INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Isotretinoin: A Comprehensive Review

Pratiksha Kadale*, Sayali Karande, Sakshi Kumbhoje, Aniket Thanekar, Dr. D. R. Jadage

Women's College of Pharmacy, Peth Vadgaon, Kolhapur, Maharashtra

ARTICLE INFO

Published: 23 Feb 2026
Keywords:
Isotretinoin; 13-cis-retinoic acid; Acne vulgaris; Systemic retinoids; Sebaceous gland suppression; Sebum regulation; Cutibacterium acnes; Anti-inflammatory therapy; Pharmacokinetics; Teratogenicity; iPLEDGE program; Hyperlipidemia; Hepatotoxicity; Low-dose isotretinoin; Extended-release formulations; Nanocarrier drug delivery; Pharmacogenetics; Biomarker-guided therapy; Retinoid receptor signaling; Dermatological therapeutics.
DOI:
10.5281/zenodo.18746697

ABSTRACT

Isotretinoin is a systemic retinoid widely regarded as the most effective therapy for severe, recalcitrant acne vulgaris. Since its introduction into clinical practice, isotretinoin has revolutionized dermatological treatment by targeting multiple pathogenic mechanisms involved in acne, including sebaceous gland suppression, reduction of sebum production, normalization of follicular keratinization, inhibition of Cutibacterium acnes proliferation, and anti-inflammatory effects. Owing to its unique multimodal mechanism of action, isotretinoin remains the gold standard for nodulocystic and treatment-resistant acne.Despite its remarkable therapeutic efficacy, isotretinoin therapy is associated with a range of dose-dependent adverse effects, including mucocutaneous dryness, hyperlipidemia, hepatotoxicity, musculoskeletal symptoms, and teratogenicity. Strict monitoring protocols and pregnancy prevention programs are therefore essential components of treatment. In recent years, research has focused on optimizing dosing regimens, exploring low-dose strategies, minimizing relapse rates, and improving patient compliance while maintaining safety.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous follicles that affects people worldwide. It is one of the most common skin conditions, with a global prevalence of around 9.4%, and is particularly widespread during adolescence, where most individuals experience

***Corresponding Author:** Pratiksha Kadale
Address: *Women's College of Pharmacy, Peth Vadgaon, Kolhapur, Maharashtra.*
Email : pratikshakadale19@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

some degree of acne. Characterized by non-inflammatory lesions such as open and closed comedones and inflammatory lesions including papules, pustules, nodules and cysts, acne frequently involves the face, neck, chest and back. Severe or persistent cases may result in scarring and pigmentation, often requiring prolonged treatment. Although acne cannot be completely prevented or cured, effective management is available. Additionally, the condition poses a significant burden, not only medically but also economically and psychosocially, as it often leads to reduced quality of life and increased healthcare costs.

Management of acne vulgaris commonly begins with topical retinoids, which normalize follicular keratinization and reduce microcomedone formation. Agents such as tretinoin, tazarotene, adapalene and trifarotene are effective for both comedonal and inflammatory lesions and are often used as first-line therapy or for long-term maintenance. Application frequency is gradually increased as tolerance develops, and irritation can be minimized with moisturizers and sunscreen. In more severe or recalcitrant cases, oral isotretinoin may be required, as it targets all major pathogenic factors of acne and is particularly effective for nodular disease with scarring. However, due to its teratogenicity and systemic adverse effects, careful monitoring and pregnancy precautions are essential.

Oral isotretinoin (13-cis-retinoic acid) was approved by the FDA in 1982 for the treatment of severe acne and remains the most clinically effective therapy available, often resulting in long-term remission or marked improvement. Its superiority stems from its unique ability to target all major pathogenic factors in acne by influencing cellular proliferation, differentiation and apoptosis. Isotretinoin dramatically reduces sebum production, decreases comedogenesis, lowers surface and ductal *P. acnes* levels and exerts anti-inflammatory effects. A dose of 0.5–1.0 mg/kg/day can reduce sebum secretion by up to 90% within six weeks. Although it exhibits minimal direct binding to retinoid nuclear receptors, isotretinoin likely acts as a prodrug that is intracellularly converted to active metabolites capable of activating RAR and RXR receptors.

This review aims to provide a comprehensive overview of oral isotretinoin as a therapeutic option in acne management. It summarizes its unique pharmacological actions, including its ability to influence all major pathogenic factors of acne, and examines evidence supporting its clinical efficacy and role in achieving long-term remission. The review also considers the safety profile of isotretinoin, including dose-related adverse effects and teratogenic risks, and discusses current monitoring recommendations. Additionally, it highlights comparisons with other treatment modalities and explores recent advancements and emerging perspectives that may guide future clinical practice.

2. Chemistry and Pharmacological Profile:

Isotretinoin is chemically named as: (2Z, 4E, 6E, 8E)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8-tetraenoic acid. Isotretinoin is a powerful synthetic retinoid (Vitamin A derivative) used for severe acne by shrinking oil glands, reducing sebum, and normalizing skin cell turnover, acting as a systemic treatment with significant risks, especially teratogenicity, requiring strict monitoring.

2.1 Chemical Structure & Classification:

Chemical Name: **(**2Z, 4E, 6E, 8E)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8-tetraenoic acid.

Molecular Formula: C20H2802

Molecular Weight: 300.44 g/mol.

Key Feature: It's an isomer of all-trans-retinoic acid (tretinoin), specifically the 13-cis isomer, which is the active form

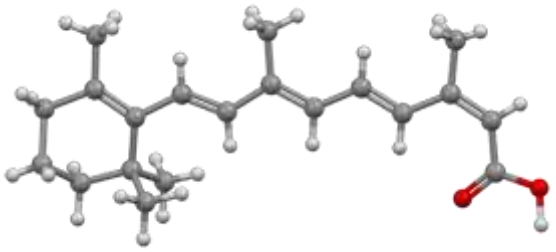

Figure 1 : Isotretinoin (ball and stick model)

Drug Class: Retinoid, Systemic Retinoid, Vitamin A derivative.

Therapeutic Class: Anti-acne agent (for severe, refractory acne).

2.2 Mechanism of Action:

2.2.1 Reduce sebaceous gland size and sebum production:

Isotretinoin works in acne mainly by reducing sebum production. It does this by causing the cells that make sebum (sebocytes) to undergo controlled cell death, called apoptosis. Inside these cells, isotretinoin is converted to all-trans retinoic acid, which increases specific proteins like TRAIL, IGFBP3 and NGAL. These proteins activate signals that safely destroy extra sebocytes. As the number of sebocytes decreases, sebum production drops, which helps clear acne.

