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Beyond Clinical Efficacy: A Literature Review on the Safety Challenges of Isotretinoin Therapy

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Abstract

Background. Acne vulgaris is a chronic inflammatory skin condition that often leads to scarring and psychological distress. Oral isotretinoin is the most effective systemic medication for severe or treatment-resistant acne, but concerns about its adverse effects remain.

Aim. This review summarizes the current state of knowledge on isotretinoin in acne therapy, highlighting safety issues and implications for everyday clinical practice.

Material and methods. A narrative literature review was conducted using PubMed/MEDLINE for articles published between January 2016 and November 2025. Human studies and reviews

on systemic isotretinoin for acne vulgaris treatment, along with selected articles providing relevant epidemiological and clinical context for acne, were included if they reported efficacy, remission, adverse effects, impact on tissue regeneration, or monitoring recommendations. Randomized trials, observational studies, systematic reviews, meta-analyses, and high-quality narrative reviews were eligible for inclusion. Non-acne indications, animal-only studies, and non-peer-reviewed publications were excluded.

Results. Isotretinoin addresses all major pathogenic mechanisms of acne, leading to high clearance and long-term remissions. Mucocutaneous dryness is the most common adverse effect, but it is manageable with proper skincare. Laboratory abnormalities involve mild, reversible dyslipidemia and liver enzyme elevations. The most dangerous side effect is teratogenicity, which requires strict pregnancy-prevention programs. Studies have not confirmed an increased incidence of depression or inflammatory bowel disease; however, clinical monitoring remains essential. Musculoskeletal and ophthalmologic adverse effects are generally mild and dose-dependent.

Conclusions. Structured risk management, regular clinical and laboratory checks, along with the lowest possible dose, enable safe and effective acne control through individualized isotretinoin treatment.

Keywords: Acne vulgaris; Retinoids; Drug-Related Side Effects and Adverse Reactions; Teratogens; Depression; Inflammatory Bowel Disease.

1. Introduction

Acne vulgaris is a common inflammatory skin disorder that affects the pilosebaceous unit. It occurs in many adolescents and often persists into adulthood with considerable physical and psychosocial impact. Standard topical treatments and oral antibiotics are effective for many patients, but some people develop serious or antibiotic-resistant cases of the disease.[1,2,3] The noticeable symptoms may lead to anxiety and depression, as well as decreased self-esteem. The primary treatment for these patients consists of oral isotretinoin, a vitamin A-derived systemic retinoid. The medication specifically targets three main acne-related mechanisms (sebaceous gland overactivity, abnormal keratinization, inflammation) and provides lasting therapy results.[2,4,5]

In the early 1980s, isotretinoin was introduced to the market and revolutionized acne treatment due to its outstanding performance.[2,6] However, despite its success, the medication can lead to many adverse effects.[7] The majority of patients experience lip inflammation (cheilitis), dry or peeling skin, mucosal dryness in the nose or eyes, and other related symptoms.[6,8,9] Less often, laboratory tests show two main issues: elevated blood triglyceride and cholesterol levels, as well as occasional increases in liver enzymes.[6,8,9] Most of these adverse effects can be managed with supportive care, including the use of moisturizers, lip balms, and regular check-ups.[9,10] The occurrence of severe liver damage is infrequent, as patients usually benefit from dose adjustments and brief interruptions of their therapy to control laboratory test results.[6,8] Regular monitoring allows patients to finish their treatment plans successfully.[1,6]

Isotretinoin has strong teratogenic properties and is associated with a high risk of severe birth defects if exposure occurs during pregnancy; a fact that demands strict pregnancy-prevention programs for women of reproductive age.[11,12] Special prescribing rules for isotretinoin in many countries require patient enrollment in risk-management programs, completion of counseling sessions, and multiple pregnancy tests.[6,11]

Research suggests a potential relation between isotretinoin and neuropsychiatric side effects, such as depression and suicidal thoughts [13,14,15], as well as gastrointestinal problems, including inflammatory bowel disease.[8,9] However, epidemiological studies have not proven a definitive connection.[16,17,18] Isotretinoin is associated with musculoskeletal complaints (arthralgias, myalgias) and rare ocular or neurological events.[19,20]

The majority of isotretinoin's adverse effects are controllable with proper medical care, but the potential for many possible complications should influence doctors when making treatment decisions. In this literature review, published data on the benefits and safety challenges of isotretinoin therapy are summarized and critically assessed to provide a better perspective on acne management.[6,8,9]

2. Methods

This article is a narrative literature review of the efficacy and safety of oral isotretinoin in the treatment of acne vulgaris, with an emphasis on clinical outcomes, adverse effects, laboratory abnormalities, monitoring strategies, and the pathophysiological mechanisms relevant to its mode of action. These issues are presented in the context of acne epidemiology, pathophysiology, and other therapeutic methods.

