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ISOTRETINOIN AND MOOD DISORDERS IN PATIENTS WITH ACNE VULGARIS - LITERATURE REVIEW

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ABSTRACT

Introduction and Aim: Acne vulgaris is among the most prevalent dermatological conditions affecting adolescents and young adults. Visible acne lesions may considerably reduce quality of life, negatively influence self-esteem, and impair social functioning. Oral isotretinoin is widely considered the treatment of choice for severe and therapy-resistant acne. Nevertheless, concerns have long been raised regarding its potential association with psychiatric symptoms, particularly mood disturbances, depression, and suicidal behaviour. The purpose of this review is to summarise current clinical evidence concerning the relationship between isotretinoin therapy and mood disorders in patients with acne vulgaris, with particular attention to factors that may explain the observed clinical outcomes.

Material and Methods: A narrative literature review was performed using advanced searches in the PubMed database. The analysis included English-language publications from the last five years, such as clinical and observational studies, systematic reviews, and meta-analyses focusing on depressive symptoms, psychiatric adverse events, and quality-of-life changes among patients receiving isotretinoin for acne vulgaris.

Conclusions: The currently available evidence does not conclusively demonstrate a clinically meaningful increase in depression risk in the general population of patients treated with isotretinoin. However, in some individuals, specific vulnerability factors may increase susceptibility to mood disturbances, supporting the need for careful psychological monitoring during therapy. In many patients, improvement in acne severity is accompanied by better well-being and enhanced quality of life. Further research is required to clarify the neurobiological mechanisms underlying isotretinoin activity and to identify patients at greatest risk of psychiatric complications. These findings emphasize the importance of individualized risk–benefit assessment and close cooperation between dermatologists, general practitioners, and mental health specialists.

KEYWORDS

Acne Vulgaris, Isotretinoin, Depression, Quality of Life, Depressive Symptoms, Mood Disorders

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1.Introduction:

Acne vulgaris is one of the most commonly encountered dermatological disorders, particularly among adolescents and young adults, and it often has a chronic or recurrent course. Inflammatory and non-inflammatory lesions, primarily located on the face, upper trunk and back, affect not only physical appearance but also self-esteem, peer relationships and occupational functioning. An increased unemployment rate has even been observed among patients with acne. A growing body of evidence indicates that inflammatory acne is associated with an increased likelihood of low mood, anxiety, body image dissatisfaction, and, in certain cases, suicidal ideation. This demonstrates that acne should be regarded as a condition with a considerable psychological impact, rather than merely a cosmetic concern.[1] Oral isotretinoin is considered the most effective therapeutic option for severe and treatment-resistant acne vulgaris. In many patients who do not respond adequately to conventional therapies, isotretinoin allows long-term clinical improvement or remission of skin lesions.[1][2] Despite its high efficacy, the possible relationship between isotretinoin and psychiatric symptoms, including depression and suicidal behaviour, has been debated for many years. This issue is highly relevant in clinical practice because it may affect treatment decisions and requires appropriate patient education as well as monitoring of mental health during therapy.[3] Clinical evidence regarding the effect of isotretinoin on mood remains inconclusive. Some studies have reported an increased incidence of depressive symptoms or worsening of pre-existing mood disturbances during treatment. Other analyses, however, have not confirmed such an association. In contrast, many investigations have shown improvement in psychological well-being and quality of life, most likely resulting from the resolution of acne lesions and

reduced emotional distress. These inconsistent findings explain why the psychiatric safety of isotretinoin continues to be an important subject of discussion among clinicians and researchers.[4][5][11] Alongside clinical observations, experimental research suggests that retinoids may influence the central nervous system through retinoid receptors located in brain regions involved in mood regulation, including the hippocampus and prefrontal cortex.[2] Potential effects on neurogenesis, synaptic plasticity, serotonergic and dopaminergic neurotransmission, and hypothalamic–pituitary–adrenal axis activity have also been described. These mechanisms may provide a biological explanation for mood changes observed in some patients. On the other hand, effective acne treatment with isotretinoin may reduce depressive and anxiety symptoms by improving appearance and decreasing psychosocial burden.[1][3][4]

Therefore, the aim of this paper is to review current clinical data on the association between isotretinoin use and mood disorders in patients with acne vulgaris, as well as to discuss possible neurobiological mechanisms that may account for these findings. Particular emphasis is placed on studies suggesting a potential risk of depression, research documenting improvements in mental health and quality of life, and the clinical implications of these observations.[5]

