication bias was visually assessed by the construction of funnel plot and statistically assessed by the Begg and Egger regression asymmetry tests [21, 22]. All statistical analyses were conducted using the software Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Study selection

A total of 632 records were retrieved from the electronic search, including 145 studies from PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After screened by titles and abstracts. Five hundred and seventy-one were excluded with the following reasons: reviews, editorials, case reports, or irrelevant studies, leaving 61 studies for full-text review. Nine cross-sectional studies, 19 studies without sufficient data, and 13 studies were review, editorial, or comments were excluded. Finally, 20 studies were pooled

into the meta-analysis [23-43]. A flow diagram of the study selection process is depicted in Figure. 1.

Study characteristics

The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two independent cohorts [24], which were analyzed separately. Except for two retrospective studies identifying depressive patients by the International Classification of Diseases code [24, 31], other studies were prospectively designed, and depression was assessed by depression symptom scales. The number of participants using isotretinoin ranged from 16 to 7195. The enrolled acne patients were distributed around the world, including 14 cohorts from Europe, 3 from North America, 3 from Asia, and 1 from Africa. The percentage of female patients ranged from 0% to 73%. Most studies compared data before and after the use of isotretinoin, except for two studies. Simic et al. compared isotretinoin with vitamin C [35]. Azoulay et al. compared isotretinoin users with nonusers [31]. Most studies prescribed isotretinoin for moderate-to-severe acne patients. The dose of isotretinoin ranged largely from 0.5 to 1.0 mg/(kg·d). The duration of the use of isotretinoin ranged from around 1 month to about half a year. The quality of included studies is shown in Supplemental 1. Most studies had satisfying high quality. The item satisfied least was the adjustment of the confounding factors.

Change in depression symptom scores after treatment

Seventeen studies reported the depression symptom scores before and after the use of isotretinoin. All studies were prospectively designed. Simic et al. (2009) presented data for

moderate and severe acne [35]. Fakour et al. showed data for males and females separately [37]. Kaymak et al. reported depression scores measured by Beck Depression Inventory (BDI) and hospital anxiety and depression scale-depression (HADS-D) scales [33]. These subgroup data were all pooled into the overall analysis. Compared with the baseline condition before therapy, the use of isotretinoin was associated with significant improvement in depressive symptoms (SMD = −0.33, 95% CI −0.51 to −0.15, $P< 0.05$) (Figure. 2). Highly significant heterogeneity was revealed ($I^2 = 76.6\%$, $P< 0.05$).

In the sensitivity analysis, the overall effect was not substantially altered when excluding any single study. In the meta-regression analysis, the number of included participants ($P = 0.995$) and the female proportion ($P = 0.56$) did not account for the source of heterogeneity. Data on subgroup analyses are shown in Table 2. The pooled effect estimate remained significant for 14 European studies (SMD = −0.35, 95% CI −0.51 to −0.19, $P< 0.05$), with moderate heterogeneity ($I^2 = 46.3\%$). However, the analysis of three Asian studies did not show significant result (SMD = −0.18, 95% CI−0.81 to 0.45, $P = 0.57$; $I^2 = 94.4\%$). Only 1 study conducted in North America and Africa, respectively. We noted the use of isotretinoin has no significant effect on depressive symptoms in North America (SMD = -0.23, 95%CI -0.59 to 0.13; P=0.21), while it could improve depressive symptoms in Africa (SMD = -0.74, 95%CI -1.22 to -0.26, $P< 0.05$). The pooled results remained significant for studies using HADS-D (SMD = −0.57, 95% CI −0.83 to −0.31, $P< 0.25$; $I^2 = 27.2\%$), and those using the Center for Epidemiological Studies Depression scale (CES-D) (SMD = −0.27, 95% CI −0.52 to −0.02, $P< 0.05$; $I^2 = 0\%$). However, the pooled effect turned to be

non-significant for studies using the BDI scale (SMD = −0.15, 95% CI −0.36 to 0.06, P = 0.17; I^2 = 62.4%) and those using theHamilton Rating Scale (HRS) (SMD = −0.55, 95% CI −1.56 to 0.46, P = 0.29; I^2 = 96.6%). The pooled effects were significant for both studies of smaller sample size (SMD = −0.38, 95% CI −0.65 to −0.12, P< 0.05) and those with larger sample size (SMD = −0.29, 95% CI −0.54 to −0.04, P< 0.05). Results for different proportions of females did not show a significant difference. The funnel plot appeared to be symmetrical (Figure. 3). No publication bias was revealed by the Egger's test (P = 0.76) or by the Begg test (P = 0.87).

Also, the sensitivity analysis was performed by pooling the WMD for studies using the same scale. The pooled results were non-significant for studies using the BDI scale (WMD = −0.84, 95% CI −2.05 to 0.38, P = 0.18; I^2 = 62.2%, P< 0.05) (Figure. 4), and those using HRS (WMD = −1.91, 95% CI −5.44 to 1.63, P = 0.29; I^2 = 97.3%, P< 0.05). In contrast, the pooled WMDs were significant for studies using HADS-D (WMD = −2.06, 95% CI −3.42 to −0.70, P< 0.05; I^2 = 66.0%, P< 0.05), studies using CES-D (WMD = −1.88, 95% CI −3.64 to −0.11, P< 0.05; I^2 =0%, P = 0.63).

Use of Isotretinoin and risk of depression

Two retrospective studies showed the adjusted RR for the association between the use of isotretinoin and risk of depression [24, 31]. Jick et al. presented data for two independent cohorts. The overall result of three cohorts showed that the use of isotretinoin was associated with an increased risk of depression (RR = 1.39, 95% CI 1.05–1.84, P = 0.02; Figure. 5), and no significant heterogeneity was shown (I^2 = 0.0%, P = 0.50). However,

there was no significant difference for the relationship between isotreinoin use and the risk of depression when pooled two prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$; Figure. 5), and substantial heterogeneity was observed ($I^2 = 61.4\%$, $P = 0.11$). The funnel plot appeared to be symmetrical (Figure. 6), and the Egger's test ($P = 0.76$) or the Begg test ($P = 1.00$) suggested no evidence of potential publication bias.

DISCUSSION

The risk of depression associated with the use of isotretinoin in patients with acne has been a major concern for a long time. Previous data showed conflicting and inconsistent results. Two previous systematic reviews on similar topic were detected [13, 44]. Although comprehensive scenarios were presented, they failed in conducting data synthesis to obtain pooled results. This meta-analysis that assessed the association between the use of isotretinoin and risk of depression. It had several strengths as follows. A comprehensive database search of worldwide cohorts was conducted, enrolling a large number of participants. The quality of included studies was largely moderate to high. Most included studies were prospectively designed. The association was investigated in several aspects. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses. The present findings showed that isotretinoin was beneficial rather than harmful for the improvement in depressive symptoms for acne patients (SMD = −0.33, $P< 0.05$). When employing WMD as the effect estimate to assess studies using the same depression scale, the benefit remained marked for studies using HADS-D and CES-D. Although no

statistically significant data were shown for studies of BDI scale or HRS, the pooled WMD was in favor of patients after the use of isotretinoin. In risk assessment, the summary RR showed that the use of isotretinoin increased the risk of depression for patients with acne when pooled retrospective studies, while this increased risk was not observed in prospective studies.

Vallerand conducted a systematic review based on 11 trials to evaluate the efficacy and safety of oral isotretinoin for acne, they point oral isotretinoin significantly reduced acne lesion counts, while greater number of psychiatric adverse events (Depressed mood, fatigue, hallucination, insomnia, lethargy) was found (32 versus 19). However, this study was not provided the result by data synthesis [45]. Further, Huang et al conducted a meta-analysis based on 31 studies and suggested the use of isotretinoin was not affected the incidence of depression. Further, they point out the treatment of acne could ameliorate depressive symptoms. However, the study summary the investigated outcomes just stratified by depression assessment tool, whether these relationships are differing according to region, study design, sample size, and female percentage were not illustrated [46] . We therefore conducted this comprehensive, quantitative synthesis based on available studies to evaluate any potential impact of the use of isotretinoin on the outcomes of depression incidence and change in the depression score.

The concern for negative mood may arise from a series of experimental studies. Oral isotretinoin significantly suppressed cell division in the hippocampus and severely disrupted the learning capacity of mice [47]. Bremner et al. found that isotretinoin, but not antibiotics,

was associated with decreased brain metabolism in the orbitofrontal cortex, which was known to mediate depression symptoms [48]. O'Reilly et al. proved that isotretinoin altered intracellular serotonin, increased 5-HT1A receptor, and serotonin reuptake transporter levels *in vitro* [49]. Thus, theoretically, isotretinoin itself may cause depressive disorders. However, the potentially increased risk of depression could be compensated by the treatment effects of isotretinoin for acne patients. Most acne patients were worried about their appearances, which might lead to a series of psychological disorders.It was inferred that the improvement in depression symptoms after the use of isotretinoin might be attributed to the treatment success. Also, isotretinoin had a gradual effect on mood over time, which was not an acute event [50].

Of note, the controversy over this topic was complicated by various confounding psychosocial and clinical factors. Aktan et al. suggested that adolescent girls were more vulnerable compared with boys to the negative psychological effects of acne [51]. Women with acne were significantly more embarrassed compared with males about their skin disease. A large database study showed that female gender and acne could jointly increase the risk of depression [52]. However, the role of gender was not revealed in meta-regression and subgroup analyses. Acne itself can exert different impacts on individual patients. The lack of knowledge, especially about prognosis, may be a source of depression [24, 53]. Approximately one-fifth of acne patients suffered from psychiatric disorders [33]. Better health education and care were important components for treating acne patients. They help eliminate the patients' misconceptions about the disease and unrealistic treatment

expectations [54]. The psychological interventions may vary between different clinical settings and lead to a bias for the effect of isotretinoin. Besides, data on the efficacy or side effect of the use of isotretinoin were insufficient in most included studies. Isotretinoin may cause teratogenic toxicity. Contraceptives are recommended for female users of fertile age to prevent pregnancy until the completion of treatment [41]. The levels of blood cholesterol and liver enzymes may be abnormal and should be monitored during the treatment phase [55]. Several shortcomings regarding this meta-analysis should be explained. The sample sizes of some included studies were still small, which might have limited the statistical power and increased the chance of missing small effects. Cohort studies may have a bias caused by participant selection and confounding factors. Most studies compared the before- and after-treatment data. Ideally, RCTs comparing isotretinoin with placebo or other agents may provide more robust findings. However, leaving moderate-to-severe acne patients without the use of isotretinoin maybe unfair and even not ethical. However, no RCT was available so far, which was a major drawback for studies on this topic. Additionally, the treatment duration, drug dose, and depression scale varied between different studies. The acne severity or the dose of isotretinoin varied and was not reported by several studies. Patients with severe acne or scars or those unresponsive to therapy may have a worse depressive mood. However, the analyses for these confounding factors were insufficient in most studies. Approximately one-fifth of acne patients suffered from psychiatric disorders [33]. Also, some studies were sponsored by corporations [24], which might have underestimated the incidence of depressive disorders. Finally, although greater risk of depression was founded

in isotretinoin used if pooled retrospective studies, whereas selection and recall biases might affect the incidence of depression. Further, these conclusions may be unreliable since smaller cohorts were included in such subsets.

This meta-analysis showed that patients may have improved depressive symptoms after the use of isotretinoin. Psychologists are encouraged to participate in the management of acne patients. Further, the use of isotretinoin in acne patients did not contribute the development of depression. While the summary results of retrospective suggested the use of isotretinoin in acne patients might increase risk of depression. Future prospective controlled trials are warranted to verify the present findings.

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Author's contribution

CQL and LK contributed to conception and design; CQL, JMC, WW, MA, QZ and LK contributed to acquisition of data, or analysis and interpretation of data; CQL, JMC, WW, MA, QZ and LK have been involved in drafting the manuscript or revising it critically for

important intellectual content; all authors have given final approval of the version to be published.

A data sharing statement

No additional data are available.