2.2.2 Normalize keratinization:

Isotretinoin helps treat acne by correcting the abnormal keratinization inside hair follicles that leads to comedones. It reduces excess cell growth, promotes healthy differentiation of keratinocytes, and alters protein expression involved in skin structure. It also weakens cell-to-cell adhesion in clogged pores and changes skin lipid composition, increasing ceramides. Together, these actions normalize follicular function and reduce comedone formation, explaining its strong anti-comedogenic effect in acne.

2.2.3 Decrease cutibacterium acne colonization:

Isotretinoin mainly affects C. acnes while leaving most of the skin microbiome unchanged. At the start of treatment, C. acnes were the major microbe in follicles, but after 20 weeks it dropped significantly only in fast responders. Viral and fungal species were present only occasionally and did not relate to acne. Isotretinoin also reshaped the diversity of C. acnes strains: the beneficial D1 strains increased and were linked to better clinical improvement, while Cluster A strains became fewer but more dominant. Overall, isotretinoin selectively reduces and restructures C. acnes strains, explaining its strong clinical effect.

2.2.4 Anti-inflammatory effect:

When isotretinoin treatment starts, a brief flare in acne may occur because inflammation temporarily rises. But as treatment continues, isotretinoin powerfully reduces inflammation by lowering sebum, blocking inflammatory signals, and calming immune cells. It decreases major inflammatory chemicals like IL-1, IL-17, TNF-α, and IFN-γ, and reduces reactions to P. acnes. It also shifts the immune system toward a more balanced, less inflammatory state. Because skin defense proteins drop slightly, there is a small risk of skin infections like Staphylococcus aureus during therapy.

2.3 Pharmacokinetics:

No clinically significant differences in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects without acne were reported in published literature.

2.3.1 Absorption:

The isotretinoin mean T-max was 6.4 hours under fed conditions and 2.9 hours under fasting conditions following administration of a single 40 mg dose. Effect on Food No clinically significant differences in isotretinoin pharmacokinetics were observed following administration with a modified high fat, high calorie meal (123.2 calories from protein, 265.6 calories from carbohydrates, and 468 calories from fat; total calories 857 calories) with reduced vitamin A content. The mean AUC0–t and C-max of isotretinoin were 6095 ng*hr/mL and 369 ng/mL, respectively, following administration of a single 40 mg isotretinoin dose. under fed conditions; which were approximately 50% and 26% higher, respectively, compared to fasting conditions. However, isotretinoin may be given with or without meals

2.3.2 Distribution:

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin. Elimination The mean elimination half lives of isotretinoin and its 4 oxo isotretinoin metabolite were:

- 18 hours and 38 hours, respectively, after a single oral isotretinoin 40 mg dose.

2.3.3 Metabolism:

Isotretinoin is primarily metabolized by CYP2C8, 2C9, 3A4, and 2B6 in vitro. Isotretinoin and its metabolites are further metabolized into conjugates.

Following oral administration of isotretinoin capsules, at least three metabolites (4 oxo isotretinoin, retinoic acid (tretinoin), and 4 oxo retinoic acid (4 oxo tretinoin)) have been identified in human plasma. The extent of formation of all metabolites was higher under fed conditions. All of these metabolites possess retinoid activity in vitro. The clinical significance is unknown.

2.3.4 Excretion:

Following oral administration of an 80 mg dose of radiolabeled isotretinoin as a liquid suspension, the metabolites of isotretinoin were excreted in feces and urine in relatively equal amounts (total of 65% to 83%).

Specific Populations:

Pediatric Patients: No clinically significant differences in the pharmacokinetics of isotretinoin were observed based on age (12 to 15 years (n=38), and ≥18 years (n=19)). In both age groups, 4 oxo isotretinoin was the major metabolite; tretinoin and 4 oxo tretinoin were also observed

Drug Interaction Studies: No clinically significant differences in the pharmacokinetics of phenytoin (CYP2C9 substrate) were observed when used concomitantly with isotretinoin.

3. Clinical uses

3.1 Primary indication: severe nodulocystic acne

Isotretinoin is widely considered the most effective systemic therapy for severe nodulocystic acne, particularly in individuals who do not respond to conventional oral or topical treatments. Approved by the FDA in 1982, it reduces sebaceous gland size and activity, thereby targeting the underlying mechanisms of deep nodular lesions. Clinical guidelines recommend its use for severe or scarring acne, with daily dosing favored over intermittent regimens. Both

traditional isotretinoin and lidose-isotretinoin are suitable options, the latter offering enhanced bioavailability through its pre-solubilized lipid matrix.

3.2 Off-Label Uses

Isotretinoin has demonstrated therapeutic utility beyond severe acne, including indications such as moderate acne, cutaneous T-cell lymphomas, and chemoprevention of cutaneous squamous cell carcinoma in high-risk populations. It also constitutes a component of multimodal treatment protocols for high-risk neuroblastoma. Dermatologically, isotretinoin has been employed in the management of rosacea, folliculitis, and pyoderma facial. Evidence from a systematic review and meta-analysis indicates that low-dose isotretinoin (≤0.5 mg/kg/day) significantly reduces inflammatory lesion counts and erythema in rosacea, with sustained post-treatment benefits. Low-dose regimens demonstrated superior efficacy to topical agents and were associated with a favorable safety and tolerability profile.

3.3 Rosacea

Although isotretinoin is primarily known for treating severe acne, it has also shown meaningful benefits in rosacea since the early 1980s. Its ability to reduce sebaceous gland activity, lower sebum production, and provide anti-inflammatory effects makes it useful for certain rosacea subtypes, especially those with inflammatory papules and pustules. Rosacea itself is a chronic facial condition with four major forms erythematotelangiectatic, papulopustular, phymatous, and ocular and patients may show more than one subtype at the same time. Because each subtype presents differently, isotretinoin is particularly helpful in papulopustular and some phymatous cases, while other subtypes require more targeted therapies. Overall, isotretinoin serves as an important option when standard rosacea treatments are insufficient.