2. Acne Vulgaris, Mental Health and Quality of Life

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit which, despite its mild course from a somatic point of view, exerts a significant impact on patients' mental health and psychosocial functioning.[12] It occurs mainly during adolescence and early adulthood, a period that is particularly sensitive for the development of identity, body image and peer relationships, which makes the psychological consequences of acne clinically relevant.[1] Epidemiological studies indicate that both the presence of acne and greater lesion severity are associated with an increased risk of depressive and anxiety disorders, along with a wide spectrum of emotional difficulties.[10] Patients with acne vulgaris more often report low mood, shyness, a sense of stigmatization and dissatisfaction with their appearance, which translates into decreased self-esteem and a negative body image.[1][2] In some studies, an association between disease severity and the intensity of psychological symptoms was observed, suggesting a dose–response relationship between the severity of acne and the psychological burden.[1] Acne significantly reduces quality of life, affecting both the emotional and social domains.[1] Patients often limit social activities, avoid situations involving social exposure and report difficulties in interpersonal relationships, which may lead to isolation and perpetuation of depressive symptoms.[1][2]In addition, the chronic nature of the disease and the risk of persistent scarring and dyspigmentation mean that psychosocial consequences may continue long after active inflammatory lesions have resolved.[1][7] Contemporary reviews emphasize the need for a holistic approach to patients with acne vulgaris, taking into account both dermatological and psychological aspects. It is highlighted that treatment – including isotretinoin therapy – should be conducted with simultaneous assessment of the impact of the disease and the applied therapy on mental well-being, as well as with active monitoring of potential symptoms of depression and anxiety disorders.[2][7] Patient education on the chronic nature of the disease and the expected time to treatment response is recommended, along with early referral of individuals with pronounced psychological distress to specialist psychological or psychiatric care.[1][7] Consequently, acne vulgaris should be perceived not only as a common dermatosis, but as a condition with important psychosocial implications, requiring an interdisciplinary therapeutic approach aimed at simultaneous improvement of skin status, quality of life and patient's mental well-being.[1][2][7]

3. Isotretinoin – Drug Characteristics and Mental Health Warnings

Isotretinoin is a synthetic vitamin A derivative from the retinoid group, administered orally in the treatment of severe acne vulgaris that is resistant to other therapeutic methods. Its main mechanism of action involves a strong reduction in sebaceous gland activity and normalization of follicular keratinization within the pilosebaceous unit. These effects lead to reduced sebaceous gland size and function, decreased microcomedone formation, and secondary suppression of inflammatory processes. The most frequently observed adverse effects are related to excessive dryness of the skin and mucous membranes. Other common abnormalities include temporary lipid profile changes and, in some patients, elevated liver enzyme levels. These potential adverse effects justify regular laboratory monitoring throughout therapy. Importantly, isotretinoin is highly teratogenic and may cause severe congenital malformations; therefore, strict pregnancy prevention programs and effective contraception are mandatory during treatment and for a defined period after its completion.[9]For many years, attention has been directed toward a possible association between isotretinoin and psychiatric disorders, particularly depression, anxiety, mood changes, and, less commonly,

suicidal thoughts or behaviours. Case reports and pharmacovigilance data have contributed to the inclusion of warnings about possible mood disturbances in product characteristics and patient information materials.[10] Regulatory authorities, including the US Food and Drug Administration and European agencies, recommend obtaining a detailed psychiatric history, informing patients and their families about possible psychological symptoms, and monitoring mental status during and after treatment. Recent recommendations, including those issued by the Medicines and Healthcare products Regulatory Agency, underline the need for standardized mental health assessment before starting isotretinoin, improved patient education regarding possible mental and sexual health adverse effects, and careful follow-up during treatment, especially in younger individuals. Although the causal relationship between isotretinoin and mood disorders remains controversial, current regulatory documents emphasize that the possibility of serious psychiatric events warrants caution, particularly in patients with previous depression, anxiety disorders, or suicidal behaviour. This context highlights the importance of clinical studies assessing the real risk of mood disorders in patients with acne and of research exploring neurobiological mechanisms that may explain psychiatric symptoms observed in selected cases.[2][4]