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Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before vs. after	1.0 mg/(kg · d)	4 months	HADS-D
Jick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before vs. after	40 mg (86%)	3–6 months (62%)	ICD code
Jick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before vs. after	20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before vs. after	0.8–1.0 mg/(kg · d)	6 months	BDI
Ferahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before vs. after	0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before vs. after	1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before vs. after	0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before vs. after	1.0 mg/(kg · d)	3–4 months	CES-D
Azoulay et al. (2008)	Canada	Retrospective	126	28	53	NA	Users vs. nonusers	NA	5 months	ICD code
Kaymak et al. (2009)	Turkey	Prospective	37	21	69	Mild to severe	Before vs. after	0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D
Bozdag et al. (2009)	Turkey	Prospective	50	20	52	Moderate to severe	Before vs. after	1.0 mg/(kg · d)	4 months	BDI

Rehn et al. (2009)	Finland	Prospective	126	20	0	Moderate to severe	Before vs. after	0.5 mg/(kg · d)	3 months	BDI
Simic et al. (2009)	Bosnia and Herzegovina	Prospective	85	19	34	Moderate to severe	Isotretinoin vs. vitamin C	1.0 mg/(kg · d)	2 months	BDI
McGrath et al. (2010)	UK	Prospective	65	20	31	Mean AGS score 3.3	Before vs. after	0.5–1.0 mg/(kg · d)	3 months	CES-D
Ergun et al. (2012)	Turkey	Prospective	65	22	73	Severe or resistant	Before vs. after	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D
Ormerod et al. (2012)	UK	Prospective	16	22	25	Severe	Before vs. after	0.5–1.0 mg/(kg · d)	3–6 months	BDI
Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to severe	Before vs. after	0.5–1.0 mg/(kg · d)	6 months	HADS-D
Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before vs. after	Total: 120 mg/kg	7 months	HADS-D
Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before vs. after	0.5 mg/(kg · d)	4 months	BDI
Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate to severe	Before vs. after	0.5 mg/(kg · d)	3 months	HRS
Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe (25%)	Before vs. after	30 mg/d	3 months	ZDS

AGS, acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	*P* value	I^2 (*P* value)
Region				
Europe	14	−0.35 (−0.51 to −0.19)	<0.05	46.3% (<0.05)
Asia	3	−0.18 (−0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	−0.23 (−0.59 to 0.13)	0.21	–
Africa	1	−0.74 (−1.22 to −0.26)	<0.05	–
Depression scale				
BDI	10	0.10 (−0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	0.57 (0.31 to 0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02 to 0.52)	<0.05	0% (0.78)
HRS	2	0.55 (−0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (−0.25 to 0.91)	0.27	–
ZDS	1	0.74 (0.26 to 1.22)	<0.05	–
Sample size				
<50	9	−0.38 (−0.65 to −0.12)	<0.05	64.0% (<0.05)
≥50	11	−0.29 (−0.54 to −0.04)	<0.05	83.1% (<0.05)
Percentage of female patients				
<50	12	−0.32 (−0.55 to −0.09)	<0.05	76.8% (<0.05)
≥50	8	−0.34 (−0.04 to −0.64)	<0.05	78.4% (<0.05)

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD, standardized mean difference; ZDS, Zung self-rating depression scale.

Figure legends:

Figure. 1. Study selection process.

Figure. 2. Forest plot showing the standardized mean difference for the comparison of depression symptom scores before and after isotretinoin treatment in acne patients.

Figure. 3. Funnel plot of studies comparing depression symptom scores before and after isotretinoin treatment in acne patients.

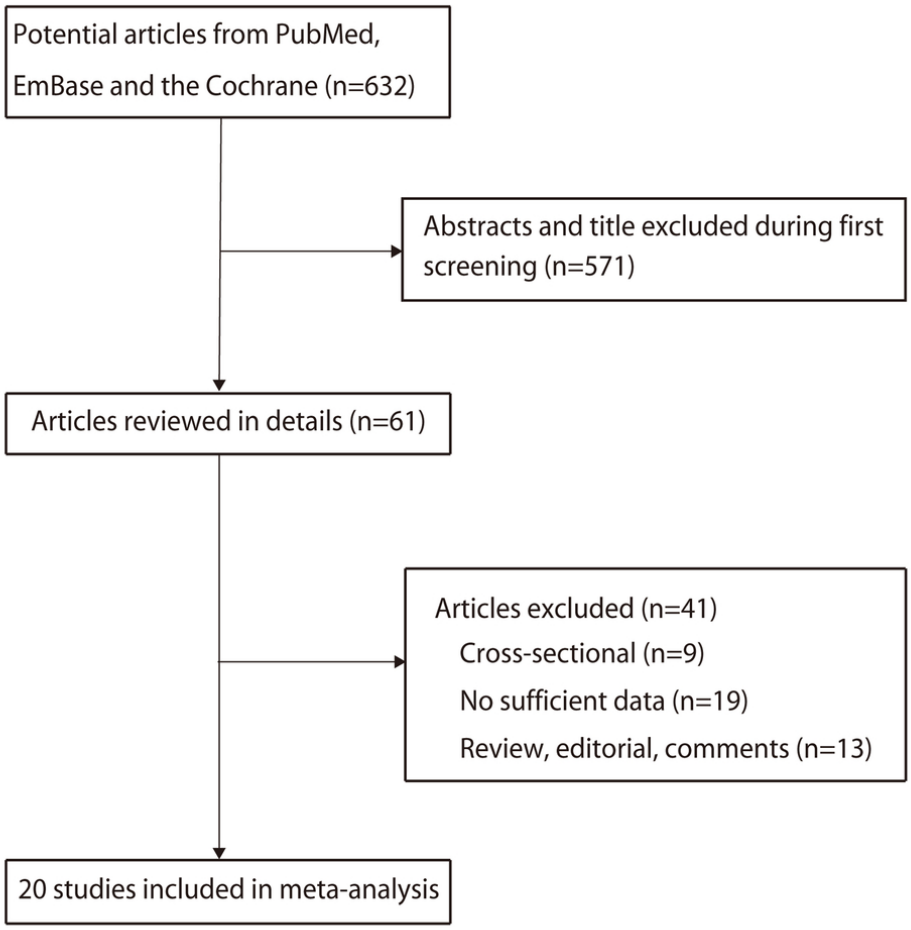
Figure. 4. Forest plot showing the weighted mean difference for the comparison of BDI scores before and after isotretinoin treatment in acne patients.

Figure. 5. Forest plot showing the association between isotretinoin treatment and depression in acne patients.

Figure. 6. Funnel plot of showing the association between isotretinoin treatment and depression in acne patients.

Legends for supporting information

Supplemental Table1. Newcastle–Ottawa scale for quality assessment of included studies



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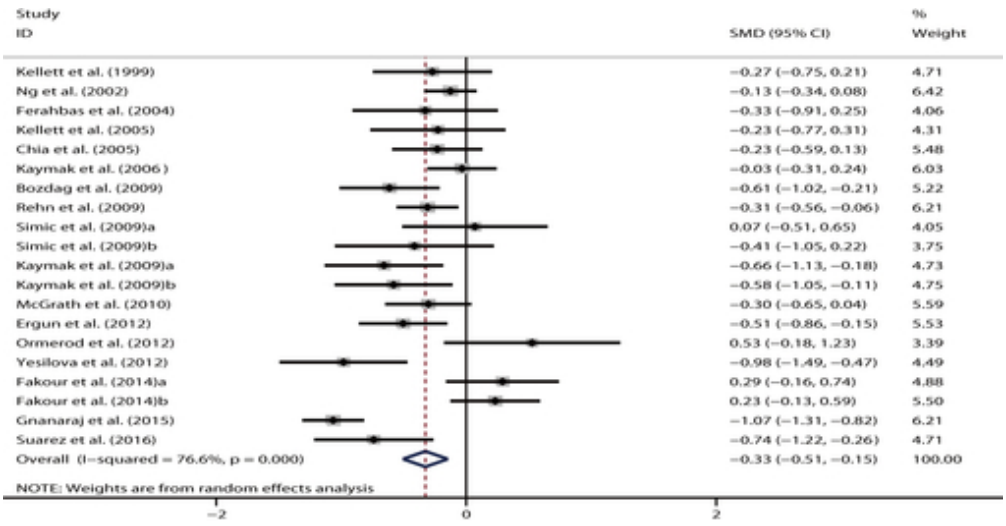

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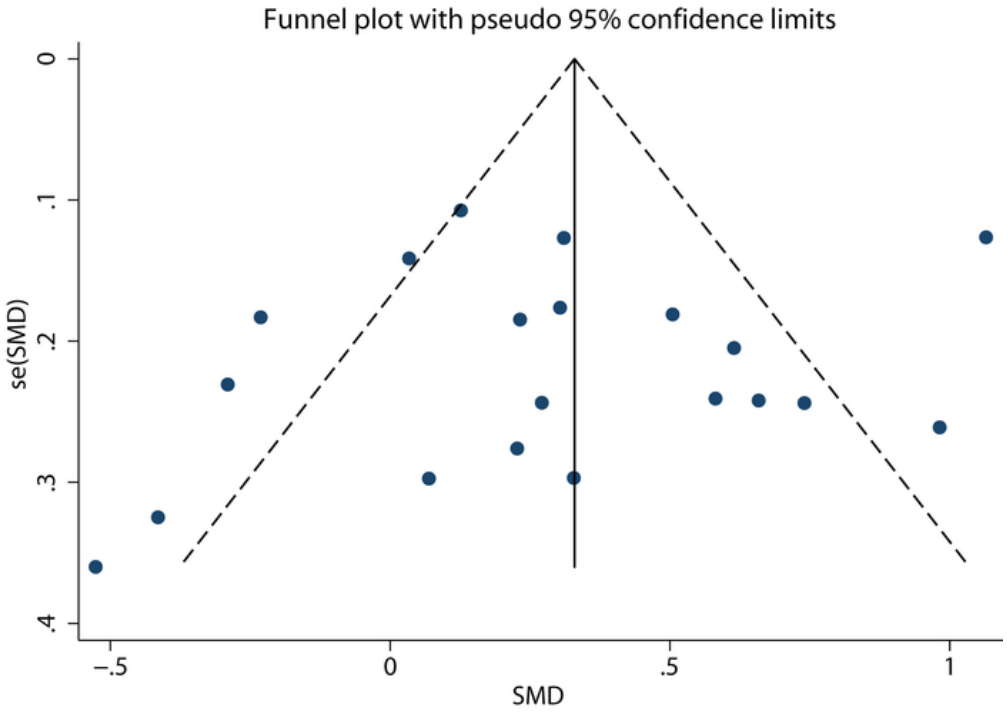

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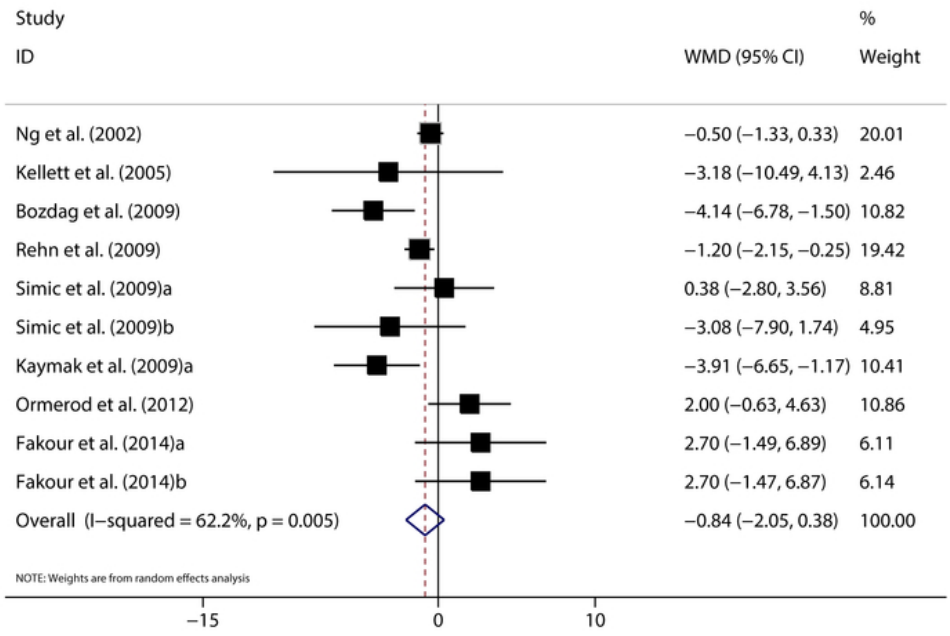

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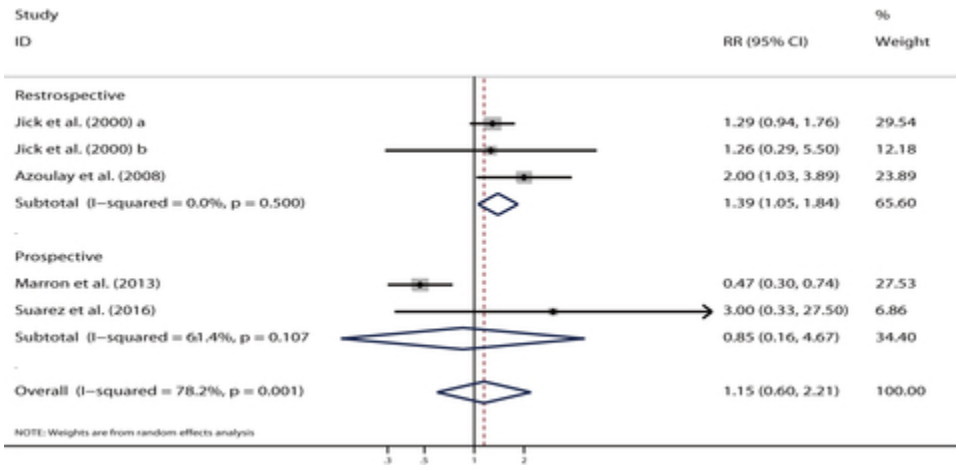