3.4 Seborrhea

Although research is limited, oral isotretinoin appears to be a promising option for moderate-to-severe seborrheic dermatitis. Low-dose therapy (10–20 mg/day) used over 2–6 months has shown meaningful improvement in SD severity, with similar benefits across doses. Clinical trials indicate that isotretinoin can reduce scalp pruritus, decrease sebaceous gland activity, and improve quality of life more effectively than standard topical treatments. A recent systematic review also found isotretinoin to be superior to therapies such as oral itraconazole, antifungal shampoos, and salicylic acid cleansers. Overall, isotretinoin may be an effective and well-tolerated option for difficult-to-treat SD, although rare cases of isotretinoin-induced SD-like eruptions have been reported**.**

3.5 Keratosis Pilaris

Keratosis Pilaris (KP) is a common disorder of keratinization characterized by rough, small follicular papules, often on the arms, thighs, or buttocks. Oral isotretinoin may help by normalizing follicular keratinocyte differentiation and reducing follicular plugging and associated inflammation. Evidence from case reports and small clinical series indicates that isotretinoin, at doses ranging from 0.1–1 mg/kg/day for several weeks to months, can significantly improve the roughness and visibility of papules, though relapse may occur after discontinuation. Combining isotretinoin with topical emollients or keratolytic can further enhance clinical outcomes and maintain skin smoothness.

3.6 Ichthyosis

Ichthyosis is a group of genetic skin disorders characterized by dry, scaly, rough, and sometimes red or itchy skin, with severity varying among patients. Oral isotretinoin has been shown to significantly improve skin symptoms, particularly in lamellar ichthyosis and epidermolytic hyperkeratosis, with typical mean doses around 2 mg/kg/day in clinical trials. In severe cases such as harlequin ichthyosis, early initiation of isotretinoin (even from day 7 of life) may improve survival. The therapeutic effects of isotretinoin are dose-dependent, with lower doses (0.5–1 mg/kg/day) often preferred for maintenance therapy to maximize improvement while minimizing cutaneous and systemic side effects.

4. Dosage forms and regimen

4.1 Available dosage form and Strength

Isotretinoin is administered orally as a capsule. The drug has low bioavailability and is highly lipophilic. The patient can maximize the oral absorption of isotretinoin by taking the drug with a meal. Isotretinoin should be taken with a full glass of water to avoid esophageal irritation. Isotretinoin is available in oral capsule formulations in strengths of 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg. Additionally, it is offered as a micronized capsule formulation in strengths of 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg.

4.2 Conventional vs. Low-Dose Therapy

4.2.1 Conventional dosing:

Standard dosing generally starts at 0.5 mg/kg/day and can increase to 1 mg/kg/day depending on tolerance.

Total cumulative dose traditionally targeted is ~120–150 mg/kg to help minimize relapse.

4.2.2 Low-dose therapy:

Lower daily doses (e.g., 10–20 mg/day or ~0.25–0.4 mg/kg/day) have been studied in mild/moderate acne with good tolerability and fewer side effects, though efficacy and relapse profiles vary across studies.

A systematic review indicated *similar or improved tolerability* with low-dose regimens versus conventional dosing.

4.3 Intermittent and micro-dosing regimen

Conventional dosing of isotretinoin (≈0.5–1 mg/kg/day given continuously) is associated with faster and more pronounced early improvement, particularly during the first 6–8 weeks of treatment. This regimen is effective for achieving rapid disease control and is traditionally preferred in severe acne. However, it results in higher cumulative drug exposure and is commonly associated with a greater incidence of adverse effects, especially mucocutaneous reactions such as cheilitis and dry skin.

In contrast, intermittent dosing regimens (low-dose isotretinoin administered on alternate days or for short periods each month) demonstrate comparable long-term efficacy to conventional continuous therapy. Although initial improvement may be slower, studies consistently show no significant difference in overall acne clearance by the end of treatment. Importantly, intermittent dosing significantly reduces cumulative dose and side-effect frequency, improving tolerability and patient adherence.

Overall, while conventional dosing provides quicker early results, intermittent dosing offers a safer and well-tolerated alternative with similar long-term outcomes, making it particularly suitable for mild to moderate acne and for patients

who are concerned about adverse effects or require prolonged therapy.

4.4. Factors influencing dose selection

Category	Factor	Clinical Considerations and Impact on Dosing
General Principles	Individualization	Dosing is tailored to balance efficacy with tolerability; ongoing dose adjustments are required throughout therapy.
Patient-Specific Factors	Body weight	Dose calculated on a mg/kg/day basis; common initiation at ~0.5 mg/kg/day with escalation up to 1.0 mg/kg/day as tolerated.
	Age	Younger patients may have higher relapse rates, potentially requiring higher cumulative doses or longer treatment duration.
	Acne severity and type	Severe nodular or conglobate acne typically requires standard to higher doses; moderate acne with scarring risk may respond to lower doses; acne fulminans requires very low initial dosing, often with systemic corticosteroids.
	Previous treatment response and relapse risk	History of relapse or poor prognostic factors (e.g., truncal acne) may justify targeting a higher cumulative dose to reduce recurrence.
	Comorbidities and laboratory parameters	Pre-existing liver dysfunction or dyslipidemia necessitates cautious dosing, lower starting doses, and frequent monitoring of liver enzymes and lipid profiles.
	Patient preference and lifestyle	Willingness to tolerate side effects, adherence potential, and ability to take medication with food influence daily dose and treatment duration.
Treatment Strategy Factors	Target cumulative dose	Most guidelines recommend a cumulative dose of 120–150 mg/kg to minimize relapse risk; achievable with higher daily doses over shorter courses or lower daily doses over longer durations.
	Side-effect management	Dose-dependent adverse effects (e.g., cheilitis, dry skin, myalgia) often require dose adjustment; gradual dose escalation ("low and slow") improves tolerability.
	Formulation type	Micronized formulations provide more consistent absorption and greater dosing flexibility, independent of meal timing.
Overall Approach	Dynamic dose adjustment	Clinicians continuously modify dosing to optimize long-term efficacy while maintaining safety and patient adherence.

5. Adverse effects

5.1 Teratogenicity

Isotretinoin is a potent teratogen, and prenatal exposure is associated with a 20–35% risk of major congenital malformations. Reported defects include craniofacial abnormalities, cardiovascular malformations, neurological defects, and thymic disorders. Even in the absence of structural malformations, neurocognitive impairments have been observed in 30–60% of children exposed in utero.

Since its introduction in 1982, multiple national programs have been implemented to prevent pregnancy during isotretinoin treatment. Early programs, including those in Canada (1988) and the USA (SMART, 2002), required dual contraception and regular pregnancy testing but showed limited effectiveness. The FDA's iPLEDGE program (2006) introduced stricter measures, including monthly pregnancy testing, mandatory documentation of contraceptive use, and patient registry enrollment. Despite these interventions, pregnancies continued to occur during isotretinoin therapy, underscoring the

critical need for thorough patient education, counseling, and adherence to contraception guidelines.