A structured search of PubMed/MEDLINE was conducted for articles published between January 2016 and November 2025. We used MeSH terms and free-text keywords related to acne and isotretinoin (e.g. “acne vulgaris”, “acne epidemiology”, “isotretinoin”, “13-cis-retinoic acid”, “retinoids”, “safety”, “adverse effects”, “teratogenicity”, “depression”, “psychiatric”, “inflammatory bowel disease”, “wound healing”, “laser therapy”, “mTOR”, “IGF-1”), combined with Boolean operators. The reference lists of key papers were screened manually. Grey literature, conference abstracts, and non-peer-reviewed sources were excluded.

We included peer-reviewed studies and reviews on oral isotretinoin that reported on efficacy, remission, mode of action, adverse effects (mucocutaneous, laboratory, gastrointestinal, psychiatric, teratogenic, musculoskeletal, neurological, and ophthalmologic), effects on tissue regeneration or wound healing, monitoring recommendations, as well as key data on acne epidemiology, pathogenesis, risk factors, and standard therapeutic approaches when relevant. Eligible designs comprised randomized controlled trials, observational studies (prospective, retrospective, cohort, case-control), systematic reviews, meta-analyses, and high-quality narrative reviews. Exceptionally well-documented case reports, or very small case series, were considered when they described rare but clinically relevant adverse presentations in acne patients. We excluded publications focused solely on non-acne indications for isotretinoin, purely animal studies without clear translational relevance, and non-peer-reviewed opinions or letters without primary data.

3. Results

3.1. Acne Vulgaris

3.1.1. General Information

Acne vulgaris is a chronic inflammatory skin disorder that affects the pilosebaceous unit. The blockade of hair follicles and oil glands results in the formation of comedones, followed by papules, pustules, and nodules. This skin condition results from multiple factors and affects millions of people worldwide, making it one of the most common dermatological conditions. Acne appears mainly during early teenage years, with boys experiencing more cases than girls. Adults can also be affected, and females often suffer from a persistent or late-onset form of the disease.[1,4]

Multiple elements in a person's background make them more likely to be affected by acne. The combination of androgens and insulin-like growth factor 1 (IGF-1) during puberty triggers activity in the sebaceous glands, increasing the risk of acne. The Western diet, including high-glycemic foods and dairy products, leads to higher IGF-1 signaling and worsens acne

symptoms. Other contributors, such as stress, smoking, specific medications, and occlusive cosmetics, trigger inflammation and follicular occlusion, which aggravate the condition. Individuals with a family history of acne are more susceptible to severe cases of this disorder.[4,5]

3.1.2. Pathophysiology

Acne vulgaris is a persistent inflammatory condition that results from multiple interacting factors. The combination of insulin-like growth factor 1 (IGF-1) and androgens activates keratinocytes and sebocytes during puberty. These endocrine signals stimulate intracellular pathways through AKT/mTORC1, which is also influenced by high-glycemic foods and dairy products. The AKT activation causes transcription factors (FoxO1 and FoxO3) to exit the nucleus through phosphorylation, which triggers a cascade of lipogenic and pro-inflammatory gene expression. In this context, transcription factors, including AR, SREBF1, and PPARγ, are upregulated, whereas GATA6, which controls normal infundibular keratinocyte development, shows decreased expression.[4,12]

The molecular events cause specific changes in the skin. The upregulation of AR, SREBF1, and PPARγ stimulates sebocytes, resulting in increased sebum production. The ubiquitin ligase MDM2, activated through AKT signaling, leads to p53 degradation and reduced sebocyte apoptosis. The absence of GATA6 and other differentiation signals causes abnormal keratinocyte development, which impairs hair follicle function. The microcomedone forms due to excessive lipid production and trapped keratinocytes, representing the first microscopic acne lesion.[4,12]

Sebum accumulation, along with skin lipid modifications, enables skin commensals such as Cutibacterium acnes to proliferate. Bacterial products and accumulated follicular debris activate keratinocytes and resident immune cells through innate immune receptors. This leads to the release of cytokines and chemokines, the recruitment of neutrophils and other leukocytes to the follicle, and a gradual increase in local inflammation. The combination of endocrine stimuli, sebum alterations, keratinization abnormalities, and microbial growth maintains the persistent inflammatory pattern of acne.[4,12]

3.1.3. Treatment

Topical medications are usually the first line of treatment for acne. Benzoyl peroxide and retinoids (adapalene or tretinoin) are initial therapy choices that help control bacterial growth and remove follicular blockages. The guidelines recommend applying benzoyl peroxide or

adapalene topically as a single treatment or in combination with other acne medications. Additional topical options include azelaic or salicylic acid and antibiotics (clindamycin, erythromycin), often in combination products.[1,2]