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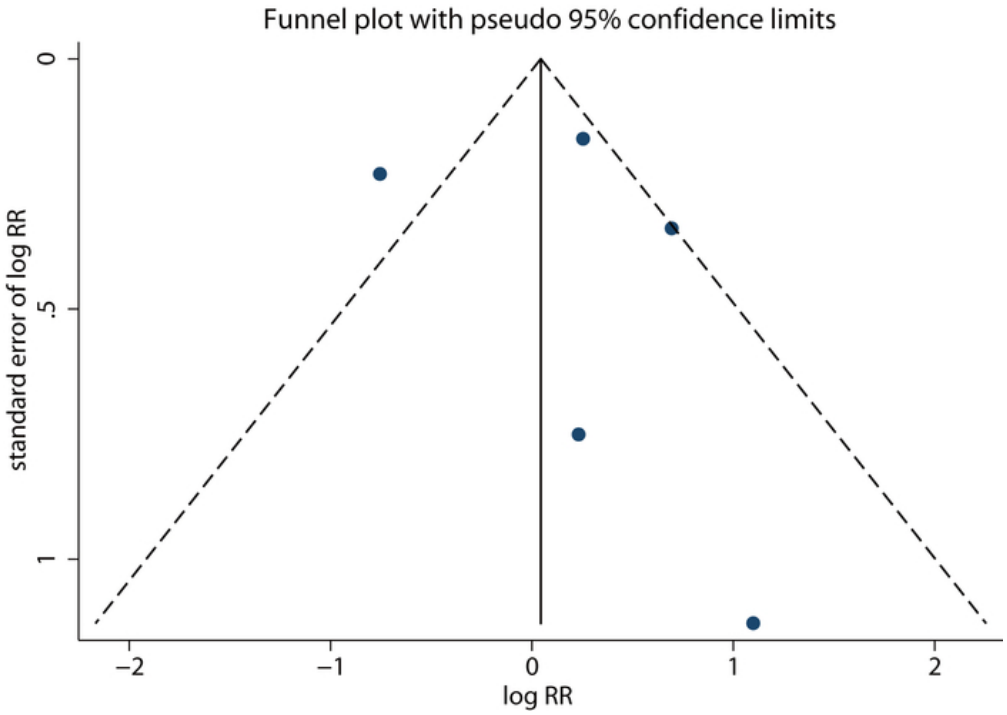

59x41mm (300 x 300 DPI)

Supplementary Table 1 Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdag et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Keywords:	Acne < DERMATOLOGY, Depression & mood disorders < PSYCHIATRY, ORAL MEDICINE

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Running title: Isotretinoin and risk of depression in patients with acne

ABSTRACT

Objective: This study aimed to investigate the association between the use of isotretinoin and the risk of depression in patients with acne.

Design: This was a meta-analysis in which the standardized mean difference (SMD) and the relative risk (RR) were used for data synthesis employed the random-effects model.

Setting: Studies were identified via electronic searches of PubMed, Embase, and the Cochrane Library up to December 28, 2017.

Participants: Patients with acne.

Interventions: Studies comparing isotretinoin with other interventions in patients with acne were included.

Results: Twenty studies were selected. The analysis of 17 studies showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment [SMD = −0.33, 95% confidence interval (CI) −0.51 to −0.15, $P < 0.05$; I^2 = 76.6%, $P < 0.05$)]. Four studies were related to the analysis of the risk of depression. The pooled data indicated no association of the use of isotretinoin with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, P = 0.14). The association of the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR = 1.39, 95% CI 1.05–1.84, P = 0.02), but this association was not evident on pooling prospective studies (RR = 0.85, 95% CI 0.60–2.21, P = 0.86).

Conclusions: This study suggested an association of the use of isotretinoin in patients with acne with significantly improved depression symptoms. Future randomized controlled trials are needed to verify the present findings.

Strengths and limitations of this study

1. Most included studies were prospectively designed, and the quality of included studies was largely moderate to high.
2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
3. The small sample sizes of some included studies might have limited the statistical power and increased the chance of missing small effects.
4. No randomized controlled trial was available so far, which was a major drawback for studies on this topic.
5. The treatment duration, drug dose, and depression scale varied between different studies.

Key words: acne; depression; isotretinoin; meta-analysis

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back [1]. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules) [2]. It is the most common skin disease around the world, with an estimated prevalence of 70%–87% [3]. The economic burden of acne is substantial. The cost is estimated to exceed $1 billion per year in the United States for direct acne therapy, with $100 million spent on various acne products [4]. Acne vulgaris may cause cosmetic defects and significantly impact the quality of life [5]. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social phobia, and even suicidal attempts [6].

The optimal treatment approach depends on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice [1, 2, 4, 7]. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects [2, 7, 8]. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months [9].

Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of major depressive disorders in the United States and Western Europe is around 13%–16% [10]. The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11% [11]. Theoretically, effective treatment may lead to an improvement in depressive symptoms of patients with acne. However, the use of systemic isotretinoin itself may potentially increase the risk of depression [12]. Experimental studies showed that isotretinoin could affect the central nervous system and was involved in the pathogenesis of depression [13]. However, some researchers disputed that the risk was extremely small and might be influenced by the background risk or nondrug confounding factors [12]. The evidence for this controversy remained incomplete and unclear. Therefore, this systematic review and meta-analysis was performed to explore the association between the use of isotretinoin and the risk of depression among patients with acne. Further, whether this relationship differed in patients with specific characteristics was also explored.

METHODS

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was followed to conduct this meta-analysis [14]. A literature search up to December 28, 2017, was performed using PubMed, Embase, and the Cochrane Library. The following groups of keywords were used in the search: ("depression" OR "depressive") AND "acne" AND "isotretinoin." The details of searching strategy in PubMed are presented in Supplemental 1.

Also, a manual search of references listed in included studies and published reviews were also performed to search for potentially eligible studies. The language was restricted to English.

Selection criteria

Studies were included if they fulfilled the following criteria: (1) being randomized controlled trial (RCT), prospective or retrospective study, nested case–control study, or population-based case–control study; (2) comparing the outcomes before and after the use of isotretinoin in patients with acne; or comparing isotretinoin with other treatment regimens in patients with acne; (3) presenting the change in depressive symptoms measured using a continuous depression scale [15]; or reporting the number of depressive patients before and after the use of isotretinoin; or directly presenting the relative risk (RR), odds ratio (OR), or hazard ratio (HR) between the use of isotretinoin and the risk of depression.

Data extraction and quality assessment

Two authors independently assessed the titles and abstracts for eligibility and extracted data in standardized electronic tables. The following data were extracted from included studies: publication year, author, study design, sample size, participant sex and age, severity of acne, compared groups, dose and duration of isotretinoin, and depression assessment tool. The quality of included studies was assessed using the 9-star Newcastle–Ottawa Scale. This scale evaluated the study quality based on three parameters: selection, comparability, and exposure (case–control study) or outcome (cohort study). A maximum of 4 points was assigned for the item of selection, 2 points for comparability, and 3 points for

exposure/outcome [16]. Studies were deemed as high quality for a score of 8–9, moderate quality for a score of 6–7, and low quality for a score ⩽5.

Statistical analysis

The continuous outcome of interest was the alteration in depressive symptoms assessed using a continuous depression scale after the use of isotretinoin. For the continuous parameter of depression score, the means and standard differences (SD) of the scores were extracted. The standard mean difference (SMD) was used as the outcome measure. The SMD was a unitless effect size estimate, which was the mean difference in the depression score between the compared groups divided by the pooled SD of the distribution of the score used in the study. The conversion of median (range/interquartile range) to mean ± SD was done by a previously proposed method [17]. The binary outcome of interest was the number of participants whose conditions were regarded as depression. RR and its corresponding 95% confidence interval (CI) were used as the outcome measure. HR was regarded as equivalent to RR in cohort studies. Given the overall low incidence of depression among the general population, OR was assumed to be an accurate estimate of RR. It was preferred to use the effect measures that reflected the greatest degree control for confounding factors. Both adjusted and crude data were analyzed. When data on different subgroups were reported by the same cohort, they were first pooled using the fixed-effects model. As the random-effects model was more robust than the fixed-effects model, the DerSimonian–Laird random-effects model was used to calculate the overall effect estimates for the association between the use of isotretinoin and the risk of depression [18]. The

heterogeneity was evaluated using the Cochrane Q test and the I^2 statistic. Heterogeneity was considered low, moderate, or high for I^2 <25%, 25%–50%, and >50%, respectively [19, 20]. Subgroup analyses were conducted based on the following confounders: region, study design, sample size, female percentage, and depression scale. Furthermore, meta-regression analyses were performed for the continuous confounders of sample size and female percentage. A sensitivity analysis was conducted by excluding a single study at a time. Also, a sensitivity analysis was conducted using the weighted mean difference (WMD) as the effect estimate for studies employing the same depression symptom scale. The publication bias was visually assessed by constructing a funnel plot and statistically assessed using the Begg's and Egger's regression asymmetry tests [21, 22]. All statistical analyses were conducted using the software Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was considered statistically significant.

Patient and public involvement statement

Patients and the public were not involved

RESULTS

Study selection

A total of 632 records were retrieved from the electronic search, including 145 studies from PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After screening by titles and abstracts, 571 studies were excluded for the following reasons: reviews, editorials, case reports, or irrelevant studies, leaving 61 studies for full-text review.

Nine cross-sectional studies, 19 studies without sufficient data, and 13 review, editorial, or comments were excluded. Finally, 20 studies were pooled into the meta-analysis [23-43]. A flow diagram of the study selection process is depicted in Figure 1.

Study characteristics

The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two independent cohorts [24], which were analyzed separately. Except for two retrospective studies identifying depressive patients using the International Classification of Diseases code [24, 31], other studies were prospectively designed, and depression was assessed using depression symptom scales. The number of participants using isotretinoin ranged from 16 to 7195. The enrolled patients with acne were distributed around the world, including 14 cohorts from Europe, 3 from North America, 3 from Asia, and 1 from Africa. The percentage of female patients ranged from 0% to 73%. Most studies compared data before and after the use of isotretinoin, except for two studies. Simic et al. compared isotretinoin with vitamin C [35]. Azoulay et al. compared isotretinoin users with nonusers [31]. Most studies prescribed isotretinoin for moderate-to-severe acne. The dose of isotretinoin ranged largely from 0.5 to 1.0 mg/(kg · d). The duration of the use of isotretinoin ranged from around 1 month to about half a year. The quality of included studies is shown in Supplemental 2. Most studies had satisfactorily high quality. The least satisfactory item was the adjustment of the confounding factors.

Change in depression symptom scores after treatment

Seventeen studies reported the depression symptom scores before and after the use of isotretinoin. All studies were prospectively designed. Simic et al. (2009) presented data for moderate and severe acne [35]. Fakour et al. showed data for males and females separately [37]. Kaymak et al. reported depression scores measured using Beck Depression Inventory (BDI) and hospital anxiety and depression scale-depression (HADS-D) scales [33]. These subgroup data were all pooled into the overall analysis. Compared with the baseline condition before therapy, the use of isotretinoin was associated with a significant improvement in depressive symptoms (SMD = −0.33, 95% CI −0.51 to −0.15, $P < 0.05$) (Fig. 2). Highly significant heterogeneity was revealed ($I^2 = 76.6\%$, $P < 0.05$).

In the sensitivity analysis, the overall effect was not substantially altered when excluding any single study. In the meta-regression analysis, the number of included participants ($P = 0.995$) and the female proportion ($P = 0.56$) did not account for the source of heterogeneity. Data on subgroup analyses are shown in Table 2. The pooled effect estimate remained significant for 14 European studies (SMD = −0.35, 95% CI −0.51 to −0.19, $P < 0.05$), with moderate heterogeneity ($I^2 = 46.3\%$). However, the analysis of three Asian studies did not show significant results (SMD = −0.18, 95% CI−0.81 to 0.45, $P = 0.57$; $I^2 = 94.4\%$). The use of isotretinoin had no significant effect on depressive symptoms in North America (SMD = –0.23, 95% CI –0.59 to 0.13; $P = 0.21$), while it was associated with improved depressive symptoms in Africa (SMD = –0.74, 95% CI –1.22 to –0.26, $P < 0.05$). The pooled results remained significant for studies using HADS-D (SMD = −0.57, 95% CI −0.83 to −0.31, $P < 0.25$; $I^2 = 27.2\%$), and those using the Center for Epidemiological

Studies Depression scale (CES-D) (SMD = −0.27, 95% CI −0.52 to −0.02, $P < 0.05$; I^2 = 0%). However, the pooled effect turned to be nonsignificant for studies using the BDI scale (SMD = −0.15, 95% CI −0.36 to 0.06, $P = 0.17$; $I^2 = 62.4\%$) and those using the Hamilton Rating Scale (HRS) (SMD = −0.55, 95% CI −1.56 to 0.46, $P = 0.29$; $I^2 = 96.6\%$). The pooled effects were significant for both studies with a smaller sample size (SMD = −0.38, 95% CI −0.65 to −0.12, $P < 0.05$) and those with a larger sample size (SMD = −0.29, 95% CI −0.54 to −0.04, $P < 0.05$). The results for different proportions of females did not show a significant difference. The funnel plot appeared to be symmetrical (Fig. 3). No publication bias was revealed using the Egger's test ($P = 0.76$) or the Begg's test ($P = 0.87$).

Also, the sensitivity analysis was performed by pooling the WMD for studies using the same scale. The pooled results were nonsignificant for studies using the BDI scale (WMD = −0.84, 95% CI −2.05 to 0.38, $P = 0.18$; $I^2 = 62.2\%$, $P < 0.05$) (Fig. 4) and those using HRS (WMD = −1.91, 95% CI −5.44 to 1.63, $P = 0.29$; $I^2 = 97.3\%$, $P < 0.05$). In contrast, the pooled WMDs were significant for studies using HADS-D (WMD = −2.06, 95% CI −3.42 to −0.70, $P < 0.05$; $I^2 = 66.0\%$, $P < 0.05$) and those using CES-D (WMD = −1.88, 95% CI −3.64 to −0.11, $P < 0.05$; $I^2 = 0\%$, $P = 0.63$).

