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ISOTRETINOIN THERAPY AND ITS IMPACT ON DEPRESSION: A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Background: The association between isotretinoin therapy and depression remains controversial. Early case reports suggested a potential link with psychiatric adverse effects, whereas contemporary large-scale studies have produced conflicting results.

Methods: A structured literature review was conducted using PubMed/MEDLINE, Cochrane Library, and Google Scholar. Studies included systematic reviews, meta-analyses, cohort studies, and mechanistic research published between 2000 and 2024.

Results: Most high-quality studies demonstrate no increased risk of depression or suicide associated with isotretinoin therapy [1–4]. Large cohort studies indicate that psychiatric risk is elevated prior to treatment initiation and decreases following therapy [3]. The most recent meta analysis including over 1.6 million participants found no increased psychiatric risk and suggested reduced long-term suicide attempts [4].

Conclusion: Current evidence does not support a causal relationship between isotretinoin and depression. The observed psychiatric burden is more likely attributable to acne itself rather than its treatment. However, rare idiosyncratic reactions cannot be excluded.

KEYWORDS

Isotretinoin; Depression; Acne Vulgaris; Mental Health; Dermatology; Pharmacovigilance

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Introduction

Acne vulgaris is a chronic inflammatory disease affecting a substantial proportion of adolescents and adults worldwide. Beyond its dermatological manifestations, acne is associated with a significant psychological burden, including depression, anxiety, and impaired quality of life [5–7]. Isotretinoin is the most effective systemic treatment for severe acne, targeting multiple pathogenic mechanisms simultaneously. Despite its efficacy, concerns regarding psychiatric adverse effects have persisted since early pharmacovigilance reports suggested a possible association with depression and suicide. However, more robust epidemiological evidence, including case–time–control studies, has not confirmed an increased risk of suicide attempts among isotretinoin users [8].

Biological plausibility exists due to isotretinoin’s effects on central nervous system pathways, including serotonin signaling and neurogenesis. However, clinical evidence remains inconclusive. Additionally, digital platforms and social media amplify anecdotal reports, influencing patient perceptions and potentially contributing to nocebo effects.

Aim

The aim of this study was to evaluate the relationship between isotretinoin therapy and depression, integrating clinical, epidemiological, and mechanistic evidence.

Materials and Methods

A structured literature review was conducted using PubMed, Cochrane Library, and Google Scholar.

Inclusion criteria:

- systematic reviews and meta-analyses
- cohort and observational studies
- clinical studies assessing psychiatric outcomes

Exclusion criteria:

- case reports without analytical value
- non-peer-reviewed publications

Results**Clinical Evidence**

Meta-analyses consistently demonstrate no increased risk of depression associated with isotretinoin [1,2]. In contrast, several studies report improvement in depressive symptoms during treatment.

Epidemiological Evidence

Cohort studies show that psychiatric risk is highest before treatment initiation and decreases afterward, suggesting acne severity as a key confounder [3].

Table 1. Summary of Key Studies on Isotretinoin and Depression

Study	Design	Findings
Huang & Cheng (2017)	Meta-analysis	No increased risk
Li et al. (2019)	Meta-analysis	Improvement in symptoms
Sundström et al. (2010)	Cohort	Risk highest before treatment
Droitcourt et al. (2019)	Case–time–control	No increased suicide risk
Tan et al. (2024)	Meta-analysis	Reduced suicide attempts

Biological Mechanisms

Isotretinoin may influence serotonin signaling and neurogenesis; however, clinical relevance remains unclear [9].

Psychosocial Factors

Acne significantly impacts mental health, and improvement in disease severity correlates with improved psychological outcomes [5].

Discussion**Mechanistic Insights**

Isotretinoin, a systemic retinoid derived from vitamin A, exerts its biological effects primarily through nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which regulate gene transcription in multiple tissues, including the central nervous system. Experimental studies suggest that retinoids may influence neuroplasticity, hippocampal neurogenesis, and serotonergic neurotransmission [9].