4. Clinical Data on the Association Between Isotretinoin and Mood Disorders

4.1. Studies Suggesting an Increased Risk of Depression and Suicidal Behaviour

In the analysed cohort of 247 patients, mood disturbances during isotretinoin treatment were reported in 10.5% of individuals. Psychiatric symptoms occurred more often in younger patients and in those with a previous history of mood disorders, suggesting that individual susceptibility may increase the risk of adverse psychiatric effects during therapy. It is also important that affected patients were treated for a longer period, although no significant differences in cumulative dose were found. This may indicate that treatment duration, rather than total dose alone, could be more relevant to the development of psychiatric symptoms. The clinical presentation of mood disturbances varied. Depressive and anxiety symptoms were most common, whereas insomnia, irritability, and concentration problems were reported less frequently. In a small number of patients, symptoms led to a new psychiatric diagnosis shortly after treatment completion. Psychiatric manifestations also tended to occur relatively early, usually within the first three months of therapy. This finding may have practical significance for patient monitoring during the initial stage of isotretinoin treatment. These observations are consistent with reports suggesting that a small but measurable proportion of patients experience mood changes during isotretinoin therapy. At the same time, they emphasize the importance of prior psychiatric history and the early treatment period as potential markers of increased risk, which has also been reflected in cohort studies and pharmacovigilance analyses.[8]

4.2. Studies Suggesting No Increased Risk or Improvement in Mood and Quality of Life

Available systematic reviews and meta-analyses suggest that isotretinoin use in acne patients is not associated with a significant increase in the risk of clinically diagnosed depression. In many studies, depressive symptom severity decreased during treatment, which may be explained by effective control of acne and reduction of the psychological burden associated with the disease. The meta-analysis by Li et al., which included 20 studies, found no significant increase in depression risk (RR 1.15; 95% CI 0.60–2.21), while also demonstrating a significant reduction in depressive symptom severity over the course of therapy. Thus, depressive symptoms in patients treated with isotretinoin often decrease as the underlying dermatological condition improves. At the same time, comprehensive safety reviews describe a wide range of isotretinoin-related adverse effects, including common mucocutaneous reactions, lipid abnormalities, liver function disturbances, musculoskeletal symptoms, and rare but potentially serious complications. Within this broader safety profile, mood disturbances are generally described as rare and idiosyncratic events rather than predictable pharmacological effects of the drug.[5][6][11][13] Individual case reports have described severe idiosyncratic psychiatric reactions to isotretinoin, including profound depression, suicidal ideation, or acute psychosis, which usually improved after discontinuation of the medication. These observations suggest that a small subgroup of patients may be particularly vulnerable to such complications. Severe insomnia has also been proposed as a possible early sign of an emerging drug-related psychiatric disorder, potentially increasing the risk of later mood disturbances. In addition, possible links have been suggested between retinoid system dysregulation and schizophrenia, as well as worsening of mood disorder symptoms, including suicidal thoughts, in patients with bipolar disorder treated with isotretinoin. These findings support the need for particular caution and close monitoring in these patient groups.[9]

