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Review Article

Isotretinoin-based treatment in patients with acne: main physiological and psychological effects

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ABSTRACT

Isotretinoin remains the most effective systemic therapy for moderate to severe acne, with the potential to achieve long-term remission. However, its clinical utility is limited by a broad spectrum of adverse effects that involve both physiological and psychological domains. Objectives were to review the principal physiological and psychological effects associated with isotretinoin therapy and discuss their clinical implications for patient selection and monitoring. A narrative synthesis was conducted using recent evidence, with emphasis on adverse events such as teratogenicity, mucocutaneous manifestations, ocular alterations, metabolic and hematologic changes, as well as the debated relationship between isotretinoin and mood disturbances. Physiological side effects consistently reported include teratogenic risk, cheilitis, xerosis, ocular surface changes, dyslipidemia, musculoskeletal pain, and alterations in hepatic function. Psychological outcomes remain controversial: while some studies suggest increased risk of depression and suicidality, others highlight improvement in psychosocial well-being due to acne resolution. These discrepancies appear to be influenced by the underlying psychological burden of acne itself. Isotretinoin is a cornerstone in acne management but requires strict monitoring and patient education. Future research should prioritize disentangling the psychiatric effects attributable to the drug from those inherent to severe acne, while optimizing strategies to mitigate physiological toxicity.

Keywords: Isotretinoin, Acne vulgaris, Physiological effects, Psychological effects, Acne treatment

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that predominantly affects adolescents and young adults, though it may persist or appear de novo in adulthood. Its estimated global prevalence surpasses 9%, ranking among the top ten most prevalent conditions worldwide.[1] Beyond its dermatological manifestations, acne has profound psychosocial repercussions, contributing to diminished self-esteem, social withdrawal, anxiety, and depression.[2] The multifactorial pathogenesis of acne involves sebaceous gland hyperplasia, follicular hyperkeratinization, colonization by *Cutibacterium acnes*, and complex immune-inflammatory responses.[3]

Therapeutic approaches are stratified by severity, ranging from topical agents (retinoids, benzoyl peroxide, antibiotics) to systemic antibiotics, hormonal therapy, and isotretinoin. Among these, oral isotretinoin remains the only agent with the potential to induce prolonged remission or cure, due to its pleiotropic effects on sebaceous gland activity, keratinization, and inflammation.[4] Since its introduction in the late 20th century, isotretinoin has become the gold standard for the treatment of moderate to severe, recalcitrant, or nodulocystic acne.[5]

However, the therapeutic benefits of isotretinoin must be weighed against its extensive profile of adverse effects. Physiological reactions include mucocutaneous dryness, cheilitis, xerosis, epistaxis, ocular surface alterations, musculoskeletal discomfort, dyslipidemia, and hepatotoxicity.[6] Teratogenicity represents its most critical risk, necessitating rigorous contraceptive measures during treatmen.[7] In parallel, psychological effects remain highly debated. While some observational studies and case reports suggest associations with depression, anxiety, or suicidal ideation, other investigations highlight improvements in mental health and quality of life secondary to acne resolution.[8,9]

These contrasting findings have fueled controversy among clinicians, regulators, and patients, underscoring the need for careful monitoring, patient education, and individualized risk-benefit assessment. Furthermore, the ongoing debate illustrates a broader issue in dermatology: the necessity to evaluate not only the physiological safety profile of systemic therapies but also their psychological and social implications.

Given the widespread use of isotretinoin and the persistence of concerns regarding its safety, an updated and comprehensive review of both its physiological and psychological effects is essential. Such evidence is pivotal to guide clinicians in clinical decision-making, optimize monitoring strategies, and inform patients about potential benefits as well as the risks associated with therapy.

LITERATURE SEARCH

It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2018 to 2024 in electronic databases such as PubMed, Elsevier, and Web of Science. The keywords used in the MesH search were: isotretinoin; acne vulgaris; physiological effects; psychological effects; acne treatment. Inclusion criteria: search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available; They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 30 sources were obtained for analysis and synthesis.