Use of isotretinoin and risk of depression

Two retrospective studies showed the adjusted RR for the association between the use of isotretinoin and the risk of depression [24, 31]. Jick et al. presented data for two independent cohorts. The overall result of three cohorts showed that the use of isotretinoin was associated with an increased risk of depression (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$;

Fig. 5), and no significant heterogeneity was shown (I^2 = 0.0%, P = 0.50). However, no significant difference was noted in the relationship between isotretinoin use and the risk of depression on pooling two prospective studies (RR = 0.85, 95% CI 0.60–2.21, P = 0.86; Fig. 5), and a substantial heterogeneity was observed (I^2 = 61.4%, P = 0.11). The funnel plot appeared to be symmetrical (Fig. 6), and the Egger's test (P = 0.76) or the Begg's test (P = 1.00) suggested no evidence of potential publication bias.

DISCUSSION

The risk of depression associated with the use of isotretinoin in patients with acne has been a major concern for a long time. Previous data showed conflicting and inconsistent results. This meta-analysis assessed the association between the use of isotretinoin and the risk of depression. It had several strengths as follows. A comprehensive database search of worldwide cohorts was conducted, enrolling a large number of participants. The quality of included studies was largely moderate to high. Most included studies were prospectively designed. The association was investigated from several aspects. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses. The present findings showed that isotretinoin improved in depressive symptoms in patients with acne. The benefit remained marked for studies using HADS-D and CES-D. In risk assessment, the summary RR showed that the use of isotretinoin was associated with an increased risk of depression in patients with acne on pooling retrospective studies, while this significant difference was not observed on pooling prospective studies.

Two previous systematic reviews on this topic were identified [13, 44]. They showed conflicting results, and hence the association between isotretinoin use and depression remained controversial. Further, although comprehensive scenarios were presented, data synthesis to obtain pooled results could not be conducted. Vallerand conducted a systematic review based on 11 trials to evaluate the efficacy and safety of oral isotretinoin for acne. Oral isotretinoin significantly reduced the counts of acne lesions but increased the frequency of psychiatric adverse events (depressed mood, fatigue, hallucination, insomnia, and lethargy; 32 vs 19). However, this study did not provide the result by data synthesis [45]. Further, Huang et al conducted a meta-analysis based on 31 studies and suggested that the use of isotretinoin did not affect the incidence of depression. Further, they showed that the treatment of acne could ameliorate depressive symptoms. However, the study summarized the investigated outcomes using the depression assessment tool. Whether these relationships differed according to the region, study design, sample size, and the female percentage was not illustrated [46]. Therefore, the present study was conducted to evaluate any potential impact of the use of isotretinoin on depression incidence and change in the depression score.

The concern for negative mood arose from a series of experimental studies. Oral isotretinoin significantly suppressed cell division in the hippocampus and severely disrupted the learning capacity of mice [47]. Bremner et al. found that the use of isotretinoin, but not antibiotics, was associated with decreased brain metabolism in the orbitofrontal cortex, which was known to mediate depression symptoms [48]. O'Reilly et al. proved that isotretinoin altered intracellular serotonin level and increased 5-HT1A receptor and

serotonin reuptake transporter levels *in vitro* [49]. Thus, theoretically, isotretinoin itself might cause depressive disorders. However, the potentially increased risk of depression could be compensated by the beneficial effects of isotretinoin on patients with acne. Most patients with acne were worried about their appearances, which might lead to a series of psychological disorders. It was inferred that the improvement in depression symptoms after the use of isotretinoin might be attributed to the treatment success. Also, isotretinoin had a gradual effect on mood over time, which was not an acute event [50].

Of note, the controversy over this topic was complicated by various confounding psychosocial and clinical factors. Aktan et al. suggested that adolescent girls were more vulnerable to the negative psychological effects of acne compared with boys [51]. Women with acne were significantly more embarrassed about their skin disease compared with males. A large database study showed that female gender and acne could jointly increase the risk of depression [52]. However, the role of gender was not revealed in meta-regression and subgroup analyses. Acne itself can exert different impacts on individual patients. The lack of knowledge, especially about prognosis, may be a source of depression [24, 53]. Approximately one fifth of patients with acne suffered from psychiatric disorders [33]. Better health education and care are important components for treating patients with acne. They help eliminate the patients' misconceptions about the disease and unrealistic treatment expectations [54]. The psychological interventions may vary between different clinical settings and lead to a bias in the effect of isotretinoin. Besides, data on the efficacy or side effect of the use of isotretinoin were insufficient in most included studies. Isotretinoin may

cause teratogenic toxicity. Contraceptives are recommended for female users of fertile age to prevent pregnancy until the completion of the treatment [41]. The levels of blood cholesterol and liver enzymes may be abnormal and should be monitored during the treatment phase [55].

This meta-analysis had several shortcomings. The sample sizes of some included studies were still small, which might have limited the statistical power and increased the chance of missing small effects. Cohort studies might have a bias caused by participant selection and confounding factors. Most studies compared the before- and after-treatment data. Ideally, RCTs comparing isotretinoin with placebo or other agents may provide more robust findings. However, leaving patients with moderate-to-severe acne without the use of isotretinoin may be unfair and even not ethical. However, no RCT was available so far, which was a major drawback for studies on this topic. Additionally, the treatment duration, drug dose, and depression scale varied between different studies. The acne severity or the dose of isotretinoin varied and was not reported by several studies. Patients with severe acne or scars or those unresponsive to therapy might have a worse depressive mood. However, the analyses for these confounding factors were insufficient in most studies. Approximately one fifth of patients with acne suffered from psychiatric disorders [33]. Also, some studies were sponsored by corporations [24], which might have underestimated the incidence of depressive disorders. Finally, although a greater risk of depression was associated with the use of isotretinoin on pooling retrospective studies, selection and recall

biases might have affected the incidence of depression. Further, these conclusions might be unreliable because smaller cohorts were included in such subsets.

This meta-analysis showed that patients might have improved depressive symptoms after the use of isotretinoin. Further, the use of isotretinoin in patients with acne did not contribute to the development of depression. However, the summary results of retrospective studies suggested that the use of isotretinoin in patients with acne might increase the risk of depression. Future prospective controlled trials are warranted to verify the present findings.

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Conflicts of interest statement

Not declared.

Author contributions

CQL and LK contributed to conception and design. CQL, JMC, WW, MA, QZ, and LK contributed to data acquisition or analysis and interpretation of data. CQL, JMC, WW, MA, QZ, and LK were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Data sharing statement

No additional data are available.

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Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before vs after	1.0 mg/(kg · d)	4 months	HADS-D
Lick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before vs. after	40 mg (86%)	3–6 months (62%)	ICD code
Lick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before vs after	20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before vs after	0.8–1.0 mg/(kg · d)	6 months	BDI
Perahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before vs after	0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before vs after	0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before vs after	1.0 mg/(kg · d)	3–4 months	CES-D

Azoulay et al. (2008)	Canada	Retrospective	126	28	53	NA	Users vs nonusers	NA	5 months	ICD code
Kaymak et al. (2009)	Turkey	Prospective	37	21	69	Mild to severe	Before vs after	0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D
Bozdag et al. (2009)	Turkey	Prospective	50	20	52	Moderate to severe	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Rehn et al. (2009)	Finland	Prospective	126	20	0	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	BDI
Simic et al. (2009)	Bosnia and Herzegovina	Prospective	85	19	34	Moderate to severe	Isotretinoin vs vitamin C	1.0 mg/(kg · d)	2 months	BDI
McGrath et al. (2010)	UK	Prospective	65	20	31	Mean AGS score 3.3	Before vs after	0.5–1.0 mg/(kg · d)	3 months	CES-D
Ergun et al. (2012)	Turkey	Prospective	65	22	73	Severe or resistant	Before vs after	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D
Ormerod et al. (2012)	UK	Prospective	16	22	25	Severe	Before vs after	0.5–1.0 mg/(kg · d)	3–6 months	BDI

Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to severe	Before vs after	0.5–1.0 mg/(kg · d)	6 months	HADS-D
Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before vs after	Total: 120 mg/kg	7 months	HADS-D
Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before vs after	0.5 mg/(kg · d)	4 months	BDI
Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	HRS
Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe (25%)	Before vs after	30 mg/d	3 months	ZDS

AGS, Acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	*P* value	I^2 (*P* value)
Region				
Europe	14	−0.35 (−0.51 to −0.19)	<0.05	46.3% (<0.05)
Asia	3	−0.18 (−0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	−0.23 (−0.59 to 0.13)	0.21	−
Africa	1	−0.74 (−1.22 to −0.26)	<0.05	−
Depression scale				
BDI	10	0.10 (−0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	0.57 (0.31–0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02–0.52)	<0.05	0% (0.78)
HRS	2	0.55 (−0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (−0.25 to 0.91)	0.27	−
ZDS	1	0.74 (0.26–1.22)	<0.05	−
Sample size				
<50	9	−0.38 (−0.65 to −0.12)	<0.05	64.0% (<0.05)
⩾50	11	−0.29 (−0.54 to −0.04)	<0.05	83.1% (<0.05)
Percentage of female patients				
<50	12	−0.32 (−0.55 to −0.09)	<0.05	76.8% (<0.05)

⩾50	8	−0.34 (−0.04 to −0.64)	<0.05	78.4% (<0.05)

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD, standardized mean difference; ZDS, Zung self-rating depression scale.

Figure legends:

Figure 1. Study selection process.

Figure 2. Forest plot showing the standardized mean difference for the comparison of depression symptom scores before and after isotretinoin treatment in patients with acne.

Figure 3. Funnel plot of studies comparing depression symptom scores before and after isotretinoin treatment in patients with acne.

Figure 4. Forest plot showing the weighted mean difference for the comparison of BDI scores before and after isotretinoin treatment in patients with acne.

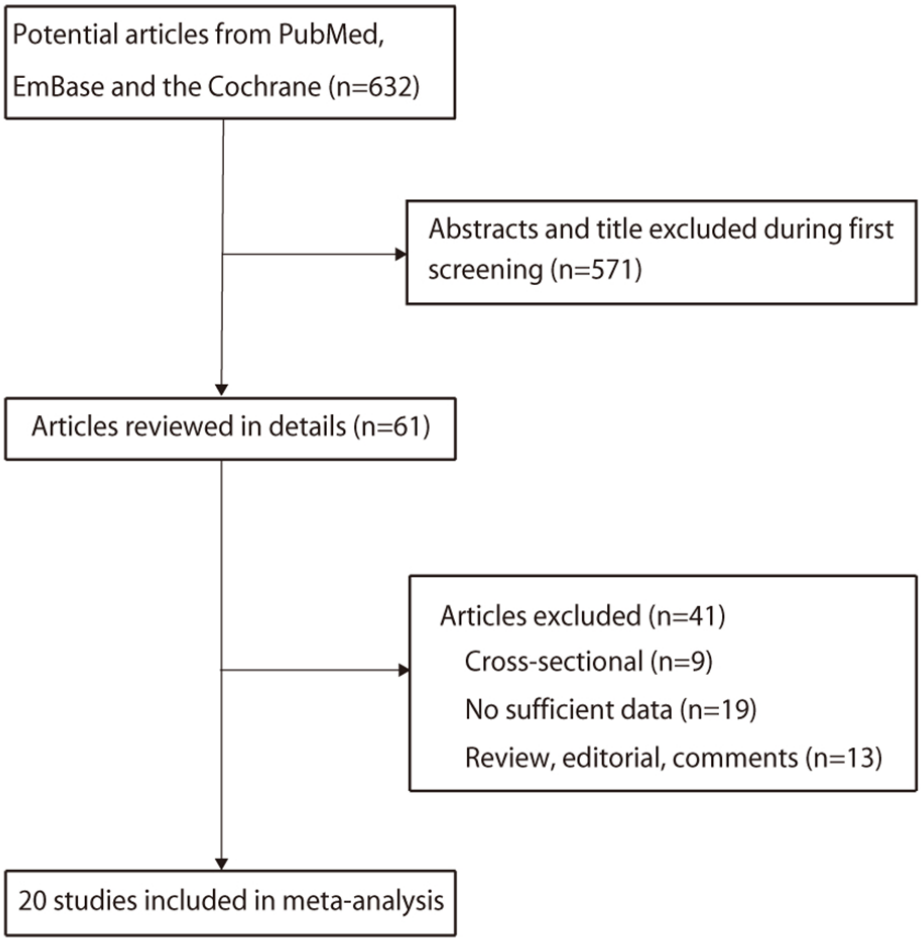
Figure 5. Forest plot showing the association between isotretinoin treatment and depression in patients with acne.

Figure 6. Funnel plot showing the association between isotretinoin treatment and depression in patients with acne.

Legends for supporting information

Supplemental 1. The details of searching strategy in PubMed.