European programs similarly recommend using at least one, preferably two, forms of contraception before, during, and for one month after isotretinoin therapy, with multiple pregnancy tests throughout the treatment period.

These findings highlight that isotretinoin remains highly teratogenic in humans, and strict pregnancy prevention measures are essential for all women of childbearing potential undergoing treatment.

5.2 Hepatotoxicity

Liver test abnormalities occur in up to 15% of patients on isotretinoin, although marked elevations above three times the upper limit of normal or requiring drug discontinuation are rare (<1%). The liver test abnormalities are typically asymptomatic and transient and can resolve even with continuing therapy. Clinically apparent liver injury due to isotretinoin is exceedingly rare. The acute liver injury with signs of hypersensitivity that occurs with etretinate and acitretin has not been described with isotretinoin therapy. Vitamin A-like effects on the liver with accumulation of lipids in non-parenchymal stellate cells has been described in rare patients on isotretinoin therapy, but the role of supplementary use of vitamin A in these cases was not ruled out. Thus, the majority of reported cases of liver injury attributed to isotretinoin have been anicteric with no or minimal symptoms. However, the lack of reports of more severe hepatitis with jaundice may be due to the close monitoring and early discontinuation of isotretinoin which is required in the use of this agent for acne.

5.3 Desturbed lipid profiles

Lipid levels in the blood including total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol—are assessed using a lipid profile, which helps evaluate an individual's risk for cardiovascular diseases such as heart disease and stroke.

Normal reference ranges are as follows:

- Total cholesterol <200 mg/dL,
- LDL cholesterol <100 mg/dL,
- HDL cholesterol >40 mg/dL (men); >50 mg/dL (women)
- Triglycerides <150 mg/dL.

These ranges may vary modestly based on age, sex, and ethnicity.

While initiating synthetic retinoid therapy, the atherogenic potential and cardiovascular risk of isotretinoin have often been overlooked. Prolonged isotretinoin use has been associated with a significant elevation of the LDL/HDL ratio (0.92 ± 0.51), suggesting increased cardiovascular risk, particularly in patients with familial hypercholesterolemia. Mechanistically, isotretinoin has been shown to increase ApoC-III expression in human hepatoma HepG2 cells, contributing to hypertriglyceridemia and an atherogenic lipid profile.

Given the potential long-term effects of isotretinoin on lipid metabolism, monitoring lipid profiles during therapy is essential. Lipids play a critical role in physiological processes, and altered lipid homeostasis can adversely impact cardiovascular health, liver function, and overall metabolic balance. Careful assessment and ongoing monitoring of lipid parameters during isotretinoin treatment are therefore recommended to optimize therapeutic outcomes and ensure patient safety.

5.4 Mood changes

Isotretinoin, a vitamin A derived retinoid widely used for the treatment of severe and refractory acne, has been consistently associated with neuropsychiatric adverse effects, despite its well-established dermatological efficacy. Although most clinical trials report overall improvements in quality of life and no significant change in mean depression scores at the population level, a substantial body of evidence from case reports, challenge dechallenge rechallenge observations, pharmacovigilance databases, and large epidemiological studies indicates that a small but clinically important subset of patients develops depression, suicidal ideation, suicide attempts, anxiety, mania, psychosis, aggression, and emotional lability during isotretinoin therapy. The biological plausibility of these effects is supported by the role of retinoids in central nervous system development and function, particularly their influence on gene transcription, neuroplasticity, and monoaminergic neurotransmission in brain regions implicated in mood regulation. Collectively, these findings suggest that isotretinoin possesses intrinsic psychotropic potential, with neuropsychiatric reactions likely occurring through idiosyncratic vulnerability rather than as a universal effect, underscoring the need for careful patient selection, informed consent, and ongoing psychiatric monitoring during treatment. Reports also exist of episodes of depression and psychosis in patients taking isotretinoin. Even though the correlation is controversial, screening for depression, suicidal ideation, past suicide attempts, and aggressive or violent behaviors should occur before prescribing isotretinoin.

6. Contraindication and Precaution

6.1 Absolute contraindication

6.1.1 Pregnancy

Isotretinoin is strictly contraindicated in pregnancy and in women of childbearing potential who are not using effective contraception, due to its well-established and severe teratogenicity. Exposure during pregnancy or shortly before conception can result in major congenital malformations involving the craniofacial region, heart, central nervous system, thymus, and ears, as well as long-term neurodevelopmental deficits. Consequently, isotretinoin is contraindicated in women who are pregnant, planning pregnancy, unable or unwilling to comply with pregnancy prevention programmes, or unable to undergo regular pregnancy testing. The drug should also not be initiated unless stringent contraceptive measures are in place before, during, and after treatment, as failure to adhere to these precautions has been repeatedly associated with isotretinoin-exposed pregnancies and serious fetal harm.

Isotretinoin was a pregnancy category X drug under the previous FDA system and is contraindicated in pregnant women or those who may become pregnant. There have been severe, documented congenital disabilities when pregnant women have taken isotretinoin. The Food and Drug Administration requires prescribers and patients to register with the iPLEDGE program to prescribe and receive isotretinoin. iPLEDGE ensures the fulfillment of appropriate requirements before dispensing isotretinoin to prevent the use of this medication during pregnancy. These requirements include negative pregnancy tests and documented abstinence or the use of birth control before and while taking isotretinoin.

6.1.2 Hypersensitivity reaction

Isotretinoin is contraindicated in patients with hypersensitivity to its components, including vitamin A and preservatives within the gel capsule.

6.2 Use in special population

6.2.1 Hepatic impairment

Liver function abnormalities occur in up to 15% of patients taking isotretinoin, although significant elevations necessitating discontinuation are uncommon. The mechanism of injury is not fully understood, but it may involve a direct toxic effect, with higher doses linked to increased frequency. These abnormalities are generally asymptomatic and transient, often resolving without discontinuation. Regular monitoring of liver tests is advised, and isotretinoin should be stopped if aminotransferase levels exceed 5 times the upper limit of normal or if symptoms like jaundice develop.

6.2.2 Contraindications related to age

Isotretinoin is contraindicated in children younger than 12 years of age due to the absence of established safety and efficacy data. Its use in adolescents with underlying bone disorders or diseases is relatively contraindicated and requires careful risk–benefit assessment because of potential effects on skeletal growth and bone metabolism. Although no absolute geriatric-specific contraindications have been identified, isotretinoin should be used with caution in elderly patients owing to an increased risk of serious adverse effects, and treatment should be avoided or closely monitored in this population when significant comorbidities are present.

