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

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

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

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

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

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

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

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

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

Abbreviations used:

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

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

CAPSULE SUMMARY

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

METHODS

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

Data source and search strategy

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

Study selection

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

Outcomes

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

Data extraction

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