GASTROINTESTINAL AND INTESTINAL EFFECTS

The impact of isotretinoin on the gastrointestinal system has been debated for decades. One of the most controversial issues is its possible association with inflammatory bowel disease (IBD), particularly ulcerative colitis and Crohn's disease. Early case reports suggested a potential link between isotretinoin exposure and the onset of IBD, raising significant concerns among clinicians.[10]

However, subsequent large population-based studies and meta-analyses have not consistently confirmed a causal association. For instance, a systematic review published in JAMA dermatology concluded that there is insufficient evidence to establish isotretinoin as a risk factor for IBD, although a slightly increased risk cannot be excluded in genetically predisposed individuals.[11]

Other gastrointestinal manifestations include nausea, abdominal pain, diarrhea, and appetite changes, which are usually mild and transient. Rarely, isotretinoin-induced hypertriglyceridemia can precipitate acute pancreatitis when triglyceride levels exceed 800-1000 mg/dL, highlighting the importance of regular metabolic monitoring during therapy.[12]

PREGNANCY AND TERATOGENICITY

Teratogenicity remains the most serious and well-documented adverse effect of isotretinoin. Exposure during pregnancy is associated with a very high risk of congenital malformations, which may affect craniofacial, cardiovascular, thymic, and central nervous system development.[13] These abnormalities, collectively termed retinoic acid embryopathy, have been described since the mid-1980s and represent a cornerstone in the safety concerns surrounding isotretinoin therapy.[14]

The risk of major congenital malformations in infants exposed in utero has been estimated to be between 20% and 35%, while spontaneous abortions occur in up to 20% of affected pregnancies.[15] Even at standard therapeutic doses, isotretinoin exerts potent teratogenic effects due to its influence on gene expression during embryogenesis.

For this reason, strict regulatory measures have been implemented worldwide. Programs such as the iPLEDGE in the United States mandate two simultaneous contraceptive methods for women of childbearing potential, mandatory monthly pregnancy tests, and restricted prescription protocols.[16] European and Latin American countries have adopted similar preventive strategies, although compliance remains a challenge.

Given the devastating consequences of in utero exposure, isotretinoin is absolutely contraindicated during pregnancy. Women receiving isotretinoin must avoid conception during treatment and for at least one month after discontinuation. Clinicians must ensure proper patient counseling and adherence to contraceptive protocols prior to initiating therapy.

ACNE FULMINANS

Acne fulminans is a rare but severe adverse effect that can occur during isotretinoin therapy. It is characterized by the sudden onset of highly inflammatory nodular and ulcerative lesions, often accompanied by systemic symptoms such as fever, arthralgia, myalgia, and

malaise.[17] This presentation is distinct from conventional severe acne and represents a dermatologic emergency due to its rapid progression and systemic involvement.

Although the exact pathogenesis remains unclear, it has been hypothesized that isotretinoin may trigger an exaggerated inflammatory response through sudden changes in follicular keratinization and immune modulation.[18] The condition is more frequently reported in adolescent males receiving high doses of isotretinoin, though it can also occur at the standard therapeutic regimens.

Management requires immediate discontinuation or dose reduction of isotretinoin and initiation of systemic corticosteroids to control inflammation. Once the acute phase subsides, isotretinoin can be cautiously reintroduced at lower doses under close medical supervision.[19]

SKIN REACTIONS

Cutaneous adverse effects are among the most frequent and expected consequences of isotretinoin therapy. The most common reactions include cheilitis, xerosis, erythema, and increased skin fragility, which result from the drug's profound impact on sebaceous gland activity and epidermal differentiation.[20] These effects are dose-dependent and typically reversible after the discontinuation.

Patients often report dry lips and skin desquamation, especially on the face and extremities. Other manifestations include photosensitivity, pruritus, and eczema-like dermatitis, which may require adjunctive treatment with emollients, sunscreen, and topical corticosteroids.[21]

More rarely, isotretinoin can trigger granulomatous reactions, nail changes, or hair thinning (telogen effluvium). There are also isolated case reports of vasculitis and erythema multiforme, though causality remains uncertain.[22]

Despite their frequency, most skin reactions are manageable with supportive care and do not necessitate discontinuation. Patient education regarding adequate skin care and sun protection is crucial to improve adherence and minimize discomfort.

