Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review
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CRD summary
This review assessed whether treatment with isotretinoin increases the risk of depression or suicide in people with acne. The authors concluded that the evidence does not show an increased risk. The evidence was examined thoroughly and supported the authors’ conclusions. Nevertheless, there was uncertainty about aspects of the review process and not all relevant studies might have been included.

Authors’ objectives
To assess the association between isotretinoin treatment and the risk of depression and suicidal behaviour in patients with acne.

Searching
MEDLINE, EMBASE, PsycINFO and BIOSIS Previews were searched; the search terms, but not dates, were reported. Published studies were eligible for inclusion; meeting abstracts, reviews, summaries, guidelines, editorials and opinion papers were excluded.

Study selection
Study designs of evaluations included in the review
Primary studies other than case series or case reports were eligible for inclusion.

Specific interventions included in the review
Studies of isotretinoin treatment of acne were eligible for inclusion. Studies of isotretinoin for other indications were excluded. The included trials compared different isotretinoin dose regimens, whereas the observational studies either compared isotretinoin with oral antibiotics or had no comparator group. Doses of isotretinoin, where reported, varied from 0.1 to 2 mg/kg per day to 40 mg per day. The duration of treatment was 16 weeks in most of the studies that reported it; one study reported a mean duration of 20 weeks.

Participants included in the review
Studies in patients with acne vulgaris were eligible for inclusion. Studies with fewer than 20 participants were excluded. The participants included in each study were not described.

Outcomes assessed in the review
Studies that reported at least one of the following as a primary outcome were eligible for inclusion: depressive symptoms, depression diagnosis, suicide attempt or completed suicide. The included studies used different assessment tools, including various standard psychiatric questionnaires, International Classification of Disease codes, symptom and adverse event questionnaires, patient interview, and prescription sequence symmetry analysis. Follow-up was limited to the 16-week (or 4-month) treatment period in five studies; in one study it was at least 6 months before treatment to 12 months after the last prescription; in the other studies it was either 10 months, 6 months, at the end of treatment, or not stated.

How were decisions on the relevance of primary studies made?
It appeared that one reviewer selected the studies and a second reviewer, who applied the inclusion criteria independently, resolved any uncertainties.

Assessment of study quality
The authors did not state that they assessed validity, although some limitations of the included studies were discussed in the text.

Data extraction
One reviewer extracted the data using a standard form. Outcome data were extracted as reported in the original studies, including confidence intervals (CIs) and p-values obtained from tests of statistical significance.

Methods of synthesis
How were the studies combined?
The studies were grouped by similar outcomes and study designs in a narrative synthesis.

How were differences between studies investigated?
Differences in the study characteristics were examined in detail in the narrative.

Results of the review
Nine studies with a total of 33,588 participants were included: two randomised controlled trials (RCTs; 158 participants), three prospective cohort studies (272 participants), a prospective descriptive study (189 participants), two retrospective cohort studies (32,092 participants) and a retrospective descriptive study (877 participants).

Methodological limitations amongst the studies included non-standardised depression rating scales used in studies assessing change of mood during isotretinoin treatment, small sample sizes, lack of follow-up data and lack of a comparison group.

Depression.
The rates of depression ranged from 1 to 11% across studies; the rates were similar in oral antibiotic groups in the three observational studies using that comparator. Overall, no significant increase in depression or depressive symptoms was shown in studies that compared depression before and after treatment.

Suicidal behaviour.
A retrospective cohort study (n=21,911) found no statistically significant increase in the risk of attempted or completed suicide as a single outcome among patients currently or recently exposed to isotretinoin or oral antibiotics when compared with periods of non-exposure after treatment. A significantly higher risk was found among patients with a history of depression or psychosis (adjusted relative risk 8.0, 95% CI: 4.1, 15.5). Although the study was large, the number of cases of attempted or completed suicide was small (37 cases in over 35,000 person-years follow-up).

Authors' conclusions
There were insufficient data to support a causal relationship between isotretinoin and an increased risk of depression or suicidal behaviour.

CRD commentary
The review addressed a clear question. A reasonable number of sources were searched for published studies, and the search strategies reported would allow an independent assessment of their performance. The authors did not mention language restrictions nor did they consider publication bias, which raises some doubt whether all relevant studies were included. The methods of study selection and data extraction did not give sufficient reassurance against reviewer bias and error. The lack of precision in the inclusion criteria concerning study design warranted a more rigorous selection process. Some limitations of the included studies were mentioned in the narrative, although study quality did not appear to have been assessed systematically.

There was a lot of detail on the characteristics of the individual studies, with the exception of the participants. The
narrative synthesis was appropriate and appeared thorough. Based on the studies reviewed, the authors' conclusion is justified.

**Implications of the review for practice and research**

Practice: The authors stated that continued vigilance for signs and symptoms of psychiatric disturbance among acne patients before, during and after isotretinoin treatment is warranted.

Research: The authors stated that large pharmacoepidemiological studies that are well designed, well conducted and carefully analysed are needed.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.