Moderate-to-severe cases of acne may require oral therapy. The standard treatment involves using tetracycline antibiotics, such as doxycycline and minocycline, paired with non-antibiotic topicals to limit the development of resistance. Women who suffer from acne due to hormonal changes can find successful treatment through anti-androgen therapy, including combined oral contraceptives and spironolactone. The most effective medication for resistant or severe nodulocystic acne is oral isotretinoin (13-cis-retinoic acid), which addresses all primary factors of acne development and creates long-lasting remissions.[1,2]

Gentle skincare, including non-comedogenic moisturizers that contain hyaluronic acid or glycerin, is the key to strengthening the skin barrier without causing acne flare-ups. It is also recommended to cleanse the skin twice daily with a gentle, oil-free cleanser and to avoid rough exfoliants or thick makeup products.[1,10]

Medical acne treatment can be complemented by dermatologic procedures, including superficial chemical peels with glycolic or salicylic acid solutions, blue/red LED phototherapy, photodynamic therapy, and fractional lasers. These interventions offer better acne control and scar improvement compared with isotretinoin alone.[1,21,22]

3.2. Isotretinoin

Isotretinoin is a highly effective acne medication for carefully selected patients.[23] Proper dosing, treatment duration, close monitoring (especially of pregnancy status and blood tests), and avoidance of contraindicated drugs help to maximize its benefits while minimizing risks.[2,6,8]

3.2.1. Mechanism of Action

The oral 13-cis-retinoic acid, known as isotretinoin, derives from vitamin A and belongs to the first generation of synthetic retinoids. This medication is indicated for severe or nodular acne that does not respond to conventional treatment. The systemic properties of isotretinoin enable it to affect multiple pathways that contribute to the development of acne.[2,4,5]

The primary mechanism of isotretinoin is the induction of programmed cell death (apoptosis) in sebaceous gland cells (sebocytes). Isotretinoin leads to an elevated production of TNF-related apoptosis-inducing ligand, IGF-binding protein-3, and neutrophil gelatinase-associated lipocalin, which induce apoptosis and cause a substantial reduction in sebaceous cell

populations. As a result, sebaceous glands become smaller and far less active, which decreases sebum production and prevents the development of new comedones.[4,5,12]

The molecular mechanism of isotretinoin's action involves binding to nuclear hormone receptors, which function as regulators of gene expression. Intracellular retinoids attach to carrier proteins that transport them into the nucleus, where they activate retinoic acid receptors (RARs) and retinoid X receptors (RXRs). The activated receptors interact with retinoic acid response elements (RAREs) in DNA to regulate genes that control cell development, differentiation, and death. Isotretinoin increases the expression of tumor suppressor proteins, including p53, FoxO1, and FoxO3, in sebocytes and activates cell death pathways, which leads to decreased oil production. The transcriptional shifts function against the insulin/IGF-1 and androgen signaling pathways, which normally promote sebaceous lipid production.[4,5,12]

Beyond its sebum-suppressive effects, isotretinoin normalizes the behavior of keratinocytes in hair follicles. It enables proper cell differentiation and shedding, which stops the formation of microcomedones. The result is fewer obstructed hair follicles and reduced development of new acne lesions.[4,12] A smaller sebum supply makes it more difficult for *Cutibacterium acnes* to obtain the necessary nutrients, leading to reduced bacterial growth and inflammation.[2,4,12]

In summary, isotretinoin targets all primary mechanisms in acne pathophysiology, including excessive sebum production, follicular hyperkeratinization, bacterial growth, and inflammation. This mechanism offers strong therapeutic effects and extended periods of acne remission, but patients need to undergo close medical supervision due to possible adverse effects.[2,4,12]

3.2.2. Indications and Patient Selection

Healthcare providers reserve isotretinoin for patients who have failed to respond to standard acne therapies. The medication is mainly used for severe cases of nodulocystic or extensive inflammatory acne. Dermatologists may also prescribe isotretinoin when moderate acne causes multiple lesions, scarring, and emotional distress. Treatment is generally limited to adolescents and adults; isotretinoin is not recommended before puberty, unless the acne is unusually aggressive.[1,2]

3.2.3. Dosage and Treatment Duration

The standard oral dose of isotretinoin is 0.5-1.0 mg/kg per day, administered in two divided doses. The total daily dose must take the patient’s weight into account and may be adjusted

during treatment based on how well the patient tolerates the medication and responds to therapy. The treatment duration typically ranges from 4 to 6 months. Specialist doctors should only approve extended treatment periods for exceptionally severe or treatment-resistant conditions. Patients should administer isotretinoin with meals because, due to its lipophilic nature, the medication requires food for better absorption.[2,24]