6.3 Contraindicated and clinically significant drug interactions with isotretinoin

The concomitant use of isotretinoin with certain antiepileptic drugs is contraindicated or strongly discouraged due to clinically significant interactions. Enzyme-inducing antiepileptics such as carbamazepine, phenytoin, and topiramate can reduce the effectiveness of hormonal contraceptives, thereby increasing the risk of unintended pregnancy and severe isotretinoin-associated teratogenicity. Additionally, isotretinoin may reduce plasma concentrations of carbamazepine, potentially increasing seizure risk.

Isotretinoin is contraindicated with rifamycin antibiotics, including rifampin and rifabutin, as these agents markedly decrease the efficacy of hormonal contraceptives, posing a high risk of contraceptive failure and fetal exposure.

Concurrent administration of isotretinoin with tetracycline antibiotics (e.g., doxycycline, minocycline, tetracycline) is contraindicated due to an increased risk of intracranial hypertension (pseudotumor cerebri), a rare but serious adverse effect.

Certain antiretroviral agents, such as efavirenz and nevirapine, are also relatively contraindicated when used with isotretinoin because they may reduce hormonal contraceptive effectiveness, thereby increasing the risk of isotretinoin-exposed pregnancy. Careful medication review and alternative therapies should be considered before initiating isotretinoin.

6.4 iPLEDGE risk-management program

iPLEDGE is a mandatory risk-management program designed to prevent fetal exposure to isotretinoin. All patients, prescribers, and dispensing pharmacies must be registered before isotretinoin can be prescribed or dispensed. Enrollment requires patient education on teratogenic risks and documented informed consent. Prescriptions are restricted to a maximum 30-day supply with no refills and require monthly clinical review. Women of childbearing potential must undergo regular, laboratory-confirmed pregnancy testing and adhere to strict timelines for

prescription authorization and dispensing. Additional safeguards include prohibition of blood donation during therapy and for one month after discontinuation, controlled dispensing within defined time windows, and verification through a unique patient identification number. Noncompliance with iPLEDGE requirements constitutes a contraindication to isotretinoin therapy.

7. Formulation Advances

7.1 Liposome

Liposomes are first-generation vesicular carriers capable of delivering both hydrophilic and lipophilic drugs. They are spherical vesicles composed of phospholipids and cholesterol and are classified as multilamellar vesicles (MLVs) or unilamellar vesicles, including large (LUVs) and small unilamellar vesicles (SUVs). Vesicle size plays a crucial role in skin penetration, with smaller vesicles showing better permeation; among these, LUVs with diameters ranging from 50–500 nm are considered optimal for penetration through the stratum corneum. Liposomal formulations of topical retinoids, such as tretinoin liposomal gel prepared by the film hydration method, have demonstrated improved therapeutic efficacy, enhanced skin tolerability, reduced irritation, and sustained drug release compared with conventional formulations. Overall, liposomes enhance retinoid stability, increase drug payload, improve dermal penetration, and allow dose and dosing-frequency reduction; however, their clinical application is limited by drug leakage, lipid oxidation and hydrolysis during storage, and high manufacturing costs.

7.2 Niosomes

Niosomes are second-generation vesicular delivery systems that resemble liposomes in structure but are composed of non-ionic surfactants rather than phospholipids. Developed to overcome the limitations of liposomes, niosomes offer improved physicochemical stability, higher drug entrapment efficiency, enhanced skin penetration, and lower production costs. They may exist as unilamellar or multilamellar vesicles, with vesicle size and structure significantly influencing drug release and encapsulation efficiency; multilamellar niosomes generally exhibit superior entrapment and release characteristics. Niosomal formulations of tretinoin have shown enhanced stability, particularly with the incorporation of cholesterol. Additional advantages include biocompatibility, non-toxicity, non-immunogenicity, high drug-loading capacity, and prevention of transepidermal water loss, although issues such as vesicle aggregation and hydrolysis of encapsulated drugs remain challenges.

7.3 Solid Nano-Particle

Solid lipid nanoparticles (SLNs) are nanoscale carriers made of solid lipids stabilized with surfactants, capable of delivering both lipophilic and hydrophilic drugs. They protect sensitive compounds like retinol, control drug release, improve skin hydration, and enhance the efficacy of topical agents such as isotretinoin. However, their drug-loading capacity, especially for hydrophilic drugs, is limited. Nanostructured lipid carriers (NLCs), the second generation of lipid nanoparticles, combine solid and liquid lipids to create a more flexible matrix, allowing higher drug loading, better stability, and sustained release. Studies show that isotretinoin-loaded SLNs and NLCs improve therapeutic outcomes, with NLCs offering superior drug encapsulation and delivery performance.

7.4. Nanoemulsions

Nanoemulsions are submicron oil-in-water dispersions (20–200 nm) used as nanocarriers for both lipophilic and hydrophilic drugs. Their high surface area allows efficient drug solubilization, while their formulations improve skin hydration and viscoelasticity. Studies have shown that incorporating retinoids like retinyl palmitate or isotretinoin into nanoemulsions enhances skin permeation and retention. For isotretinoin, nanoemulsion formulations using oils like coconut oil and surfactants such as Tween 80 provide controlled, zero-order drug release, improving therapeutic efficacy and reducing side effects.

7.5. Nanocapsules

Polymeric nanocapsules are effective nanocarriers in drug delivery, consisting of a lipid core surrounded by a polymeric shell. Lipophilic drugs, such as retinoids, can be dissolved in the lipid core, which provides protection from environmental degradation and improves drug stability. Both natural and synthetic lipids and polymers can be used in their construction. For example, tretinoin-loaded nanocapsules using poly-ε-caprolactone as the polymer and capric/caprylic triglycerides or sunflower oil as the lipid phase showed a twofold increase in photostability compared with tretinoin in methanol. These systems can be prepared via high-pressure homogenization or solvent-extraction methods, making nanocapsules a promising strategy for enhancing the efficacy and stability of retinoid therapies for acne.