Supplemental 2. Newcastle–Ottawa Scale for quality assessment of included studies



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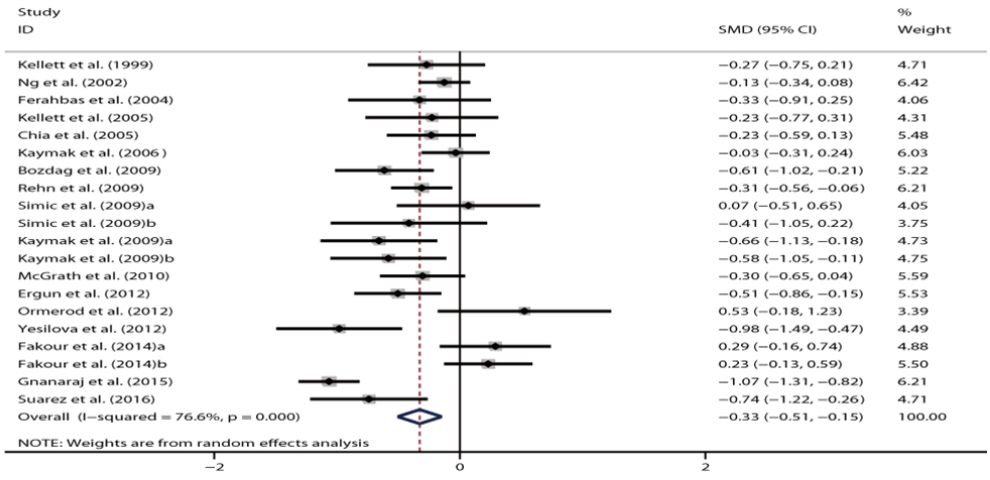

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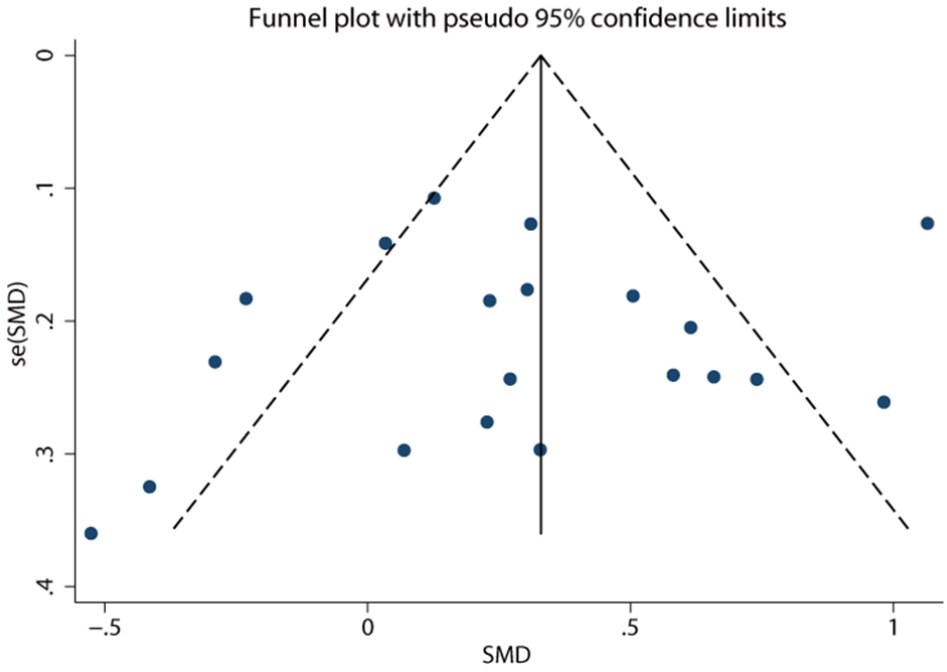

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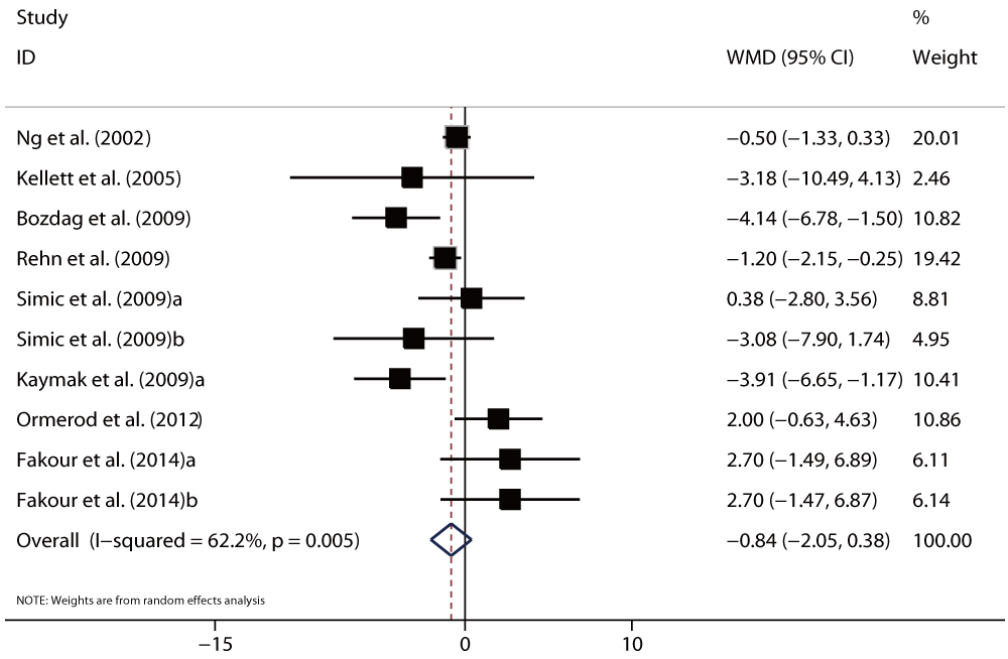

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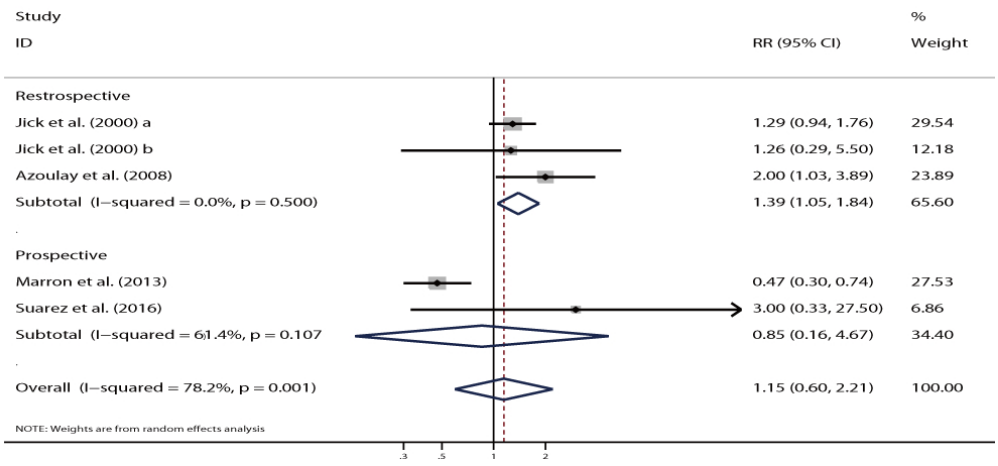

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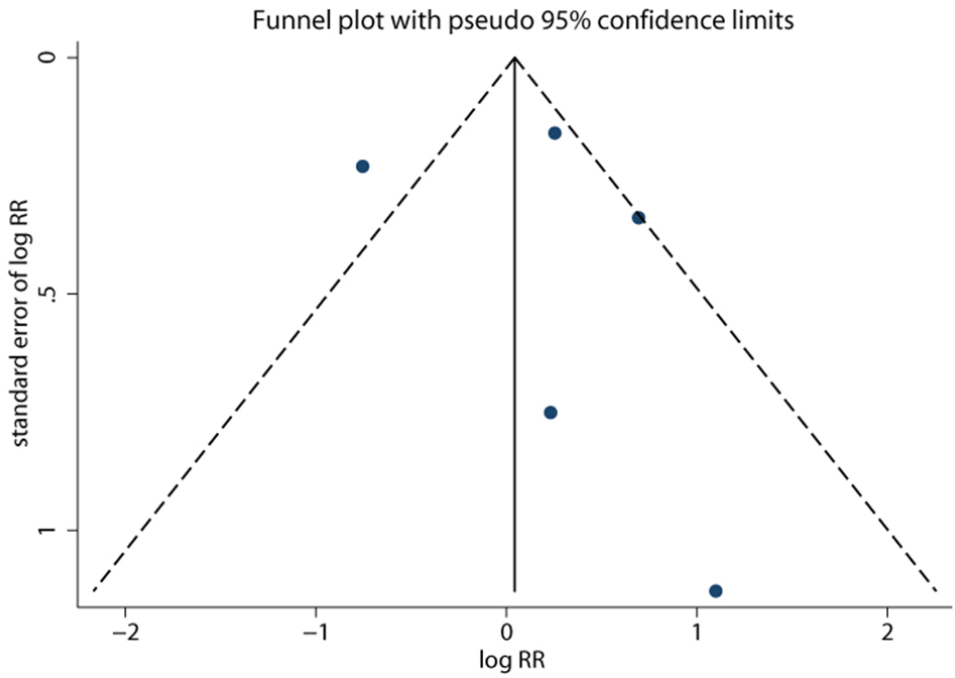

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Searching strategy in PubMed:

((("depression"[Mesh] OR "depression") OR "depressive"[Mesh] OR "depressive") AND ("acne"[Mesh] OR "acne") AND ("isotretinoin"[Mesh] OR "isotretinoin"))

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Supplemental Table 1. Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdag et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS and length of follow-up) and report characteristics (e.g., years considered, language, and publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS and funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio and difference in means).	4–5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4–5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias and selective reporting within studies).	4–5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6–7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses and meta-regression [see Item 16]).	6–7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	7–9
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research and reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Running title: Isotretinoin and risk of depression in patients with acne

ABSTRACT

Objective: This study aimed to investigate the association between the use of isotretinoin and the risk of depression in patients with acne.

Design: This was a meta-analysis in which the standardized mean difference (SMD) and the relative risk (RR) were used for data synthesis employed the random-effects model.

Setting: Studies were identified via electronic searches of PubMed, Embase, and the Cochrane Library from inception up to December 28, 2017.

Participants: Patients with acne.

Interventions: Studies comparing isotretinoin with other interventions in patients with acne were included.

Results: Twenty studies were selected. The analysis of 17 studies showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment [SMD = −0.33, 95% confidence interval (CI) −0.51 to −0.15, $P < 0.05$; I^2 = 76.6%, $P < 0.05$)]. Four studies were related to the analysis of the risk of depression. The pooled data indicated no association of the use of isotretinoin with the risk of depressive disorders (RR = 1.15, 95% CI 0.60–2.21, $P = 0.14$). The association of the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR = 1.39, 95% CI 1.05–1.84, $P = 0.02$), but this association was not evident on pooling prospective studies (RR = 0.85, 95% CI 0.60–2.21, $P = 0.86$).

Conclusions: This study suggested an association of the use of isotretinoin in patients with acne with significantly improved depression symptoms. Future randomized controlled trials are needed to verify the present findings.

Strengths and limitations of this study

1. Most included studies were prospectively designed, and the quality of included studies was largely moderate to high.
2. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.
3. The small sample sizes of some included studies might have limited the statistical power and increased the chance of missing small effects.
4. No randomized controlled trial was available so far, which was a major drawback for studies on this topic.
5. The treatment duration, drug dose, and depression scale varied between different studies.

Key words: acne; depression; isotretinoin; meta-analysis

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit of the face, neck, chest, and back [1]. As a pleomorphic skin disease, it may present as noninflammatory lesions (open and closed comedones) or inflammatory lesions (papules, pustules, or nodules) [2]. It is the most common skin disease around the world, with an estimated prevalence of 70%–87% [3]. The economic burden of acne is substantial. The cost is estimated to exceed $1 billion per year in the United States for direct acne therapy, with $100 million spent on various acne products [4]. Acne vulgaris may cause cosmetic defects and significantly impact the quality of life [5]. It may provoke a wide range of mental problems, including depression, anxiety, poor self-esteem, social phobia, and even suicidal attempts [6].

The optimal treatment approach depends on the morphology and severity of acne. Mild cases are suggested to be treated with topical retinoids. For moderate cases, systemic drugs are always needed, including oral antibiotics, hormonal therapy, and oral retinoids. However, for severe or resistant moderate acne, isotretinoin is the treatment of choice [1, 2, 4, 7]. Isotretinoin is a vitamin A-derivative 13-*cis*-retinoic acid, which is the most effective therapy for acne to date. It targets all four processes during acne development, including normalization of follicular desquamation, reduction of sebaceous gland activity, inhibition of the proliferation of *Propionibacterium acnes*, and anti-inflammatory effects [2, 7, 8]. The meta-analysis suggested that isotretinoin cured around 85% of patients after an average treatment course of 4 months [9].

Depressive disorders are highly prevalent in the Western world. The lifetime prevalence of major depressive disorders in the United States and Western Europe is around 13%–16% [10].