3.2.4. Monitoring and Safety Precautions

The beginning of isotretinoin therapy requires baseline laboratory testing. Standard laboratory tests include liver function tests (AST and ALT), a fasting lipid profile (cholesterol and triglycerides), a complete blood count, and a blood glucose test.[6,8,25] Women of reproductive age need to provide two negative pregnancy test results before starting isotretinoin treatment. Due to its teratogenic properties, absolute pregnancy prevention is required; women should use two birth control methods and perform monthly pregnancy tests throughout the entire treatment period.[11,12]

Laboratory tests should be performed at scheduled times. Healthcare providers need to monitor liver enzymes and lipid levels 1-2 months after starting therapy, then every 3-4 months, or more frequently if abnormalities appear.[6,8,25] It is also recommended to perform thyroid and prolactin tests at regular intervals, as isotretinoin can affect these hormone levels in some patients.[25,26] The treatment plan requires immediate modification when laboratory tests reveal relevant abnormalities, such as a significant rise in transaminases or triglycerides. It is also essential to critically assess all aspects of the patient's health status. While a direct link between isotretinoin and depression has not been established, individuals with a history of mood disorders should be monitored carefully.[13,14,18]

3.2.5. Efficacy and Relapse

The specific acne-treatment properties of isotretinoin come from its ability to address multiple aspects that contribute to acne development. The medication decreases sebaceous gland activity, controls follicular keratinization, and indirectly reduces inflammation in the skin. For most individuals, significant acne improvement occurs during the second to third month of treatment. Most patients will achieve complete or near-complete acne clearance after finishing their full therapy course. The long-term success mainly depends on using the correct isotretinoin dose and maintaining treatment for an adequate period. Patients who complete their prescribed cumulative treatment dose experience longer and more persistent remission.[2,24,25]

Nevertheless, acne is a long-term condition, and recurrences can happen. If acne does recur after completing a course, it is often milder than before and may be managed with topical treatments or a brief course of isotretinoin. To reduce the risk of relapse, clinicians need to ensure that therapy does not end too soon. A practical guideline is to continue treatment until all inflammatory lesions have cleared, and then continue therapy for another 1 to 2 months. Patients who complete their isotretinoin treatment should practice proper skin care while using topical retinoids or other maintenance medications for multiple months to prevent their acne from returning.[2,24]

3.2.6. Drug Interactions and Contraindications

The medical team needs to follow specific guidelines when prescribing isotretinoin to their patients. Due to its teratogenicity, this medication should not be given to lactating women. Both male and female patients need to avoid pregnancy throughout their treatment period and for one month after stopping the medication.[11,12] Doctors should provide alternative treatment methods for patients with a known allergy to isotretinoin or any component of its formulation. Special care is essential for patients with severe liver problems, kidney issues, uncontrolled lipid disorders, and bone marrow suppression, as isotretinoin can make these conditions worse.[6,8,27]

Healthcare providers should perform thorough assessments of all medications that patients are currently using. The combination of isotretinoin with tetracycline antibiotics, including doxycycline, can lead to pseudotumor cerebri, also known as benign intracranial hypertension. During therapy, patients need to avoid other retinoids and high-dose vitamin A supplements, as these substances may increase the risk of toxic adverse effects. Doctors need to be particularly careful with patients who take medications that increase blood lipid levels or affect mood, because isotretinoin can make these conditions worse. Good practice requires medical specialists to check for any medical issues that may make the treatment inappropriate and to evaluate all medications and dietary supplements that patients are taking before prescribing isotretinoin.[6,8,9]

3.2.7. Adverse Effects

Isotretinoin is a highly effective acne therapy for carefully selected patients. The treatment benefits are maximized with correct dosing, appropriate treatment duration, and close monitoring, for example, regular pregnancy checks and blood tests. The extent of adverse effects that patients experience depends mainly on their individual characteristics and the

amount of medication they receive. It is essential for healthcare providers to understand these factors in order to ensure patient safety when delivering optimal care.[2,6,24]

1. Mucocutaneous Effects

Isotretinoin therapy leads to reduced sebaceous gland function and a significant decrease in skin oil production. The most common adverse effect is dryness that affects both the skin and mucous membranes. The majority of patients report cheilitis (inflamed, cracked lips), xerosis (dry, rough skin), occasional skin itching, mild redness, and facial skin peeling.[6,8,9] The nasal mucosa becomes dry, which can cause nosebleeds (epistaxis) in people who are prone to this condition.[25,29] Hair follicle death from apoptosis may lead to telogen effluvium, which results in widespread hair loss in patients who take isotretinoin.[8] Some patients experience dry eyes and mild blepharitis, but these conditions respond well to eye drop treatments.[20,28] The drug can also cause rare instances of severe mucocutaneous toxicity, which includes extensive dermatitis.[6,8,12]