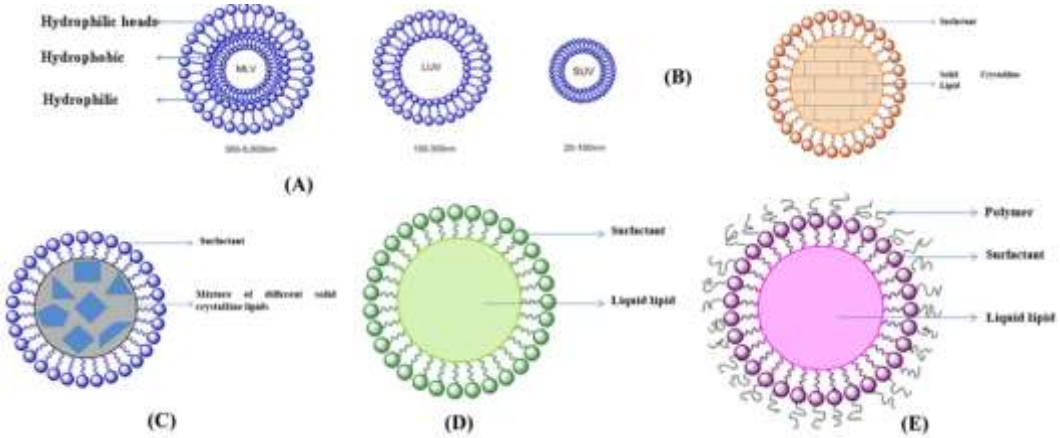

Figure 1 Schematic presentation of (A) Liposomes; (B) Solid lipid nanoparticles; (C) Nano lipid carriers; (D) Nanoemulsion; (E) Nanocapsules.

7.6 Isomer specific preparation

Dienolate formation:

A strong base (e.g., LDA generated from n-BuLi and diisopropylamine) abstracts the acidic α-proton of methyl 3,3-dimethylacrylate, producing a resonance-stabilized dienolate nucleophile.

C–C bond formation (nucleophilic addition):

The dienolate carbon attacks the aldehydic carbonyl carbon of β-ionylidene acetaldehyde at −60 to −80 °C, forming a new C–C bond and a β-alkoxide intermediate.

Intramolecular lactonization:

The alkoxide undergoes intramolecular nucleophilic attack on the ester carbonyl, leading to cyclization and formation of a transient lactone intermediate with elimination of methoxide.

Lactone opening (base-assisted):

On warming to 25–45 °C, the released methoxide attacks the lactone carbonyl, opening the ring to generate the isotretinoin carboxylate.

Protonation:
Aqueous acidic work-up protonates the carboxylate to afford isotretinoin (13-cis-retinoic acid), with minimal isomerization to all-trans retinoic acid (tretinoin) .

7.7 Low-dose extended-release formulation

Low-dose extended-release and advanced isotretinoin formulations have been developed to overcome the limitations of conventional isotretinoin, including poor aqueous solubility, marked food-dependent absorption, and dose-related adverse effects. Lidose isotretinoin, developed and marketed by Sun Pharmaceutical Industries, Inc. (USA) under the brand name *Absorica*®, employs a lipid-based encapsulation technology that presolubilizes isotretinoin in a lipid matrix, thereby reducing dependence on high-fat, high-calorie meals and improving bioavailability. More recently, micronized isotretinoin, also developed by Sun Pharmaceutical Industries, Inc. and marketed as *Absorica LD*®, combines lipid-carrier technology with particle-size reduction to achieve enhanced dissolution, prolonged drug release, and higher absorption at lower doses, even under fasting conditions. These innovations allow effective acne control with reduced daily dosing, improved patient adherence, lower variability in systemic exposure, and a potentially improved safety profile, representing a significant advancement in the long-term management of severe and recalcitrant acne .

8. Current research and future prospect

8.1 Genetic predictors of response

Table 1: Genetic predictors of responce

Gene / Pathway	Type of Genetic Influence	Clinical Impact on Isotretinoin Therapy
RARA (Retinoic Acid Receptor-α)	Receptor polymorphisms	Alters therapeutic response and predisposes to adverse effects such as headache, myalgia, arthralgia, epistaxis, and liver enzyme elevation
RXR (Retinoid X Receptor)	Receptor interaction variants	Modifies retinoid signaling; implicated in autoimmune thyroiditis and immune-related adverse effects
CYP3A4 / CYP3A family	Drug-metabolizing enzyme variants	Influences isotretinoin metabolism to 4-oxo-isotretinoin; altered activity may affect efficacy, drug–drug interactions, and toxicity
CYP26A1 / CYP26B1 / CYP26C1	Retinoic acid–clearing enzymes	Regulate retinoic acid degradation; variability may affect systemic exposure and treatment response
UGT2B7	Phase II metabolism polymorphisms	May alter isotretinoin clearance and systemic accumulation
CYP2C8	Oxidative metabolism variants	Contributes to interindividual variability in pharmacokinetics
PPARγ	Epigenetically regulated transcription factor	Suppression linked to sebaceous gland atrophy and reduced sebum production (therapeutic effect)
FoxO1 / FoxO3	Epigenetic regulation	Associated with sebocyte apoptosis and cell-cycle arrest
IL-6, immune signaling genes	Expression modulation	May contribute to inflammatory and immune-mediated adverse effects

LEP (Leptin gene)	Metabolic polymorphisms (e.g., rs7799039)	Associated with isotretinoin-induced dyslipidemia and altered lipid profile
ADIPOQ (Adiponectin gene)	Metabolic gene variants	Influences HDL cholesterol changes during therapy
KRT10	Structural protein variants	Associated with skeletal adverse effects such as hyperostosis and avascular necrosis
CYP2D6	Enzyme suppression by isotretinoin	Alters metabolism of co-administered psychotropic and cardiovascular drugs

Overall, genetic and epigenetic variability in retinoid signaling, drug metabolism, immune regulation, and lipid pathways contributes substantially to differences in isotretinoin efficacy and safety, supporting the future role of pharmacogenetic-guided isotretinoin therapy **.**

8.2 Biomarker guided therapy

Biomarker-guided therapy of isotretinoin has gained attention as a strategy to individualize treatment response and monitor inflammatory burden in acne vulgaris. Recent evidence demonstrates that serum YKL-40 (chitinase-3-like protein 1), an inflammation-associated glycoprotein, is significantly elevated in patients with moderate to severe acne compared with healthy controls and shows a marked reduction following oral isotretinoin therapy. The decline in YKL-40 levels parallels clinical improvement assessed by global acne severity scores, supporting its role as a dynamic biomarker reflecting therapeutic response rather than disease severity. These findings suggest that baseline and follow-up measurement of YKL-40 may aid in identifying patients with higher inflammatory activity, predicting responsiveness to isotretinoin, and objectively monitoring treatment efficacy. Overall, biomarker-guided approaches using YKL-40 could complement clinical assessment and contribute to a more personalized, mechanism-based use of isotretinoin in acne management.