The frequency of depressive disorders during the use of isotretinoin varies from 1% to 11% [11]. Theoretically, effective treatment may lead to an improvement in depressive symptoms of patients with acne. However, the use of systemic isotretinoin itself may potentially increase the risk of depression [12]. Experimental studies showed that isotretinoin could affect the central nervous system and was involved in the pathogenesis of depression [13]. However, some researchers disputed that the risk was extremely small and might be influenced by the background risk or nondrug confounding factors [12]. The evidence for this controversy remained incomplete and unclear. Therefore, this systematic review and meta-analysis was performed to explore the association between the use of isotretinoin and the risk of depression among patients with acne. Further, whether this relationship differed in patients with specific characteristics was also explored.

METHODS

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was followed to conduct this meta-analysis [14]. A literature search for articles published between May 1984 and December 28, 2017, was performed using PubMed, Embase, and the Cochrane Library. The following groups of keywords were used in the search: ("depression" OR "depressive") AND "acne" AND "isotretinoin." The details of searching strategy in PubMed are presented in Supplemental 1. Also, a manual search of references listed in included studies

and published reviews were also performed to search for potentially eligible studies. The language was restricted to English.

Selection criteria

Studies were included if they fulfilled the following criteria: (1) being randomized controlled trial (RCT), prospective or retrospective study, nested case–control study, or population-based case–control study; (2) comparing the outcomes before and after the use of isotretinoin in patients with acne; or comparing isotretinoin with other treatment regimens in patients with acne; (3) presenting the change in depressive symptoms measured using a continuous depression scale [15]; or reporting the number of depressive patients before and after the use of isotretinoin; or directly presenting the relative risk (RR), odds ratio (OR), or hazard ratio (HR) between the use of isotretinoin and the risk of depression.

Data extraction and quality assessment

Two authors independently assessed the titles and abstracts for eligibility and extracted data in standardized electronic tables. The following data were extracted from included studies: publication year, author, study design, sample size, participant sex and age, severity of acne, compared groups, dose and duration of isotretinoin, and depression assessment tool. The quality of included studies was assessed using the 9-star Newcastle–Ottawa Scale. This scale evaluated the study quality based on three parameters: selection, comparability, and exposure (case–control study) or outcome (cohort study). A maximum of 4 points was assigned for the item of selection, 2 points for comparability, and 3 points for exposure/outcome [16]. Studies

were deemed as high quality for a score of 8–9, moderate quality for a score of 6–7, and low quality for a score ⩽5.

Statistical analysis

The continuous outcome of interest was the alteration in depressive symptoms assessed using a continuous depression scale after the use of isotretinoin. For the continuous parameter of depression score, the means and standard differences (SD) of the scores were extracted. The standard mean difference (SMD) was used as the outcome measure. The SMD was a unitless effect size estimate, which was the mean difference in the depression score between the compared groups divided by the pooled SD of the distribution of the score used in the study. The conversion of median (range/interquartile range) to mean ± SD was done by a previously proposed method [17]. The binary outcome of interest was the number of participants whose conditions were regarded as depression. RR and its corresponding 95% confidence interval (CI) were used as the outcome measure. HR was regarded as equivalent to RR in cohort studies. Given the overall low incidence of depression among the general population, OR was assumed to be an accurate estimate of RR. It was preferred to use the effect measures that reflected the greatest degree control for confounding factors. Both adjusted and crude data were analyzed. When data on different subgroups were reported by the same cohort, they were first pooled using the fixed-effects model. As the random-effects model was more robust than the fixed-effects model, the DerSimonian–Laird random-effects model was used to calculate the overall effect estimates for the association between the use of isotretinoin and the risk of depression [18]. The heterogeneity was evaluated using the Cochrane Q test and the I^2 statistic. Heterogeneity

was considered low, moderate, or high for I^2 <25%, 25%–50%, and >50%, respectively [19, 20]. Subgroup analyses were conducted based on the following confounders: region, study design, sample size, female percentage, and depression scale. Furthermore, meta-regression analyses were performed for the continuous confounders of sample size and female percentage. A sensitivity analysis was conducted by excluding a single study at a time. Also, a sensitivity analysis was conducted using the weighted mean difference (WMD) as the effect estimate for studies employing the same depression symptom scale. The publication bias was visually assessed by constructing a funnel plot and statistically assessed using the Begg's and Egger's regression asymmetry tests [21, 22]. All statistical analyses were conducted using the software Stata 12.0 (StataCorp, TX, USA). A *P* value less than 0.05 was considered statistically significant.

Patient and public involvement statement

Patients and the public were not involved

RESULTS

Study selection

A total of 632 records were retrieved from the electronic search, including 145 studies from PubMed, 469 records from Embase, and 18 records from the Cochrane Library. After screening by titles and abstracts, 571 studies were excluded for the following reasons: reviews, editorials, case reports, or irrelevant studies, leaving 61 studies for full-text review. Nine cross-sectional studies, 19 studies without sufficient data, and 13 review, editorial, or comments were excluded.

Finally, 20 studies were pooled into the meta-analysis [23-43]. A flow diagram of the study selection process is depicted in Figure 1.

Study characteristics

The characteristics of the included 20 studies are shown in Table 1. Jick et al. reported two independent cohorts [24], which were analyzed separately. Except for two retrospective studies identifying depressive patients using the International Classification of Diseases code [24, 31], other studies were prospectively designed, and depression was assessed using depression symptom scales. The number of participants using isotretinoin ranged from 16 to 7195. The enrolled patients with acne were distributed around the world, including 14 cohorts from Europe, 3 from North America, 3 from Asia, and 1 from Africa. The percentage of female patients ranged from 0% to 73%. Most studies compared data before and after the use of isotretinoin, except for two studies. Simic et al. compared isotretinoin with vitamin C [35]. Azoulay et al. compared isotretinoin users with nonusers [31]. Most studies prescribed isotretinoin for moderate-to-severe acne. The dose of isotretinoin ranged largely from 0.5 to 1.0 mg/(kg · d). The duration of the use of isotretinoin ranged from around 1 month to about half a year. The quality of included studies is shown in Supplemental 2. Most studies had satisfactorily high quality. The least satisfactory item was the adjustment of the confounding factors.

Change in depression symptom scores after treatment

Seventeen studies reported the depression symptom scores before and after the use of isotretinoin. All studies were prospectively designed. Simic et al. (2009) presented data for

moderate and severe acne [35]. Fakour et al. showed data for males and females separately [37]. Kaymak et al. reported depression scores measured using Beck Depression Inventory (BDI) and hospital anxiety and depression scale-depression (HADS-D) scales [33]. These subgroup data were all pooled into the overall analysis. Compared with the baseline condition before therapy, the use of isotretinoin was associated with a significant improvement in depressive symptoms (SMD = −0.33, 95% CI −0.51 to −0.15, $P < 0.05$) (Fig. 2). Highly significant heterogeneity was revealed ($I^2 = 76.6\%$, $P < 0.05$).

In the sensitivity analysis, the overall effect was not substantially altered when excluding any single study. In the meta-regression analysis, the number of included participants ($P = 0.995$) and the female proportion ($P = 0.56$) did not account for the source of heterogeneity. Data on subgroup analyses are shown in Table 2. The pooled effect estimate remained significant for 14 European studies (SMD = −0.35, 95% CI −0.51 to −0.19, $P < 0.05$), with moderate heterogeneity ($I^2 = 46.3\%$). However, the analysis of three Asian studies did not show significant results (SMD = −0.18, 95% CI−0.81 to 0.45, $P = 0.57$; $I^2 = 94.4\%$). The use of isotretinoin had no significant effect on depressive symptoms in North America (SMD = –0.23, 95% CI –0.59 to 0.13; $P = 0.21$), while it was associated with improved depressive symptoms in Africa (SMD = –0.74, 95% CI –1.22 to –0.26, $P < 0.05$). The pooled results remained significant for studies using HADS-D (SMD = −0.57, 95% CI −0.83 to −0.31, $P < 0.25$; $I^2 = 27.2\%$), and those using the Center for Epidemiological Studies Depression scale (CES-D) (SMD = −0.27, 95% CI −0.52 to −0.02, $P < 0.05$; $I^2 = 0\%$). However, the pooled effect turned to be nonsignificant for studies using the BDI scale (SMD = −0.15, 95% CI −0.36 to 0.06, $P =$

0.17; I^2 = 62.4%) and those using the Hamilton Rating Scale (HRS) (SMD = −0.55, 95% CI −1.56 to 0.46, P = 0.29; I^2 = 96.6%). The pooled effects were significant for both studies with a smaller sample size (SMD = −0.38, 95% CI −0.65 to −0.12, P < 0.05) and those with a larger sample size (SMD = −0.29, 95% CI −0.54 to −0.04, P < 0.05). The results for different proportions of females did not show a significant difference. The funnel plot appeared to be symmetrical (Fig. 3). No publication bias was revealed using the Egger's test (P = 0.76) or the Begg's test (P = 0.87).

Also, the sensitivity analysis was performed by pooling the WMD for studies using the same scale. The pooled results were nonsignificant for studies using the BDI scale (WMD = −0.84, 95% CI −2.05 to 0.38, P = 0.18; I^2 = 62.2%, P < 0.05) (Fig. 4) and those using HRS (WMD = −1.91, 95% CI −5.44 to 1.63, P = 0.29; I^2 = 97.3%, P < 0.05). In contrast, the pooled WMDs were significant for studies using HADS-D (WMD = −2.06, 95% CI −3.42 to −0.70, P < 0.05; I^2 = 66.0%, P < 0.05) and those using CES-D (WMD = −1.88, 95% CI −3.64 to −0.11, P < 0.05; I^2 = 0%, P = 0.63).

Use of isotretinoin and risk of depression

Two retrospective studies showed the adjusted RR for the association between the use of isotretinoin and the risk of depression [24, 31]. Jick et al. presented data for two independent cohorts. The overall result of three cohorts showed that the use of isotretinoin was associated with an increased risk of depression (RR = 1.39, 95% CI 1.05–1.84, P = 0.02; Fig. 5), and no significant heterogeneity was shown (I^2 = 0.0%, P = 0.50). However, no significant difference was noted in the relationship between isotretinoin use and the risk of depression on pooling

two prospective studies (RR = 0.85, 95% CI 0.60–2.21, P = 0.86; Fig. 5), and a substantial heterogeneity was observed (I^2 = 61.4%, P = 0.11). The funnel plot appeared to be symmetrical (Fig. 6), and the Egger's test (P = 0.76) or the Begg's test (P = 1.00) suggested no evidence of potential publication bias.

DISCUSSION

The risk of depression associated with the use of isotretinoin in patients with acne has been a major concern for a long time. Previous data showed conflicting and inconsistent results. This meta-analysis assessed the association between the use of isotretinoin and the risk of depression. It had several strengths as follows. A comprehensive database search of worldwide cohorts was conducted, enrolling a large number of participants. The quality of included studies was largely moderate to high. Most included studies were prospectively designed. The association was investigated from several aspects. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses. The present findings showed that isotretinoin improved in depressive symptoms in patients with acne. The benefit remained marked for studies using HADS-D and CES-D. In risk assessment, the summary RR showed that the use of isotretinoin was associated with an increased risk of depression in patients with acne on pooling retrospective studies, while this significant difference was not observed on pooling prospective studies.

Two previous systematic reviews on this topic were identified [13, 44]. They showed conflicting results, and hence the association between isotretinoin use and depression remained

controversial. Further, although comprehensive scenarios were presented, data synthesis to obtain pooled results could not be conducted. Vallerand conducted a systematic review based on 11 trials to evaluate the efficacy and safety of oral isotretinoin for acne. Oral isotretinoin significantly reduced the counts of acne lesions but increased the frequency of psychiatric adverse events (depressed mood, fatigue, hallucination, insomnia, and lethargy; 32 vs 19). However, this study did not provide the result by data synthesis [45]. Further, Huang et al conducted a meta-analysis based on 31 studies and suggested that the use of isotretinoin did not affect the incidence of depression. Further, they showed that the treatment of acne could ameliorate depressive symptoms. However, the study summarized the investigated outcomes using the depression assessment tool. Whether these relationships differed according to the region, study design, sample size, and the female percentage was not illustrated [46]. Therefore, the present study was conducted to evaluate any potential impact of the use of isotretinoin on depression incidence and change in the depression score.

The concern for negative mood arose from a series of experimental studies. Oral isotretinoin significantly suppressed cell division in the hippocampus and severely disrupted the learning capacity of mice [47]. Bremner et al. found that the use of isotretinoin, but not antibiotics, was associated with decreased brain metabolism in the orbitofrontal cortex, which was known to mediate depression symptoms [48]. O'Reilly et al. proved that isotretinoin altered intracellular serotonin level and increased 5-HT1A receptor and serotonin reuptake transporter levels *in vitro* [49]. Thus, theoretically, isotretinoin itself might cause depressive disorders. However, the potentially increased risk of depression could be compensated by the beneficial effects of

isotretinoin on patients with acne. Most patients with acne were worried about their appearances, which might lead to a series of psychological disorders. It was inferred that the improvement in depression symptoms after the use of isotretinoin might be attributed to the treatment success. Also, isotretinoin had a gradual effect on mood over time, which was not an acute event [50].