The severity of dryness symptoms depends mostly on the amount of medication and the length of the treatment period. These events occur less frequently and become less severe with low daily doses or during intermittent treatment.[24,25] To prevent discomfort, patients should start prophylactic care at the beginning of therapy through daily use of gentle cleansers, emollients, lip balms, eye drops, and nasal lubricants.[6,10,30]

2. Laboratory Abnormalities

In comparison to mucocutaneous reactions, changes in laboratory results are less common and remain within mild ranges. Clinical studies have shown that patients who received isotretinoin developed dyslipidemia more frequently than participants in control groups. The lipid profiles indicated three primary changes, which included: elevated LDL cholesterol, triglycerides, and decreased HDL cholesterol. The majority of patients who received isotretinoin treatment experienced minor, short-term increases in liver enzyme levels (aminotransferases). Severe liver damage occurs only in exceptional cases.[6,8,24,25]

Most laboratory changes associated with isotretinoin treatment resolve on their own. Doctors can treat mild increases in liver enzymes and lipids by lowering the treatment dose or taking short breaks from medication until the values return to normal. The therapy needs to stop when liver enzyme levels reach more than three times the upper limit of normal. Monitoring laboratory results enables healthcare providers to protect patients from harm while maintaining the effectiveness of their acne treatment.[6,8,25]

3. Gastrointestinal Effects

The gastrointestinal adverse effects of isotretinoin are rare, but doctors once suspected that it could cause inflammatory bowel disease (IBD). The drug triggers intestinal epithelial cells to die via apoptosis, which may increase the risk of developing IBD. Despite this mechanism, multiple reviews have not found evidence that isotretinoin causes new cases of IBD. In reality, the occurrence of IBD in acne patients may already be higher than in individuals who do not use isotretinoin, due to skin inflammation combined with prolonged antibiotic treatment, such as tetracyclines.[8,9]

4. Psychiatric Adverse Effects

Multiple large meta-analyses have not demonstrated an overall increase in the risk of mood disturbances or suicidal thoughts with isotretinoin treatment.[13,14,15] A 2019 systematic review analyzed twenty studies, which showed that patients experienced better management of depressive symptoms when taking isotretinoin. The pooled standardized mean difference was -0.33 (95% confidence interval -0.51 to -0.15) compared to pre-treatment levels. In the same analysis, four depression incidence studies revealed that patients developed depressive disorders at 1.15 times (95% CI 0.60-2.21) the pre-treatment rate, but the results did not reach statistical significance.[13]

The 2024 meta-analysis, which studied 1.63 million acne patients, showed that depression developed in 3.8% (95% CI 2.45-5.93) of patients during their first year of isotretinoin treatment, and suicidal behavior occurred in less than 0.5% of patients.[14] The research data indicate that isotretinoin treatment is not associated with higher rates of depression or suicide attempts at the population level.[14,16,17] Furthermore, clearing acne helps patients overcome their anxiety and depressive symptoms.[15,18]

5. Teratogenicity

The main serious adverse effect of isotretinoin is related to its teratogenicity. The presence of isotretinoin triggers the activation of pro-apoptotic transcription factors (p53, FoxO1), which results in neural crest cell death and embryopathic effects. The prevention of fetal harm requires absolute measures to prevent pregnancy from occurring. Women need to show proof of a negative pregnancy test and maintain dual contraceptive methods from the start of treatment until one month after stopping the medication.[11,12]

Research shows that pregnancies exposed to isotretinoin can result in spontaneous abortions and birth defects in babies who survive. The most common congenital disorders include ear deformities, palate fissures, an underdeveloped thymus, and heart problems. Importantly, isotretinoin use does not result in permanent fertility issues after patients complete their therapy.[11,12]

6. Musculoskeletal and Neurological Effects

Patients who receive isotretinoin may develop musculoskeletal problems. The primary symptoms include arthralgia and myalgia, along with nonspecific stiffness. Most of these adverse effects are mild, and treatment through dose modification leads to resolution. The combination of long-term treatment with high doses can lead to diffuse skeletal hyperostosis, which shows as mild reversible changes on imaging tests. Sacroiliitis, an inflammatory spondyloarthropathy, may occur in exceptionally rare cases.[19,24,25]

The use of isotretinoin in developing children can result in permanent closure of growth plates, which affects their bone development. Standard acne treatment with isotretinoin has been associated with growth plate fusion in the knee joints of adolescents, but this condition seems to occur rarely; young patients need close monitoring of their bone development.[5,19,24]

Neurological adverse effects appear infrequently. The medical condition, benign intracranial hypertension, also known as pseudotumor cerebri, is rare and causes headaches and visual disturbances, mainly affecting overweight female patients between the teenage and early adult years. The medical literature contains only a few reports of isotretinoin users developing acute encephalitis. Severe neurological complications occur in patients at a very low rate.[6,8,16]