In particular, alterations in serotonin signaling have been proposed as a potential mechanism linking isotretinoin to mood changes. Preclinical data indicate that retinoids may downregulate serotonin transporters and affect neuronal signaling pathways associated with emotional regulation. Functional neuroimaging studies have demonstrated changes in orbitofrontal cortex activity in patients receiving isotretinoin, a region implicated in mood disorders [9].

However, it is critical to emphasize that these findings are largely derived from small experimental studies and animal models. Their direct clinical relevance remains uncertain, and large-scale clinical studies have not confirmed a consistent association between isotretinoin and depression. Therefore, while biological plausibility exists, it does not establish causality.

Confounding Factors and Bias

One of the most important methodological challenges in assessing the relationship between isotretinoin and depression is confounding by indication. Patients prescribed isotretinoin typically present with severe acne, which itself is strongly associated with depression, anxiety, and reduced quality of life [5–7].

Large observational studies have demonstrated that the risk of depression and suicidal behavior is often elevated before the initiation of isotretinoin therapy, suggesting that the underlying disease rather than the treatment may be the primary driver of psychiatric symptoms [3].

Furthermore, reporting bias and media influence have historically contributed to the perception of isotretinoin as a psychiatric risk factor. Early pharmacovigilance reports, including spontaneous adverse event reporting systems, are inherently limited by lack of control groups and susceptibility to overreporting.

Modern study designs, including case–time–control analyses, have addressed many of these limitations and have not confirmed an increased risk of suicide attempts associated with isotretinoin use [8].

Risk Stratification and Clinical Safety

Although current evidence does not support a causal relationship between isotretinoin and depression at the population level, it is widely accepted that individual susceptibility may vary.

Patients with a history of psychiatric disorders, including depression or anxiety, may represent a subgroup requiring closer monitoring during isotretinoin therapy. Clinical guidelines generally recommend baseline mental health assessment and periodic follow-up throughout treatment.

Importantly, several studies suggest that effective treatment of acne with isotretinoin may actually lead to improvements in psychological well-being, likely due to enhanced self-esteem and social functioning [5].

Therefore, from a clinical perspective, isotretinoin should not be withheld solely due to concerns about depression, but rather prescribed with appropriate patient selection and monitoring strategies.

Clinical Implications

The findings of this review have direct implications for dermatological practice. First, clinicians should recognize that acne itself is a significant contributor to psychological distress and that effective treatment may alleviate depressive symptoms.

Second, the current evidence base supports the overall psychiatric safety of isotretinoin when used appropriately. Concerns regarding depression should be contextualized within the broader clinical picture, rather than serving as an absolute contraindication.

Third, patient education plays a critical role. Addressing misconceptions, particularly those arising from non-scientific sources, may reduce anxiety and improve treatment adherence.

Finally, a multidisciplinary approach involving dermatologists, primary care physicians, and mental health professionals may be beneficial in selected cases.

Future Directions

Despite substantial progress, several gaps remain in the current literature. Future research should focus on:

- large-scale prospective cohort studies with standardized psychiatric assessments
- identification of genetic or biological markers associated with susceptibility to mood changes
- differentiation between the effects of isotretinoin and the psychological burden of acne
- long-term psychiatric outcomes following treatment

Additionally, further investigation into the neurobiological effects of retinoids in humans is warranted to clarify potential mechanisms underlying mood alterations.

The current body of evidence does not support a causal relationship between isotretinoin and depression. Instead, acne itself appears to be the primary driver of psychiatric morbidity. The discrepancy between early reports and modern large-scale studies may be explained by confounding factors, reporting bias, and methodological limitations. High-quality studies, including case–time–control analyses, provide strong reassurance regarding the psychiatric safety of isotretinoin [8].

Moreover, effective acne treatment is associated with improved self-esteem and reduced psychological distress, further supporting the beneficial role of isotretinoin in overall patient well-being.

Digital environments and social media play an increasingly important role in shaping patient perceptions and should be considered in clinical practice.

Limitations

- heterogeneity of included studies
- variability in psychiatric assessment tools
- limited randomized controlled trials

Conclusions

Isotretinoin is not associated with an increased risk of depression at the population level. The psychiatric burden observed in patients with acne is more likely related to the disease itself. Nevertheless, appropriate monitoring remains essential.

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All authors have read and agreed to the published version of the manuscript.

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