Of note, the controversy over this topic was complicated by various confounding psychosocial and clinical factors. Aktan et al. suggested that adolescent girls were more vulnerable to the negative psychological effects of acne compared with boys [51]. Women with acne were significantly more embarrassed about their skin disease compared with males. A large database study showed that female gender and acne could jointly increase the risk of depression [52]. However, the role of gender was not revealed in meta-regression and subgroup analyses. Acne itself can exert different impacts on individual patients. The lack of knowledge, especially about prognosis, may be a source of depression [24, 53]. Approximately one fifth of patients with acne suffered from psychiatric disorders [33]. Better health education and care are important components for treating patients with acne. They help eliminate the patients' misconceptions about the disease and unrealistic treatment expectations [54]. The psychological interventions may vary between different clinical settings and lead to a bias in the effect of isotretinoin. Besides, data on the efficacy or side effect of the use of isotretinoin were insufficient in most included studies. Isotretinoin may cause teratogenic toxicity. Contraceptives are recommended for female users of fertile age to prevent pregnancy until the completion of the treatment [41].

The levels of blood cholesterol and liver enzymes may be abnormal and should be monitored during the treatment phase [55].

This meta-analysis had several shortcomings. The sample sizes of some included studies were still small, which might have limited the statistical power and increased the chance of missing small effects. The current pooled analysis based on observational studies and no RCT was available, which may overestimate the association between isotretinoin use and depression risk. Moreover, included study designed as observational design might have a bias caused by participant selection and confounding factors. Ideally, RCTs comparing isotretinoin with placebo or other agents may provide more robust findings, whereas most included studies compared the before- and after-treatment data. However, leaving patients with moderate-to-severe acne without the use of isotretinoin may be unfair and even not ethical. Additionally, the treatment duration, drug dose, and depression scale varied between different studies. The acne severity or the dose of isotretinoin varied and was not reported by several studies. Patients with severe acne or scars or those unresponsive to therapy might have a worse depressive mood. However, the analyses for these confounding factors were insufficient in most studies. Approximately one fifth of patients with acne suffered from psychiatric disorders [33]. Also, some studies were sponsored by corporations [24], which might have underestimated the incidence of depressive disorders. Finally, although a greater risk of depression was associated with the use of isotretinoin on pooling retrospective studies, selection and recall biases might have affected the incidence of depression. Further, these conclusions might be unreliable because smaller cohorts were included in such subsets.

This meta-analysis showed that patients might have improved depressive symptoms after the use of isotretinoin. Further, the use of isotretinoin in patients with acne did not contribute to the development of depression. However, the summary results of retrospective studies suggested that the use of isotretinoin in patients with acne might increase the risk of depression. Future prospective controlled trials are warranted to verify the present findings.

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Conflicts of interest statement

Not declared.

Author contributions

CQL and LK contributed to conception and design. CQL, JMC, WW, MA, QZ, and LK contributed to data acquisition or analysis and interpretation of data. CQL, JMC, WW, MA, QZ, and LK were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Data sharing statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.ft545hs

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Table 1. Characteristics of included studies

Author (year)	Region	Design	Isotretinoin users	Mean/Median age (year)	Female (%)	Acne severity	Comparison groups	Dose	Treatment duration	Depression assessment
Kellett et al. (1999)	UK	Prospective	34	24	44	NA	Before vs after	1.0 mg/(kg · d)	4 months	HADS-D
Jick et al. (2000) a	Canada	Retrospective	7195	<30 (75%)	47	NA	Before vs. after	40 mg (86%)	3–6 months (62%)	ICD code
Jick et al. (2000) b	UK	Retrospective	340	<30 (78%)	42	NA	Before vs after	20 mg (75%)	1–2 months (81%)	ICD code
Ng et al. (2002)	Australia	Prospective	174	20	41	Moderate to severe	Before vs after	0.8–1.0 mg/(kg · d)	6 months	BDI

Ferahbas et al. (2004)	Turkey	Prospective	23	20	43	Severe	Before vs after	0.5–1.0 mg/(kg · d)	4 months	MADRS
Kellett et al. (2005)	UK	Prospective	33	25	36	NA	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Kaymak et al. (2006)	Turkey	Prospective	24	100	58	Moderate	Before vs after	0.75–1.0 mg/(kg · d)	5–7 months	HRS
Chia et al. (2005)	USA	Prospective	59	12–19	25	Moderate to severe	Before vs after	1.0 mg/(kg · d)	3–4 months	CES-D
Azoulay et al. (2008)	Canada	Retrospective	126	28	53	NA	Users vs nonusers	NA	5 months	ICD code
Kaymak et al. (2009)	Turkey	Prospective	37	21	69	Mild to severe	Before vs after	0.5–0.8 mg/(kg · d)	> 5 months	BDI, HADS-D

Bozdag et al. (2009)	Turkey	Prospective	50	20	52	Moderate to severe	Before vs after	1.0 mg/(kg · d)	4 months	BDI
Rehn et al. (2009)	Finland	Prospective	126	20	0	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	BDI
Simic et al. (2009)	Bosnia and Herzegovina	Prospective	85	19	34	Moderate to severe	Isotretinoin vs vitamin C	1.0 mg/(kg · d)	2 months	BDI
McGrath et al. (2010)	UK	Prospective	65	20	31	Mean AGS score 3.3	Before vs after	0.5–1.0 mg/(kg · d)	3 months	CES-D

Ergun et al. (2012)	Turkey	Prospective	65	22	73	Severe or resistant	Before vs after	0.5–1.0 mg/(kg · d)	≈ 5 months	HADS-D
Ormerod et al. (2012)	UK	Prospective	16	22	25	Severe	Before vs after	0.5–1.0 mg/(kg · d)	3–6 months	BDI
Yesilova et al. (2012)	Turkey	Prospective	43	23	70	Mild to severe	Before vs after	0.5–1.0 mg/(kg · d)	6 months	HADS-D
Marron et al. (2013)	Spain	Prospective	346	21	59	Moderate	Before vs after	Total: 120 mg/kg	7 months	HADS-D
Fakour et al. (2014)	Iran	Prospective	98	22	61	Severe	Before vs after	0.5 mg/(kg · d)	4 months	BDI
Gnanaraj et al. (2015)	India	Prospective	143	21	34	Moderate to severe	Before vs after	0.5 mg/(kg · d)	3 months	HRS

Suarez et al. (2016)	Venezuela	Prospective	36	21	44	Severe (25%)	Before vs after	30 mg/d	3 months	ZDS

AGS, Acne grading scale; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Asberg depression rating scale; NA, not available; ZDS, Zung self-rating depression scale.

Table 2. Subgroup analysis for studies presenting depressive symptom scores after isotretinoin compared with the baseline

Subgroups	Number of cohorts	SMD (95% CI)	*P* value	I^2 (*P* value)
Region				
Europe	14	−0.35 (−0.51 to −0.19)	<0.05	46.3% (<0.05)
Asia	3	−0.18 (−0.81 to 0.45)	0.57	94.4% (<0.05)
North America	1	−0.23 (−0.59 to 0.13)	0.21	–
Africa	1	−0.74 (−1.22 to −0.26)	<0.05	–
Depression scale				
BDI	10	0.10 (−0.12 to 0.32)	0.38	65.2% (<0.05)
HADS-D	4	0.57 (0.31–0.83)	<0.05	27.2% (0.25)
CES-D	2	0.27 (0.02–0.52)	<0.05	0% (0.78)
HRS	2	0.55 (−0.46 to 1.56)	0.29	96.6% (<0.05)
MADRS	1	0.33 (−0.25 to 0.91)	0.27	–
ZDS	1	0.74 (0.26–1.22)	<0.05	–
Sample size				

<50	9	−0.38 (−0.65 to −0.12)	<0.05	64.0% (<0.05)
⩾50	11	−0.29 (−0.54 to −0.04)	<0.05	83.1% (<0.05)
Percentage of female patients				
<50	12	−0.32 (−0.55 to −0.09)	<0.05	76.8% (<0.05)
⩾50	8	−0.34 (−0.04 to −0.64)	<0.05	78.4% (<0.05)

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; HADS-D, hospital anxiety and depression scale-depression; HRS, Hamilton Rating Scale; MADRS, Montgomery–Asberg depression rating scale; SMD, standardized mean difference; ZDS, Zung self-rating depression scale.

Figure legends:

Figure 1. Study selection process.

Figure 2. Forest plot showing the standardized mean difference for the comparison of depression symptom scores before and after isotretinoin treatment in patients with acne.

Figure 3. Funnel plot of studies comparing depression symptom scores before and after isotretinoin treatment in patients with acne.

Figure 4. Forest plot showing the weighted mean difference for the comparison of BDI scores before and after isotretinoin treatment in patients with acne.

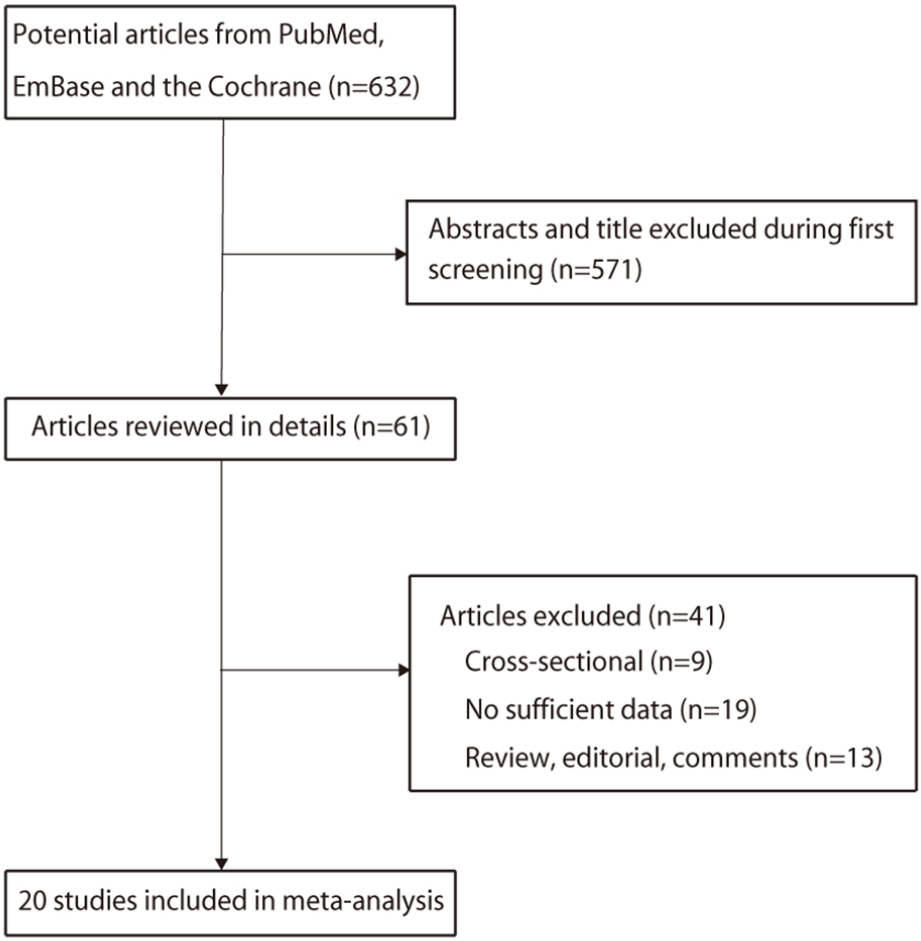
Figure 5. Forest plot showing the association between isotretinoin treatment and depression in patients with acne.

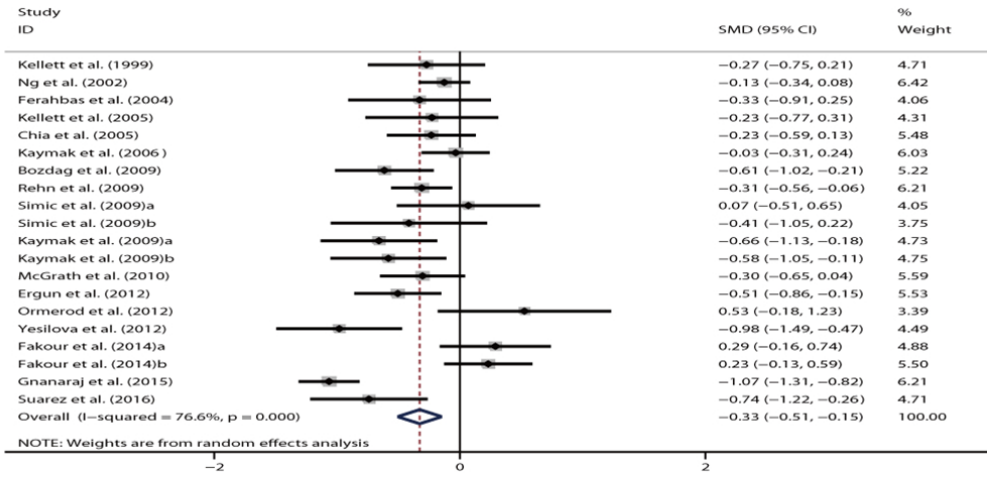
Figure 6. Funnel plot showing the association between isotretinoin treatment and depression in patients with acne.