OCULAR REACTIONS

Ocular adverse reactions are relatively common during isotretinoin therapy, largely due to its effect on the sebaceous glands of the eyelids and the Meibomian glands. The most frequent manifestations include dry eye syndrome, conjunctivitis, and blepharitis, resulting from a reduction in the quality and quantity of the tear film.[23] Patients often report ocular irritation, redness, and intolerance to contact lenses.[24]

Night vision disturbances have also been described, with reduced dark adaptation attributed to the effects of isotretinoin on retinal function and vitamin A metabolism. Although infrequent, there are reports of decreased visual acuity and blurred vision, generally reversible after discontinuation of the drug.[25]

PSYCHOLOGICAL EFFECTS

The psychological impact of isotretinoin therapy has been a matter of ongoing debate since its introduction. Early case reports raised concerns about potential associations with depression, suicidal ideation, and even completed suicides. These reports prompted regulatory agencies to issue warnings regarding psychiatric risks and to recommend close monitoring of mental health during treatment.[26]

Several observational studies have described increased rates of depressive symptoms and anxiety among isotretinoin users compared to patients treated with antibiotics or topical regimens. Proposed mechanisms include isotretinoin's modulation of central nervous system retinoid receptors, which may influence serotonin pathways and neuroplasticity.[27]

Nonetheless, confounding factors such as the psychosocial burden of acne complicate the interpretation of these associations.

Conversely, many studies have demonstrated significant improvements in quality of life, self-esteem, and social functioning after isotretinoin therapy. Acne itself is strongly linked to psychological distress, social withdrawal, and higher risk of depression, particularly in adolescents and young adults. Thus, effective clearance of acne often results in improved mood and decreased psychological morbidity.[28]

Meta-analyses have attempted to clarify this controversy, but findings remain inconclusive. A systematic review published in the British journal of dermatology concluded that isotretinoin does not significantly increase the risk of depression or suicide, though individual susceptibility cannot be excluded.[29] Therefore, while population-level risk appears minimal, vigilance at the individual level remains crucial.

Current guidelines recommend baseline mental health assessment and routine follow-up for patients undergoing isotretinoin therapy, particularly those with a history of psychiatric illness.

Multidisciplinary collaboration between dermatologists, psychiatrists, and primary care providers is encouraged to ensure safe and effective management.[30]

This integrated approach helps balance the undeniable dermatologic benefits of isotretinoin with careful attention to mental health outcomes.

Table 1: Main physiological and psychological effects of isotretinoin.

System/category	Main effects	Notes
Mucocutaneous	Cheilitis, xerosis, epistaxis, erythema, photosensitivity	Most frequent, dose-dependent, reversible
Musculoskeletal	Myalgia, arthralgia, back pain, hyperostosis (rare)	More common in athletes or prolonged use
Metabolic/Hepatic	Hypertriglyceridemia, elevated transaminases	Requires monitoring; risk of pancreatitis
Gastrointestinal	Abdominal pain, diarrhea, possible IBD association	Link to IBD not clearly established
Ocular	Dry eye, conjunctivitis, blepharitis, night vision disturbances	May affect contact lens tolerance
Reproductive	Severe teratogenicity, risk of congenital malformations	Absolute contraindication in pregnancy
Dermatological	Eczema-like dermatitis, granulomatous reactions, alopecia	Supportive care usually sufficient
Severe reaction	Acne fulminans	Rare but requires corticosteroid treatment
Cardiovascular/neurological	Headaches, rare intracranial hypertension, vasculitis	Very rare, requires monitoring
Psychological	Depression, anxiety, suicidal ideation (controversial)	Requires baseline and follow-up screening

DISCUSSION

The present review highlights the broad spectrum of physiological and psychological effects associated with isotretinoin therapy. While isotretinoin remains the gold standard for the management of severe and refractory acne, its safety profile continues to generate significant debate in both dermatological and psychiatric literature.

First, mucocutaneous adverse effects such as cheilitis, xerosis, and skin fragility were confirmed as the most frequent reactions. These manifestations, though bothersome, are predictable and manageable, rarely requiring discontinuation. Preventive measures including emollients, sunscreen, and patient education significantly reduce their clinical impact.[20-21]

Gastrointestinal involvement remains controversial, particularly regarding the risk of inflammatory bowel disease. Although early case reports suggested a potential causal link, larger meta-analyses have not confirmed a definitive association. The evidence suggests that while isotretinoin may exacerbate pre-existing conditions in genetically predisposed individuals, it is unlikely to act as an independent etiologic factor.[10,11]

Metabolic disturbances, particularly hypertriglyceridemia and elevated liver enzymes, are clinically relevant. Pancreatitis is a rare but potentially life-threatening complication, highlighting the importance of baseline and periodic biochemical monitoring throughout therapy.[12]

These laboratory abnormalities are usually reversible upon dose reduction or discontinuation.