7. Ophthalmologic Side Effects

Isotretinoin can lead to eye discomfort as one of its adverse effects. The medication affects patients' ability to see in dimly lit environments and causes dryness, redness, and burning sensations in their eyes. The study results showed that eye dryness and irritation are the most common ocular adverse effects, followed by conjunctivitis and eye pain.[20,28] Other ocular issues include temporary nearsightedness, occasional increased intracranial pressure (papilledema), and transient cataract changes. Most eye symptoms disappear within several weeks after treatment cessation, especially when patients use artificial tears and practice proper eyelid care from the start of therapy.[20]

8. Acne Flare-ups

Research studies show that some patients with severe cystic acne experience worsening of their inflammatory skin lesions before any improvement occurs.[8,24,25] Isotretinoin triggers cell transformations and the release of inflammatory mediators, which cause the skin to flare up during the initial phase of therapy. This condition usually resolves on its own, but patients may experience acne fulminans-like symptoms, including painful nodules and skin ulcers without fever.[31] To control acne flare-ups, doctors should start treatment by giving patients 0.1-0.2 mg/kg/day of isotretinoin, sometimes with the addition of oral prednisone at 0.5-1.0 mg/kg/day for two to four weeks. The combination of steroid dose reduction with isotretinoin dose escalation helps to prevent early flare-ups.[7,8,24]

3.2.8. Effects on Tissue Regeneration and Healing

Most patients who receive isotretinoin treatment do not experience difficulties with their wound healing. Research has shown that patients who take low-dose isotretinoin do not develop hypertrophic scars or keloids when they undergo procedures, including superficial chemical peels, laser treatments, microneedling, and skin biopsies.[21] Studies indicate that patients who receive 10–20 mg of low-dose isotretinoin daily in combination with non-ablative laser therapy achieve even better results for their acne and scar management.[22] The majority of medical professionals agree that patients can safely undergo minor dermatologic and cosmetic procedures during or after isotretinoin therapy as long as they stay away from aggressive methods. Many clinicians recommend waiting several months after completing isotretinoin treatment before undergoing invasive or fully ablative procedures, such as dermabrasion, deep chemical peels, and major surgical excisions.[21]

4. Discussion

Isotretinoin serves as the main therapy for severe and treatment-resistant acne that can result in scarring and emotional burden.[1,2] The medication works by shrinking sebaceous glands, correcting follicular keratinization patterns, and reducing inflammation to create enduring remission that other treatments often fail to achieve.[2,4,5] Doctors need to achieve therapeutic goals through carefully selected treatment strategies that deliver beneficial results.[1,2]

Almost all patients develop mucocutaneous dryness. Healthcare providers should initiate preventive measures, such as gentle cleansers, moisturizers, lip balm, sun protection, and ocular or nasal lubricants, at the beginning of treatment.[6,10,30] The majority of laboratory changes

consist of small lipid increases and liver enzyme elevations, which are reversible with proper monitoring, especially for patients with metabolic or hepatic conditions.[6,8,25] The evidence shows that using reduced medication doses and taking breaks between doses helps to reduce these adverse effects while maintaining effective treatment.[24,25]

One of the most serious adverse effects of isotretinoin is teratogenicity.[11,12] Isotretinoin causes fetal death and severe birth defects when pregnant women are exposed to even small amounts of the medication, so pregnancy prevention is necessary.[11,12] Women of reproductive age need to use dual birth control methods, undergo regular pregnancy tests, and fully understand the treatment risks before starting isotretinoin therapy.[2,11,12] The treatment program should be stopped if patients demonstrate any signs of non-compliance.[11,12]

The two main points of disagreement center on the safety of psychiatric and gastrointestinal systems.[8,9,13] Research into depression, suicidal behavior, and inflammatory bowel disease suggests possible connections with isotretinoin,[8,9,15] but studies based on population data and meta-analyses do not support these risks.[13,14,16] The psychological impact of severe acne makes it difficult to distinguish between drug side effects and the emotional strain of living with acne, so healthcare providers need to perform initial assessments and monitor symptoms while referring patients to specialists when any issues arise.[13,15,18]

Musculoskeletal, neurological, and ophthalmologic adverse events are usually mild [6,8,19], but clinicians need to monitor for them, especially in patients who take isotretinoin in high doses or for longer treatment durations.[6,8,20] Established protocols for dose adjustments, treatment interruptions, and medical consultations are particularly important when patients experience severe back pain, persistent headaches, or visual disturbances, as these symptoms may indicate more serious conditions.[6,19,20]