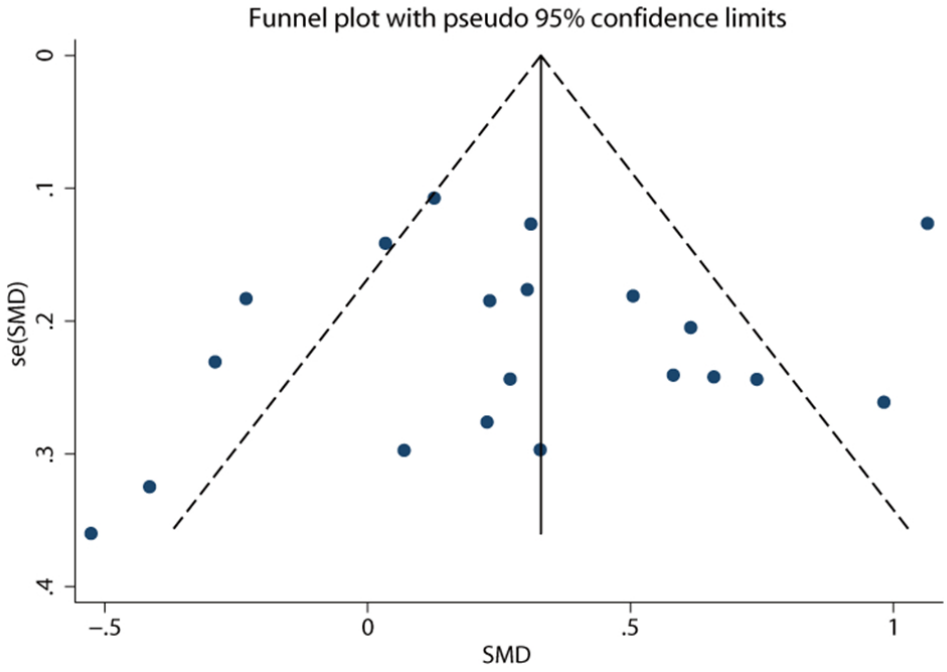
Legends for supporting information

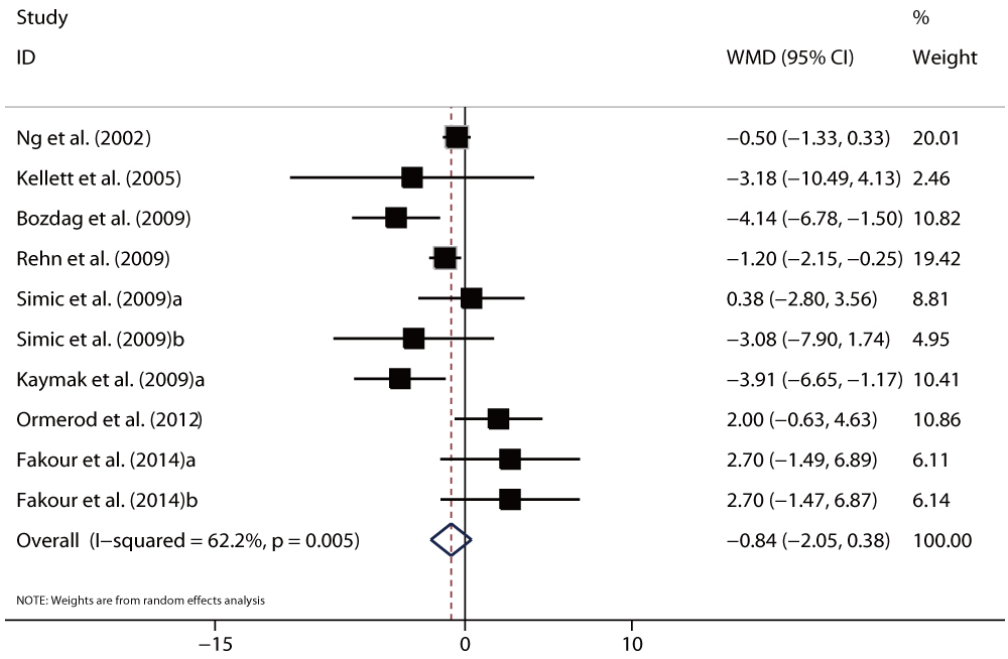
Supplemental 1. The details of searching strategy in PubMed.

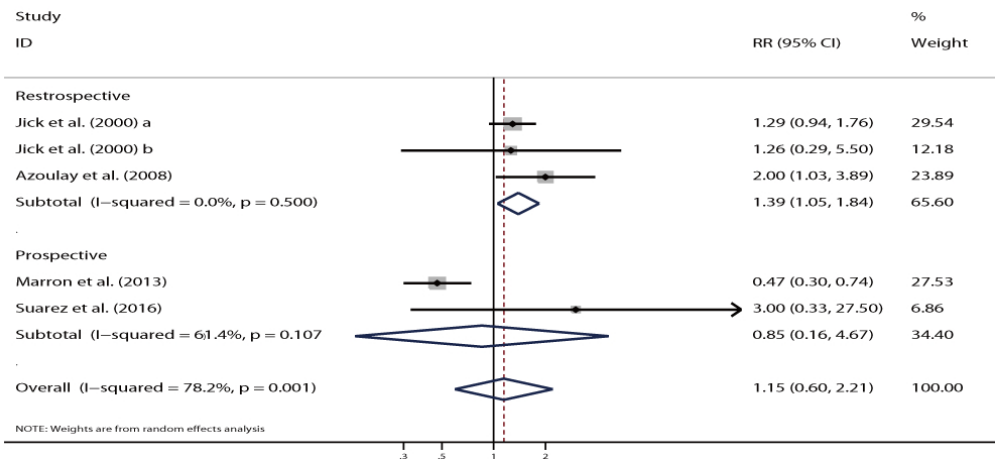
Supplemental 2. Newcastle–Ottawa Scale for quality assessment of included studies

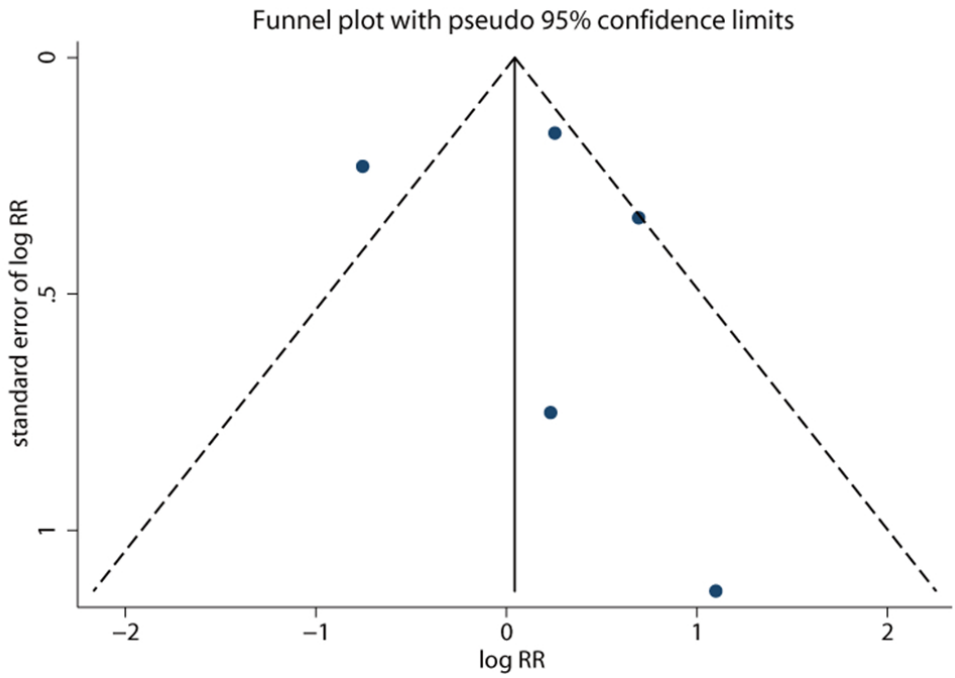

Potential articles from PubMed, EmBase and the Cochrane (n=632)
Abstracts and title excluded during first screening (n=571)
Articles reviewed in details (n=61)
Articles excluded (n=41)
Cross-sectional (n=9)
No sufficient data (n=19)
Review, editorial, comments (n=13)
20 studies included in meta-analysis


Study
ID
SMD (95% CI)
%
Weight
Kellett et al. (1999) −0.27 (−0.75, 0.21) 4.71
Ng et al. (2002) −0.13 (−0.34, 0.08) 6.42
Ferahbas et al. (2004) −0.33 (−0.91, 0.25) 4.06
Kellett et al. (2005) −0.23 (−0.77, 0.31) 4.31
Chia et al. (2005) −0.23 (−0.59, 0.13) 5.48
Kaymak et al. (2006) −0.03 (−0.31, 0.24) 6.03
Bozdag et al. (2009) −0.61 (−1.02, −0.21) 5.22
Rehn et al. (2009) −0.31 (−0.56, −0.06) 6.21
Simic et al. (2009)a 0.07 (−0.51, 0.65) 4.05
Simic et al. (2009)b −0.41 (−1.05, 0.22) 3.75
Kaymak et al. (2009)a −0.66 (−1.13, −0.18) 4.73
Kaymak et al. (2009)b −0.58 (−1.05, −0.11) 4.75
McGrath et al. (2010) −0.30 (−0.65, 0.04) 5.59
Ergun et al. (2012) −0.51 (−0.86, −0.15) 5.53
Ormerod et al. (2012) 0.53 (−0.18, 1.23) 3.39
Yesilova et al. (2012) −0.98 (−1.49, −0.47) 4.49
Fakour et al. (2014)a 0.29 (−0.16, 0.74) 4.88
Fakour et al. (2014)b 0.23 (−0.13, 0.59) 5.50
Gnanaraj et al. (2015) −1.07 (−1.31, −0.82) 6.21
Suarez et al. (2016) −0.74 (−1.22, −0.26) 4.71
Overall (I−squared = 76.6%, p = 0.000) −0.33 (−0.51, −0.15) 100.00
NOTE: Weights are from random effects analysis
−2
0
2


Funnel plot with pseudo 95% confidence limits
se(SMD)
0
.1
.2
.3
.4
−.5
0
.5
1
SMD


Study
ID
WMD (95% CI)
%
Weight
Ng et al. (2002)
−0.50 (−1.33, 0.33)
20.01
Kellett et al. (2005)
−3.18 (−10.49, 4.13)
2.46
Bozdag et al. (2009)
−4.14 (−6.78, −1.50)
10.82
Rehn et al. (2009)
−1.20 (−2.15, −0.25)
19.42
Simic et al. (2009)a
0.38 (−2.80, 3.56)
8.81
Simic et al. (2009)b
−3.08 (−7.90, 1.74)
4.95
Kaymak et al. (2009)a
−3.91 (−6.65, −1.17)
10.41
Ormerod et al. (2012)
2.00 (−0.63, 4.63)
10.86
Fakour et al. (2014)a
2.70 (−1.49, 6.89)
6.11
Fakour et al. (2014)b
2.70 (−1.47, 6.87)
6.14
Overall (I−squared = 62.2%, p = 0.005)
−0.84 (−2.05, 0.38)
100.00
NOTE: Weights are from random effects analysis
−15
0
10


Study
ID
RR (95% CI)
%
Weight
Restrospective
Jick et al. (2000) a
1.29 (0.94, 1.76)
29.54
Jick et al. (2000) b
1.26 (0.29, 5.50)
12.18
Azoulay et al. (2008)
2.00 (1.03, 3.89)
23.89
Subtotal (I–squared = 0.0%, p = 0.500)
1.39 (1.05, 1.84)
65.60
Prospective
Marron et al. (2013)
0.47 (0.30, 0.74)
27.53
Suarez et al. (2016)
3.00 (0.33, 27.50)
6.86
Subtotal (I–squared = 61.4%, p = 0.107
0.85 (0.16, 4.67)
34.40
Overall (I–squared = 78.2%, p = 0.001)
1.15 (0.60, 2.21)
100.00
NOTE: Weights are from random effects analysis
.3
.5
1
2


Funnel plot with pseudo 95% confidence limits
standard error of log RR
0
.5
1
−2
−1
0
1
2
log RR

Searching strategy in PubMed:

((("depression"[Mesh] OR "depression") OR "depressive"[Mesh] OR "depressive") AND ("acne"[Mesh] OR "acne") AND ("isotretinoin"[Mesh] OR "isotretinoin"))

Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis

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Supplemental Table 1. Newcastle–Ottawa scale for quality assessment of included studies

Study	Selection	Comparability	Outcome
Kellett et al. (1999)	****	*	***
Jick et al. (2000) a	****	**	**
Jick et al. (2000) b	****	**	**
Ng et al. (2002)	****	*	***
Ferahbas et al. (2004)	****	*	***
Kellett et al. (2005)	****	*	***
Kaymak et al. (2006)	****	*	***
Chia et al. (2005)	***	*	***
Azoulay et al. (2008)	****	**	**
Kaymak et al. (2009)	****	*	***
Bozdag et al. (2009)	****	*	***
Rehn et al. (2009)	***	*	***
Simic et al. (2009)	****	*	***
McGrath et al. (2010)	****	*	***
Ergun et al. (2012)	****	*	***
Ormerod et al. (2012)	***	*	***
Yesilova et al. (2012)	****	*	***
Marron et al. (2013)	****	*	***
Fakour et al. (2014)	****	*	***
Gnanaraj et al. (2015)	****	*	***
Suarez et al. (2016)	****	*	***

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS and length of follow-up) and report characteristics (e.g., years considered, language, and publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS and funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio and difference in means).	4–5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4–5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias and selective reporting within studies).	4–5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	6–7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6–7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses and meta-regression [see Item 16]).	6–7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	7–9
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research and reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

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