The teratogenic potential of isotretinoin represents the most critical safety concern. Retinoic acid embryopathy, characterized by craniofacial, cardiac, and central nervous system malformations, is well documented and underscores the need for stringent pregnancy prevention programs.[13,14] The iPLEDGE system in the United States and similar protocols worldwide demonstrate the necessity of regulatory frameworks to minimize fetal exposure.[16]

Cutaneous severe adverse effects, such as acne fulminans, though rare, represent dermatological emergencies. Their pathogenesis remains unclear but may involve abrupt inflammatory responses triggered by isotretinoin. Corticosteroid therapy followed by cautious reintroduction of isotretinoin at lower doses remains the cornerstone of management.[18,19]

Ocular reactions including dry eye, conjunctivitis, and impaired dark adaptation are frequent but generally mild. Rare reports of decreased visual acuity emphasize the need for ophthalmological referral in selected cases.[23-25] Patient counseling regarding contact lens intolerance and the use of ocular lubricants enhances adherence and improves tolerability.

Neurological adverse events such as headaches and pseudotumor cerebri have been described, though their incidence is extremely low. These effects are most often reported in association with concomitant tetracycline use, highlighting the importance of avoiding drug interactions.[22] Although rare, clinicians must remain vigilant for warning signs of increased intracranial pressure.

The psychological effects of isotretinoin remain the most debated. While some observational studies report higher incidence of depression and suicidality, confounding variables such as the psychosocial burden of acne complicate interpretation. In contrast, other studies consistently demonstrate improvements in quality of life and mental health outcomes after acne resolution.[26-28]

Meta-analyses have not identified a clear causal association between isotretinoin and depression at the population level. However, the possibility of individual susceptibility cannot be excluded.[29] This underscores the importance of mental health screening before and during treatment, particularly in patients with personal or family history of psychiatric disorders.

Guidelines emphasize the value of multidisciplinary collaboration, involving dermatologists, psychiatrists, and primary care providers, to ensure holistic patient care. This integrative approach balances the dermatological benefits of isotretinoin with vigilant monitoring of psychological well-being.[30]

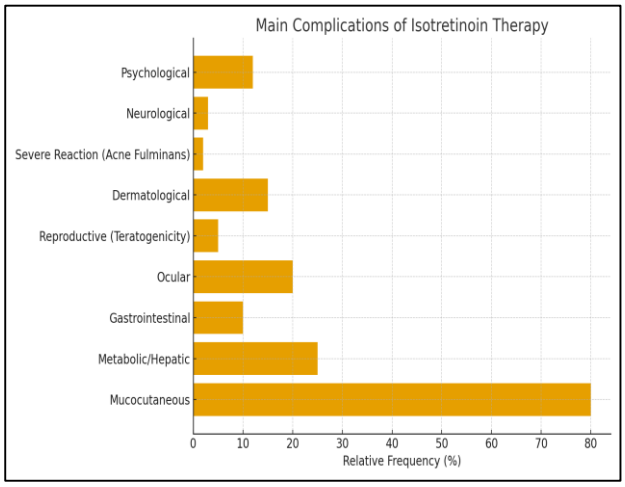

Figure 1: Main complications of isotretinoin therapy.

CONCLUSION

Isotretinoin remains the most effective therapeutic option for severe and refractory acne, with a well-documented safety profile. Most adverse effects, including mucocutaneous, gastrointestinal, ocular, and metabolic reactions, are predictable and reversible when adequate monitoring and preventive measures are applied. The most critical risks are teratogenicity and rare but severe complications such as acne fulminans, which demand strict clinical vigilance.

The psychological effects of isotretinoin continue to be debated. Current evidence suggests no causal association with depression or suicide at the population level, although individual vulnerabilities may exist. Comprehensive patient management requires a multidisciplinary approach, balancing dermatologic benefits with careful monitoring of mental health and strict pregnancy prevention protocols.

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