Medical professionals should follow strict rules for prescribing isotretinoin and monitor patients' health throughout the entire therapy period.[2,6,8] Pre-treatment education and established knowledge about possible adverse effects improve benefits and patients’ safety during isotretinoin therapy.[6,24,25]

5. Conclusions

Oral isotretinoin serves as the main systemic treatment for patients with severe acne who have not responded to standard therapies. The medication offers superior acne clearance and extended disease-free periods by targeting all essential mechanisms that cause the condition.
The review shows that this advantage is achieved at the cost of a broad, but largely predictable, range of adverse effects. The majority of patients experience skin and mucous membrane

dryness, and some also develop minor laboratory changes that depend on their prescribed dosage. The reversible nature of these adverse effects allows patients to control their symptoms by following skin care guidelines, undergoing laboratory tests, and making medication adjustments under medical supervision.

The absolute non-negotiable safety concern is teratogenicity. The prescription of isotretinoin to women of reproductive age requires strict prevention of pregnancy. Clinical practice calls for the use of dual contraceptive methods, pregnancy testing, and formal risk management systems to support this approach.

The scientific evidence linking isotretinoin to depression, suicide attempts, or inflammatory bowel disease remains unclear. Current evidence shows that these conditions occur infrequently and often as a result of underlying medical conditions. Further high-quality, long-term studies are needed, particularly among patients who receive high-dose or prolonged isotretinoin treatment.

Medical professionals should provide access to isotretinoin for patients with severe acne that leads to scarring and psychological distress. The medication must be prescribed through established safety protocols. Doctors need to evaluate patients' risk factors and monitor them throughout the entire treatment, obtaining specialist help when necessary. This therapeutic approach enables patients to maintain the benefits of isotretinoin while minimizing the risk of serious adverse effects.

Disclosure

Author's Contribution

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References

1. Santer M, Burden-Teh E, Ravenscroft J. Managing acne vulgaris: an update. Drug Ther Bull. 2023;62(1):6-10. doi:10.1136/dtb.2023.000051
2. Costa CS, Bagatin E, Martimbianco ALC, da Silva EM, Lúcio MM. Oral isotretinoin for acne. Cochrane Database Syst Rev. 2018;11(11):CD009435. doi:10.1002/14651858.CD009435.pub2
3. Heng AHS, Chew FT. Systematic review of the epidemiology of acne vulgaris. Sci Rep. 2020;10(1):5754. doi:10.1038/s41598-020-62715-3
4. Melnik BC. Acne Transcriptomics: Fundamentals of Acne Pathogenesis and Isotretinoin Treatment. Cells. 2023;12(22):2600. doi:10.3390/cells12222600
5. Khalil S, Bardawil T, Stephan C, Darwiche N, Abbas O, Kibbi AG. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. J Dermatolog Treat. 2017;28(8):684-696. doi:10.1080/09546634.2017.1309349

6. Fallah H, Rademaker M. Isotretinoin for acne vulgaris - an update on adverse effects and laboratory monitoring. J Dermatolog Treat. 2022;33(5):2414-2424. doi:10.1080/09546634.2021.1967269

7. Bettoli V, Guerra-Tapia A, Herane MI, Piquero-Martín J. Challenges and Solutions in Oral Isotretinoin in Acne: Reflections on 35 Years of Experience. Clin Cosmet Investig Dermatol. 2019;12:943-951. doi:10.2147/CCID.S234231

8. Kapała J, Lewandowska J, Placek W, Owczarczyk-Saczonek A. Adverse Events in Isotretinoin Therapy: A Single-Arm Meta-Analysis. Int J Environ Res Public Health. 2022;19(11):6463. doi:10.3390/ijerph19116463

9. Rajput I, Anjankar VP. Side Effects of Treating Acne Vulgaris With Isotretinoin: A Systematic Review. Cureus. 2024;16(3):e55946. doi:10.7759/cureus.55946

10. Reyes-Hadsall S, Ju T, Keri JE. Use of Oral Supplements and Topical Adjuvants for Isotretinoin-Associated Side Effects: A Narrative Review. Skin Appendage Disord. 2024;10(1):1-9. doi:10.1159/000533963

11. Draghici C, Miulescu R, Petca R, Petca A, Dumitrașcu MC, Șandru F. Teratogenic effect of isotretinoin in both fertile females and males (Review). Exp Ther Med. 2021;21(5):534. doi:10.3892/etm.2021.9966

12. Melnik BC. Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. Acta Derm Venereol. 2017;97(2):173-181. doi:10.2340/00015555-2535

13. Li C, Chen J, Wang W, Ai M, Zhang Q, Kuang L. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis. BMJ Open. 2019;9(1):e021549. doi:10.1136/bmjopen-2018-021549