8.3 Emerging retinoids with better safety profile

Emerging retinoids are being developed to retain the therapeutic efficacy of classical retinoids while improving safety, tolerability, and patient adherence. A key advancement is the development of receptor-selective and fourth-generation retinoids, such as Trifarotene, developed by Galderma, which selectively targets retinoic acid receptor-γ (RAR-γ) the predominant isoform in the skin thereby reducing systemic exposure and adverse effects. Other well-established retinoids, including Adapalene (Galderma) and Tazarotene (AbbVie/Allergan), also demonstrate improved receptor selectivity and favorable tolerability profiles compared to earlier agents like tretinoin. Formulation innovations have further enhanced retinoid therapy; for example, microsphere-based tretinoin formulations developed by Johnson & Johnson improve photostability and minimize skin irritation through controlled release. Additionally, pro-retinoids such as retinyl retinoate enable gradual conversion to active retinoic acid within the skin, reducing irritation while maintaining efficacy. Collectively, these advances aim to minimize common adverse effects, including teratogenicity, mucocutaneous toxicity, and inflammation, while preserving strong comedolytic and anti-inflammatory actions, positioning emerging retinoids as safer and more patient-friendly options for the long-term

management of acne and other disorders of keratinization.

8.4 Ongoing clinical trails

8.4.1 Acne Vulgaris Trial — *Assessment of Serum Catestatin Level*

Clinical Trial ID: *NCT07054398*

Status: Recruiting

Location: Aswan University Hospital, *Aswan, Egypt*

❖ **Purpose**

This interventional study is investigating how oral isotretinoin therapy affects *serum levels of catestatin* (a peptide related to inflammation) in patients with *moderate to severe acne vulgaris*. It also tracks clinical improvement in acne severity following treatment.

❖ **Study Design**

Interventional, parallel-group design

Two groups:

Group I (Study Group): ~30 patients with moderate/severe acne receiving oral isotretinoin

Group II (Control Group): ~30 healthy persons not affected by acne (for comparison)

❖ **Eligibility Criteria**

***Inclusion*:**

Adults of both sexes with *moderate and severe acne vulgaris*

***Exclusion*:**

Pregnant or breastfeeding women

Immunocompromised patients

Severe anemia

Chronic liver disease

Hyperlipidemia: Subjects with non-inflammatory acne conditions

History of neurologic, cardiovascular, or neoplastic disorders

Recent systemic acne treatment (e.g., systemic retinoids within 4 weeks, topicals within 2 weeks)

Known hypersensitivity to isotretinoin

❖ **Primary Outcomes**

Changes in *serum catestatin levels* over 12 weeks Clinical improvement in acne (graded by reduction in lesion counts)

Note : Study uses oral isotretinoin doses around 0.5mg/kg/day up to 40/mg/kg/day in acne group.

CONCLUSION

Isotretinoin has established itself as a transformative therapy in dermatology, revolutionizing the management of severe, treatment-resistant acne and achieving long-term remission rates unmatched by conventional treatments. Its multifactorial mechanism comprising reduction of sebaceous gland size and sebum production, normalization of keratinization, suppression of *Cutibacterium acnes*, and potent anti-inflammatory effects supports its efficacy not only in severe nodulocystic acne but also in moderate acne resistant to therapy, rosacea, seborrhea, and keratinization disorders such as ichthyosis and keratosis pilaris. Clinical evidence highlights the critical role of cumulative dosing in reducing relapse risk, while evolving strategies such as low-

dose, intermittent, and micro-dosing regimens aim to maintain therapeutic benefit with improved tolerability.

Despite its effectiveness, isotretinoin carries the potential for significant adverse effects, including teratogenicity, hepatotoxicity, hyperlipidemia, and rare neuropsychiatric events, necessitating rigorous patient selection, ongoing monitoring, and adherence to structured safety programs such as iPLEDGE. Advances in formulation such as liposomal and nano-formulations, isomer-specific preparations, and extended-release systems promise enhanced bioavailability, reduced systemic toxicity, and improved patient compliance.

Looking forward, biomarker-guided therapy, genetic predictors of response, and emerging retinoids with improved safety profiles are paving the way toward more personalized and precise isotretinoin treatment. Additionally, ongoing clinical trials exploring its role in oncology and systemic inflammatory conditions underscore the drug's expanding therapeutic potential beyond dermatology.In conclusion, isotretinoin remains a cornerstone of dermatologic therapy, with enduring clinical relevance and a trajectory of innovation that continues to optimize efficacy, safety, and individualized care, ensuring its pivotal role in the management of acne and related disorders for years to come.

REFERENCES

1. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. Br J Dermatol. 2018;178(1):76–85. doi:10.1111/bjd.15668
2. Ward A, Brogden RN, Heel RC, et al. Isotretinoin: A review of its pharmacological properties and therapeutic efficacy. Drugs. 1984;28(1):6–37. doi:10.2165/00003495-198428010-00002
3. Sadeghzadeh-Bazargan A, Ghassemi M, Goodarzi A, et al. Low-dose isotretinoin in acne vulgaris: A systematic review. Dermatol Ther. 2021;34(1):e14438. doi:10.1111/dth.14438
4. Paichitrojjana A. Oral isotretinoin and its uses in dermatology: A review. Drug Des Devel Ther. 2023;17:2573-2591. doi:10.2147/DDDT.S427530
5. Khan A, Khan C, Ahmed S. The history and development of isotretinoin: A review. Clin Exp Dermatol. 2025. doi:10.1093/ced/llaf523
6. Fallah H, Rademaker M. Isotretinoin in acne vulgaris: Practical prescribing. Int J Dermatol. 2021;60(4):451-460. doi:10.1111/ijd.15089
7. Bagatin E, Costa CS, Rocha MA, et al. Consensus on the use of oral isotretinoin. An Bras Dermatol. 2020;95(S1):19-38. doi:10.1016/j.abd.2020.09.001
8. Costa CS, Dreno B, Gollnick H, et al. Oral isotretinoin for acne (Cochrane Review). Cochrane Database Syst Rev. 2018;CD009435. doi:10.1002/14651858.CD009435.pub2
9. Orfanos CE, Ehlert R, Gollnick H. The retinoids: Clinical pharmacology and therapeutic use. Drugs. 1987;34(4):459-503. doi:10.2165/00003495-198734040-00003
10. Khalil NY, Darwish IA, Al-Qahtani AA. Isotretinoin profile. Profiles Drug Subst Excip Relat Methodol. 2020;45:119-157. doi:10.1016/bs.podrm.2019.10.005
11. Ding RL, et al. Physiological and psychological effects of isotretinoin. Clin Cosmet Investig Dermatol. 2023. doi:10.2147/CCID.S416267
12. Honeybrook A, Bernstein E. Oral isotretinoin in photoaging. J Cosmet Dermatol. 2020;19(7):1548-1554. doi:10.1111/jocd.13467