5. Discussion

This narrative review summarizes clinical and experimental evidence concerning the relationship between isotretinoin therapy and mood disturbances in patients with acne vulgaris. The findings are considered in the wider context of acne-related psychosocial burden and possible neurobiological mechanisms. Overall, the available data support a balanced interpretation. Isotretinoin does not appear to significantly increase depression risk at the population level, yet rare but clinically important psychiatric adverse events may occur in susceptible individuals. This perspective has relevant implications for both clinical decision-making and future research. One important observation from the reviewed data, including the cohort of 247 patients, is that mood changes during isotretinoin therapy affected only a minority of patients, namely 10.5%. These symptoms were more frequent in younger individuals and in those with a previous history of mood disorders. This pattern suggests that isotretinoin may contribute to psychiatric symptoms in the presence of pre-existing vulnerability, rather than acting as a universal trigger of mood disturbances in all treated patients. The finding that affected patients had longer treatment exposure, despite comparable cumulative doses, indicates that the duration of therapy and persistence of disease may be more relevant than total dose alone. From a clinical perspective, these results support increased vigilance in younger patients and in those with a documented psychiatric history, while also cautioning against applying this risk equally to the entire acne population. Equally important is the repeated observation from prospective studies that depressive symptoms and quality of life often improve during isotretinoin treatment. This improvement is plausibly related to effective management of a chronic and stigmatizing dermatological condition that can strongly impair self-esteem, social functioning, and general well-being. In this sense, isotretinoin may indirectly reduce psychological distress by removing an important source of emotional burden. Consequently, avoiding isotretinoin solely because of concerns about depression may deprive many patients of a treatment that could improve both dermatological and psychological outcomes. Instead, current evidence supports an individualized assessment of risks and benefits, taking into account both the possible psychiatric complications and the psychosocial advantages of acne remission. The coexistence of studies showing psychological improvement in most patients and case reports describing severe depression, suicidality, or psychosis after isotretinoin exposure continues to raise questions about causality. Experimental findings concerning retinoid activity in the central nervous system offer a possible explanatory framework. Retinoids may influence hippocampal neurogenesis, synaptic plasticity, monoaminergic neurotransmission, and hypothalamic–pituitary–adrenal axis regulation, all of which are involved in mood disorder pathophysiology. These mechanisms make it biologically plausible that isotretinoin could contribute to psychiatric decompensation in individuals with specific genetic, neurobiological, or psychosocial vulnerabilities. Therefore, future research should move beyond a simple “cause or no cause” approach and instead focus on differential susceptibility, where isotretinoin interacts with existing risk factors. The reviewed evidence also indicates that insomnia and other early psychiatric symptoms may serve as warning signs of developing mental health complications during isotretinoin therapy. New-onset severe insomnia, pronounced mood instability, or psychotic-like symptoms occurring in the early months of treatment should be treated as clinically significant red flags. Early recognition of these symptoms may allow timely intervention and prevent progression to more severe psychiatric episodes. Similarly, possible relationships between retinoid dysregulation, schizophrenia, and worsening of bipolar disorder symptoms suggest that patients with these diagnoses require particularly careful management. This may include psychiatric consultation before treatment initiation and close follow-up throughout therapy. From a broader perspective, the results reinforce the concept that acne vulgaris itself is associated with a substantial psychological burden. This has two important consequences. First, studies evaluating isotretinoin and mood must adequately account for the psychiatric impact of acne itself, using baseline assessments and appropriate comparison groups to reduce confounding by indication. Second, psychological screening should become an integral element of dermatological care, even before systemic treatment is introduced. Such an approach may improve the detection of underlying depression or anxiety disorders independently of pharmacological exposure and supports a more holistic, patient-centred model of acne management. The current literature also reveals several important gaps. Future studies should be large, prospective, and controlled, with standardized psychiatric outcome measures and follow-up extending beyond treatment completion. More precise assessment of cumulative dose, treatment duration, baseline mental health status, and psychosocial stressors is also needed. Incorporation of biological markers related to retinoid signalling, stress response, and neuroplasticity could further clarify mechanisms and support better identification of high-risk patients. Such research would help move the debate from general and often polarized statements toward more precise clinical guidance regarding who is most vulnerable, when risk is greatest, and how it can be minimized without limiting the substantial dermatological and psychosocial

benefits of isotretinoin. Overall, isotretinoin should not be viewed either as completely neutral from a psychiatric perspective or as a drug that broadly induces depression. Rather, it should be understood as a highly effective treatment whose psychiatric risk profile depends strongly on individual vulnerability and clinical context. For clinicians and researchers, the key message is the need for nuanced, evidence-based, and patient-specific decision-making that combines dermatological efficacy with careful attention to mental health.

6. Conclusions

Isotretinoin remains a key therapeutic option for severe and refractory acne vulgaris. In many patients, its use leads to significant improvement in quality of life and reduction of the psychological distress associated with visible skin disease. The available clinical evidence does not clearly demonstrate a clinically significant increase in depression risk among the overall population of isotretinoin-treated patients. Nevertheless, some studies and case reports describe mood disorders and suicidal behaviour in selected subgroups. Current analyses suggest that the risk of mood disturbances during isotretinoin therapy may be influenced by individual factors, including previous psychiatric illness, younger age, longer duration of treatment, and coexisting psychosocial stressors. At the same time, many prospective studies report improvement in mood and quality of life during treatment, which is associated with acne resolution and decreased depressive or anxiety symptoms. Experimental and review data indicate biologically plausible mechanisms linking retinoids with mood regulation, including effects on hippocampal neurogenesis, synaptic plasticity, monoaminergic neurotransmission, and hypothalamic–pituitary–adrenal axis activity. These mechanisms may increase vulnerability to mood disorders in a subset of patients, particularly when additional risk factors are present. Therefore, isotretinoin should be used with appropriate caution in individuals at elevated psychiatric risk. These conclusions support the need for individualized assessment of the benefit–risk ratio before initiating isotretinoin. Such assessment should include psychiatric history, current mental status, and systematic monitoring for depressive and anxiety symptoms during and after treatment. Further prospective studies with long-term follow-up are needed to clarify the roles of cumulative dose, treatment duration, and pre-existing psychiatric disorders, as well as to identify high-risk groups and develop optimal monitoring and management strategies.

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