14. Tan NKW, Tang A, MacAlevey NCYL, Tan BKJ, Oon HH. Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users: A Meta-Analysis. JAMA Dermatol. 2024;160(1):54-62. doi:10.1001/jamadermatol.2023.4579

15. Gupta N, Gupta M. The Controversies Surrounding Acne and Suicide: Essential Knowledge for Clinicians. Cureus. 2023;15(8):e43867. doi:10.7759/cureus.43867

16. Paljarvi T, McPherson T, Luciano S, Herttua K, Fazel S. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. Br J Dermatol. 2022;187(1):64-72. doi:10.1111/bjd.21049

17. Singer S, Tkachenko E, Sharma P, Barbieri JS, Mostaghimi A. Psychiatric Adverse Events in Patients Taking Isotretinoin as Reported in a Food and Drug Administration Database From 1997 to 2017. JAMA Dermatol. 2019;155(10):1162-1166. doi:10.1001/jamadermatol.2019.1416

18. Botsali A, Kocyigit P, Uran P. The effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients. J Dermatolog Treat. 2020;31(7):734-738. doi:10.1080/09546634.2019.1606396

19. Acar EM, Şaş S, Koçak FA. Evaluation of musculoskeletal adverse effects in patients on systemic isotretinoin treatment: A cross-sectional study. Arch Rheumatol. 2022;37(2):223-229. doi:10.46497/ArchRheumatol.2022.8645

20. Lamberg O, Strome A, Jones F, Mleczek J, Jarocki A, Troost J, et al. Ocular side effects of systemic isotretinoin - a systematic review and summary of case reports. J Dermatolog Treat. 2023;34(1):2213364. doi:10.1080/09546634.2023.2213364

21. Spring LK, Krakowski AC, Alam M, Bhatia A, Brauer J, Cohen J, et al. Isotretinoin and Timing of Procedural Interventions: A Systematic Review With Consensus Recommendations. JAMA Dermatol. 2017;153(8):802-809. doi:10.1001/jamadermatol.2017.2077

22. He S, Wang Y, Wang J, Tang L, Yang L, Ye F. Isotretinoin Combined Laser/Light-Based Treatments Versus Isotretinoin Alone for the Treatment of Acne Vulgaris: A Meta-Analysis. J Cosmet Dermatol. 2025;24(1):e16639. doi:10.1111/jocd.16639

23. Paichitrojjana A, Paichitrojjana A. Oral Isotretinoin and Its Uses in Dermatology: A Review. Drug Des Devel Ther. 2023;17:2573-2591. doi:10.2147/DDDT.S427530

24. Lin L, Lin W, Zheng Y, Cai H. Effectiveness and safety of different dosing regimens of isotretinoin for acne vulgaris: a systematic review. Postepy Dermatol Alergol. 2025;42(4):346-353. doi:10.5114/ada.2025.153322

25. Feszak IJ, Brzeziński P, Feszak S, Kitowska A, Waśkow M, Kawczak P, et al. Isotretinoin Treatment for Acne Vulgaris: A Five-Year Retrospective Analysis of

Clinical and Biochemical Adverse Effects. J Clin Med. 2025;14(18):6473. doi:10.3390/jcm14186473

26. Uyar B, Solak A, Saklamaz A, Akyildiz M, Genc B, Gökduman A. Effects of isotretinoin on the thyroid gland and thyroid function tests in acne patients: A preliminary study. Indian J Dermatol Venereol Leprol. 2016;82(5):587-588. doi:10.4103/0378-6323.182794

27. Forouzani-Haghighi B, Karimzadeh I. Isotretinoin and the Kidney: Opportunities and Threats. Clin Cosmet Investig Dermatol. 2020;13:485-494. doi:10.2147/CCID.S259048

28. Yılmaz U, Küçük E, Koç Ç, Özköse A. Investigation of the effects of systemic isotretinoin treatment on retinal nerve fiber layer and macula. J Dermatolog Treat. 2017;28(4):314-317. doi:10.1080/09546634.2016.1254146

29. Tasli H, Yurekli A, Gokgoz MC, Karakoc O. Effects of oral isotretinoin therapy on the nasal cavities. Braz J Otorhinolaryngol. 2020;86(1):99-104. doi:10.1016/j.bjorl.2018.10.004

30. Anaam MS, AlShibl DA, Alfadly S, Aloyuni MY, Al Harbi FH, Alhmoud H. Adverse Effects and Precautionary Measures for Isotretinoin Use in Patients with Acne Vulgaris: A Single-Center Study. Healthcare (Basel). 2025;13(13):1617. doi:10.3390/healthcare13131617

31. Woźna J, Korecka K, Stępka J, Bałoniak A, Żaba R, Schwartz RA. Acne fulminans treatment: case report and literature review. Front Med (Lausanne). 2024;11:1450666. doi:10.3389/fmed.2024.1450666