13. Colburn WA, Gibson DM. Food increases bioavailability of isotretinoin. J Clin Pharmacol. 1983;23(11-12):534-539. doi:10.1002/j.1552-4604.1983.tb01800.x
14. Rabello-Fonseca RM, Azulay DR, Luiz RR, et al. Oral isotretinoin for photoaging. J Eur Acad Dermatol Venereol. 2009;23(2):115-123. doi:10.1111/j.1468-3083.2008.02947.x
15. Faghihi G, Mokhtari F, Fard NM. Low-dose vs conventional isotretinoin therapy. J Res Pharm Pract. 2017;6(4):233-238. doi:10.4103/jrpp.JRPP_17_30
16. Nofal A, Khedr A, Fathy M. High vs low-dose isotretinoin for warts. Dermatol Ther. 2022;35(12):e15964. doi:10.1111/dth.15964
17. Giray B, Van Gemert MJ. Hidradenitis suppurativa treated with isotretinoin. J Am Acad Dermatol. 1999;40(1):73–76. doi:10.1016/S0190-9622(99)70530-X
18. Pasmatzi E, Kapranos N, Monastirli A, et al. Isotretinoin therapy clinical evaluation. Arch Gynecol Obstet. 1996;258(1):35–41. doi:10.1007/BF01370930
19. Reyna-Rodríguez IL, Chavez-Alvarez S, Garza-Rodríguez V, et al. Low-dose isotretinoin outcomes. Arch Dermatol Res. 2021;313(10):815–827. doi:10.1007/s00403-020-02182-y
20. Ahmad HM. Clinical efficacy and side effects of isotretinoin. Dermatol Ther. 2015;28(3):151–157. doi:10.1111/dth.12213
21. Shetti SA, Nagesh HN, Hanumantharaya N. Continuous vs intermittent isotretinoin therapy. Natl J Physiol Pharm Pharmacol. 2017;7(9):941–946. doi:10.5455/njppp.2017.7.0305804052017
22. Layton A. The use of isotretinoin in acne. Dermatol Clin. 2009;27(1):33-45. doi:10.1016/j.det.2008.09.004
23. Leyden JJ, Del Rosso JQ, Baum EW. Clinical considerations in isotretinoin therapy. J Clin Aesthet Dermatol. 2014;7(Suppl 2):S3-S21.
24. Johnson BA, Nunley JR. Systemic agents in acne including isotretinoin. Am Fam Physician. 2000;62(8):1823-1830.
25. Blume-Peytavi U, et al. Isotretinoin in rosacea. Dermatology. 1999;218(2):134-135. doi:10.1159/000182261
26. Paichitrojjana A. Demodicosis treated with isotretinoin. JAAD Case Rep. 2022;26:98-100. doi:10.1016/j.jdcr.2022.06.017
27. Niazi S, Shehzad A. Fixed low-dose regimens in acne. J Pak Assoc Dermatol. 2016;25(4):291-297.
28. Colburn WA. Pharmacokinetics of isotretinoin. J Clin Pharmacol. 1983;23(11-12):534-539. doi:10.1002/j.1552-4604.1983.tb01800.x
29. Costa CS, et al. Isotretinoin dosing strategies. Br J Dermatol. 2019;180(4):784-790. doi:10.1111/bjd.17375
30. Lee YH, Scharnitz TP, Muscat J, et al. Isotretinoin and depression risk meta-analysis. J Am Acad Dermatol. 2016;74(1):56-63. doi:10.1016/j.jaad.2015.09.023
31. Bremner JD, Shearer KD, McCaffery PJ. Retinoic acid and depression link. J Clin Psychiatry. 2012;73(1):37-50. doi:10.4088/JCP.10r06260
32. Huang YC, Cheng YC. Isotretinoin treatment and inflammatory markers. Dermatology. 2017;233(3):179-185. doi:10.1159/000477338
33. Strauss JS, Rapini RP, Shalita AR, et al. Guidelines of care for acne vulgaris. J Am Acad Dermatol. 2007;56(4):651-663. doi:10.1016/j.jaad.2006.08.048
34. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Acne vulgaris guidelines update. J Am Acad Dermatol. 2016;74(5):945-973. doi:10.1016/j.jaad.2015.12.037
35. Sardana K, Garg VK. Low-dose isotretinoin in acne: Evidence review. Indian J Dermatol

Venereol Leprol. 2010;76(1):7-13. doi:10.4103/0378-6323.58664

36. Rademaker M. Isotretinoin dose and relapse risk. Australas J Dermatol. 2013;54(3):157-162. doi:10.1111/ajd.12034
37. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin treatment study. J Am Acad Dermatol. 2006;54(4):644-646. doi:10.1016/j.jaad.2005.11.1091
38. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remission of cystic acne with isotretinoin. N Engl J Med. 1982;306(19):1156-1161. doi:10.1056/NEJM198205133061902
39. McLane J. Analysis of common side effects of isotretinoin. J Am Acad Dermatol. 2001;45(5):S188-S194. doi:10.1067/mjd.2001.117009
40. Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide with isotretinoin. J Am Acad Dermatol. 2001;45(4):515-519. doi:10.1067/mjd.2001.117730
41. Bremner JD, Fani N, Ashraf A, et al. Functional brain imaging alterations in acne patients treated with isotretinoin. Am J Psychiatry. 2005;162(5):983-991. doi:10.1176/appi.ajp.162.5.983
42. Shalita AR, Cunningham WJ, Leyden JJ, et al. Isotretinoin revisited: Clinical response and safety considerations. J Am Acad Dermatol. 1988;19(5 Pt 1):887-895. doi:10.1016/S0190-9622(88)70269-0

HOW TO CITE: Pratiksha Kadale, Sayali Karande, Sakshi Kumbhoje, Aniket Thanekar, Dr. D. R. Jadage, Isotretinoin: A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 2, 3731-3748. https://doi.org/10.5281/zenodo.18746697